

Y 4
. L 11/2
D 56/
975

1043

946
975
2 11/2
946

REGULATION OF DIETHYLSTILBESTROL (DES), 1975

GOVERNMENT

Storage

626 1975

JOINT HEARING

KANSAS STATE UNIVERSITY

LIBRARY

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON

LABOR AND PUBLIC WELFARE

AND THE

SUBCOMMITTEE ON

ADMINISTRATIVE PRACTICE AND PROCEDURE

OF THE

COMMITTEE ON THE JUDICIARY

UNITED STATES SENATE

NINETY-FOURTH CONGRESS

FIRST SESSION

ON

S. 963

TO AMEND THE FEDERAL FOOD, DRUG, AND COSMETIC
ACT TO PROHIBIT THE ADMINISTRATION OF THE DRUG
DIETHYLSTILBESTROL (DES) TO ANY ANIMAL INTENDED
FOR USE AS FOOD, AND FOR OTHER PURPOSES

FEBRUARY 27, 1975



Printed for the use of the Committee on Labor and Public Welfare

U.S. GOVERNMENT PRINTING OFFICE

WASHINGTON : 1975

55-647 C

COMMITTEE ON LABOR AND PUBLIC WELFARE

HARRISON A. WILLIAMS, JR., New Jersey, *Chairman*

JENNINGS RANDOLPH, West Virginia
CLAIBORNE PELL, Rhode Island
EDWARD M. KENNEDY, Massachusetts
GAYLORD NELSON, Wisconsin
WALTER F. MONDALE, Minnesota
THOMAS F. EAGLETON, Missouri
ALAN CRANSTON, California
WILLIAM D. HATHAWAY, Maine

JACOB K. JAVITS, New York
RICHARD S. SCHWEIKER, Pennsylvania
ROBERT TAFT, JR., Ohio
J. GLENN BEALL, JR., Maryland
ROBERT T. STAFFORD, Vermont
PAUL LAXALT, Nevada

DONALD ELISBURG, *General Counsel*
MARJORIE M. WHITTAKER, *Chief Clerk*
JAY B. CUTLER, *Minority Counsel*

SUBCOMMITTEE ON HEALTH

EDWARD M. KENNEDY, Massachusetts, *Chairman*

HARRISON A. WILLIAMS, JR., New Jersey
GAYLORD NELSON, Wisconsin
THOMAS F. EAGLETON, Missouri
ALAN CRANSTON, California
CLAIBORNE PELL, Rhode Island
WALTER F. MONDALE, Minnesota
WILLIAM D. HATHAWAY, Maine

RICHARD S. SCHWEIKER, Pennsylvania
JACOB K. JAVITS, New York
J. GLENN BEALL, JR., Maryland
ROBERT TAFT, JR., Ohio
ROBERT T. STAFFORD, Vermont

LEROY G. GOLDMAN, *Professional Staff Member*
JAY B. CUTLER, *Minority Counsel*

COMMITTEE ON THE JUDICIARY

JAMES O. EASTLAND, Mississippi, *Chairman*

JOHN L. McCLELLAN, Arkansas
PHILIP A. HART, Michigan
EDWARD M. KENNEDY, Massachusetts
BIRCH BAYH, Indiana
QUENTIN N. BURDICK, North Dakota
ROBERT C. BYRD, West Virginia
JOHN V. TUNNEY, California
JAMES ABOUREZK, South Dakota

ROMAN L. HRUSKA, Nebraska
HIRAM L. FONG, Hawaii
HUGH SCOTT, Pennsylvania
STROM THURMOND, South Carolina
CHARLES McC. MATHIAS, JR., Maryland
WILLIAM L. SCOTT, Virginia

SUBCOMMITTEE ON ADMINISTRATIVE PRACTICE AND PROCEDURE

EDWARD M. KENNEDY, Massachusetts, *Chairman*

PHILIP A. HART, Michigan
BIRCH BAYH, Indiana
QUENTIN N. BURDICK, North Dakota
JOHN V. TUNNEY, California

STROM THURMOND, South Carolina
CHARLES McC. MATHIAS, JR., Maryland
EDWARD J. GURNEY, Florida
HUGH SCOTT, Pennsylvania

THOMAS M. SUSMAN, *Counsel*
WALTER J. SHERIDAN, *Chief Investigator*
STEPHEN L. JONES, *Minority Counsel*

CONTENTS

Text of:	Page
S. 963, as introduced-----	3

CHRONOLOGICAL LIST OF WITNESSES

THURSDAY, FEBRUARY 27, 1975

Malloy, Mrs. John, San Diego, Calif., accompanied by Mrs. Albert Green, Glencove, Long Is., and Mrs. Janice Luder, Los Angeles, Calif., a panel--	5
Greenwald, Peter, M.D., director, Cancer Control Bureau of New York State Department of Health, clinical assistant professor of medicine at the Albany Medical School, and assistant attending physician at the Albany Medical Center Hospital, accompanied by Robert H. Pantell, M.D., consulting pediatrician and clinical scholar at the Stanford University School of Medicine, and Ms. Belita H. Cowan, college instructor of health care in Ann Arbor, Mich., a panel-----	11
Seife, Dr. Marvin, Director of the Generic Drug Division, Bureau of Drugs, Food and Drug Administration, accompanied by Dr. Vincent Karusaitis, obstetrician and gynecologist, medical officer in the Generic Drug Division, Food and Drug Administration-----	26
Furman Robert H., M.D., vice president, Lilly Research Laboratories, Eli Lilly, Inc., accompanied by Robert L. Pillarella, president, Tablicaps, Inc., Franklinville, N.J.-----	32
Rauscher, Frank, Ph. D., Director, National Cancer Institute, National Institutes of Health, accompanied by Alexander M. Schmidt, M.D., Commissioner, Food and Drug Administration; J. Richard Crout, M.D., Director, Bureau of Drugs; Peter Barton Hutt, General Counsel; and Robert C. Wetherell, Jr., Director, Office of Legislative Services-----	39

STATEMENTS

Furman, Robert H., M.D., vice president, Lilly Research Laboratories, Eli Lilly, Inc., accompanied by Robert L. Pillarella, president, Tablicaps, Inc., Franklinville, N.J.-----	32
Greenwald, Peter, M.D., director, Cancer Control Bureau of New York State Department of Health, clinical assistant professor of medicine at the Albany Medical School, and assistant attending physician at the Albany Medical Center Hospital, accompanied by Robert H. Pantell, M.D., consulting pediatrician and clinical scholar at the Stanford University School of Medicine, and Ms. Belita H. Cowan, college instructor of health care in Ann Arbor, Mich., a panel-----	11
Malloy, Mrs. John, San Diego, Calif., accompanied by Mrs. Albert Green, Glencove, Long Is., and Mrs. Janice Luder, Los Angeles, Calif., a panel--	5
Rauscher, Frank, Ph. D., Director, National Cancer Institute, National Institutes of Health, accompanied by Alexander M. Schmidt, M.D., Commissioner, Food and Drug Administration; J. Richard Crout, M.D., Director, Bureau of Drugs; Peter Barton Hutt, General Counsel; and Robert C. Wetherell, Jr., Director, Office of Legislative Services-----	39
Seife, Dr. Marvin, Director of the Generic Drug Division, Bureau of Drugs, Food and Drug Administration, accompanied by Dr. Vincent Karusaitis, obstetrician and gynecologist, medical officer in the Generic Drug Division, Food and Drug Administration-----	26

IV

APPENDIX

Schmidt, Alexander M., M.D., Commissioner, Food and Drug Administration, Public Health Service, Department of Health, Education, and Welfare, prepared statement-----	Page 65
Greenwald, Peter, M.D., director, Cancer Control Bureau of New York State Department of Health, clinical assistant professor of medicine at the Albany Medical School, and assistant attending physician at the Albany Medical Center Hospital, prepared statement (with attachments)-----	11
Pantell, Robert H., M.D., consulting pediatrician and clinical scholar, Stanford University School of Medicine, prepared statement-----	89
Cowan, Belita H., college instructor of health care in Ann Arbor, Mich., prepared statement-----	94
Seife, Marvin, M.D., Director of the Generic Drug Division, Bureau of Drugs, Food and Drug Administration, curriculum vitae of-----	26
Rauscher, Frank J., Jr., Ph. D., director, National Cancer Program, National Cancer Institute, National Institutes of Health, prepared statement-----	104
Vaginal Cancer After Maternal Treatment With Synthetic Estrogens, by Peter Greenwald, M.D., Joseph J. Barlow, M.D., Philip C. Nasca, M.S., and William S. Burnett, M.D., from the New England Journal of Medicine, vol. 285, August 12, 1971-----	113
Diethylstilbestrol Contraindicated in Pregnancy, FDA Drug Bulletin, November 1971-----	116
Adenocarcinoma of the Vagina, Association of Maternal Stilbestrol Therapy with Tumor Appearance in Young Women, by Arthur L. Herbst, M.D., Howard Ulfelder, M.D. and David C. Poskanzer, M.D., from the New England Journal of Medicine, April 22, 1971-----	120
Postcoital Diethylstilbestrol, FDA Drug Bulletin, May 1973-----	123
Prenatal Exposure to Stilbestrol, a prospective comparison of exposed female offspring with unexposed controls, by Arthur L. Herbst, M.D., David C. Poskanzer, M.D., Stanley J. Robboy, M.D., Lawrence Friedlander, M.D., and Robert E. Scully, M.D., from the New England Journal of Medicine, vol. 292, No. 7, February 13, 1975-----	127
Postcoital Contraception With Diethylstilbestrol, by Lucile Kirtland Kuchera, M.D., from Jama, vol. 218, No. 4, October 25, 1971-----	133
Diethylstilbestrol as a "Morning After" Pill, paper from the University of Michigan-----	135
Certain Estrogens for Oral or Parenteral Use, from the Federal Register, vol. 38, No. 186, September 26, 1973-----	136
DES Label and Packaging Changes When Used as Emergency "Morning After" Contraceptive, news release of FDA, September 21, 1973-----	139
New Drugs—Diethylstilbestrol as Postcoital Oral Contraceptive: Patient Labeling, from the Federal Register, vol. 40, No. 25, February 5, 1975-----	142
Morning After Pill: Diethylstilbestrol (DES), FDA talk paper, February 5, 1975 (with attachments)-----	147
Furman, Robert H., M.D., vice president, Lilly Research Laboratories, prepared statement (with attachments)-----	32
Tablicaps, Inc., Robert L. Pillarella, president, prepared statement (with attachments)-----	132
Regulation of Diethylstilbestrol (DES), 1972, excerpt from Health Subcommittee hearing, July 20, 1972-----	191
Text of:	
S. 963, as reported-----	157
Senate Report 94-264-----	270

REGULATION OF DIETHYLSTILBESTROL (DES), 1975

THURSDAY, FEBRUARY 27, 1975

U.S. SENATE,
SUBCOMMITTEE ON HEALTH OF THE
COMMITTEE ON LABOR AND PUBLIC WELFARE;
SUBCOMMITTEE ON ADMINISTRATIVE PRACTICE AND
PROCEDURE OF THE COMMITTEE ON THE JUDICIARY,
Washington, D.C.

The subcommittee met, pursuant to notice, at 9:34 a.m., in room 4232, Dirksen Senate Office Building, Senator Edward M. Kennedy (chairman of the Subcommittee on Health), presiding.

Present: Senators Kennedy and Schweiker.

Committee staff present: LeRoy G. Goldman and Walter Sheridan, professional staff members; and Jay B. Cutler, minority counsel.

Senator KENNEDY. The subcommittees will come to order.

DES is a drug out of control. It is known to cause cancer in the daughters of some mothers who take it during pregnancy.

It is in widespread use in the United States as a morning after contraceptive and has been for many years. The knowledge of this wide and inappropriate usage is, in part, responsible for FDA's recent decision to approve it as a morning after pill in emergency situations. In previous testimony before the Health Subcommittee, FDA has defined such emergencies to be rape, incest, or a similar tragedy.

All experts agree that, because it does cause human cancer, DES must be used with great caution and only in emergency situations. Most experts also agree that continued widespread misuse would present a major health hazard. These statistics which exist must make one skeptical that the drug will be used as advised by the FDA.

It is ironic and disheartening that the FDA, through a major bureaucratic error, has contributed to the national confusion about DES.

In May 1973, the FDA sent out its drug bulletin to physicians, informing them that the agency had approved DES as a morning after pill for emergency situations. The bulletin was wrong. The drug was not approved until this month—almost 2 years later—but the error was never corrected.

In effect then, in the real world, doctors have been operating since 1973 under the assumption that the drug has been approved for emergencies.

Thus, for example, the University of Michigan has been informing its coeds that the drug is FDA approved since that time. At that university, the definition of emergency has gone far beyond rape and incest.

The fact that the Commissioner acknowledges widespread use of the drug as a morning after pill in his statement this morning must be interpreted in light of the fact that doctors were explicitly, although incorrectly, told by FDA that its use was for emergencies only.

Why, then, should it be assumed that appropriate use will result from the now official approval of the drug?

My concern is for those times that DES does not work and female children are born. How many times will that happen if the drug is widely misused?

How many times will the patient be lost to followup or take the drug when already pregnant?

How sure are we that there will be no risk to the mother at all?

The tragic consequences of misuse of DES will be made dramatically clear at this hearing. Who should be responsible if misuse of the drug continues and more American daughters fall victim to a deadly cancer?

Is it the FDA's responsibility to assure appropriate use?

Is it the drug industry's?

Is it the medical profession's?

Will any group assume the responsibility?

DES is also still being used as a cattle feed additive. The FDA has been trying, administratively, to remove it from the market for 2 years. Because of procedural difficulties, the District of Columbia Court of Appeals overturned their ban on DES in January 1974. Now, we are back where we started.

DES is once again appearing on the American dinner table. In the week of January 31, 1975, residues were reported to be as high as 4.1 parts per billion. The Department of Agriculture has reinstituted its certification program.

The Director of the National Cancer Institute, who we will hear from this morning, is on record supporting the removal of DES from cattle feed. So is the Director of the Cancer Control Bureau of New York State, who is also with us this morning. So is the U.S. Senate, which passed a ban on DES in 1972. So is FDA, which moved, although inadequately, to remove it from the market.

Over 20 countries prohibit its use. Two countries have banned the importation of American DES-fed meat. Yet, when this Nation sits down to eat around the dinner table tonight, if they have meat, they may still be ingesting DES.

What will it take to get it out of meat?

If we do not get assurances today of prompt action by FDA on this matter, I will reintroduce legislation to ban the use of DES in cattle feed, and hopefully will be joined by many of my colleagues in the U.S. Senate.

Given the substantive relevance of the health subcommittee's past hearings on the public health problems associated with the use of DES in animals, I intend to incorporate in this hearing record pertinent portions of the 1972 hearings in the appendix.

[The bill subsequently introduced follows:]

94TH CONGRESS
1ST SESSION

S. 963

IN THE SENATE OF THE UNITED STATES

MARCH 5, 1975

Mr. KENNEDY (for himself and Mr. SCHWEIKER) introduced the following bill; which was read twice and referred to the Committee on Labor and Public Welfare

A BILL

To amend the Federal Food, Drug, and Cosmetic Act to prohibit the administration of the drug diethylstilbestrol (DES) to any animal intended for use as food, and for other purposes.

1 *Be it enacted by the Senate and House of Representa-*
2 *tives of the United States of America in Congress assembled,*
3 That section 301 of the Federal Food, Drug, and Cosmetic
4 Act is amended by adding at the end thereof the following
5 new subsections:

6 “(q) The administering of the drug diethylstilbestrol
7 (DES) to any animal intended for use as food or any animal
8 the product of which is intended for use as food.

1 “(r) The introduction or delivery for introduction into
2 interstate commerce the drug diethylstilbestrol (DES) for
3 use as a postcoital contraceptive for a one-year period begin-
4 ning on the date of the enactment of this subsection”.

Senator KENNEDY. Senator Schweiker?

Senator SCHWEIKER. Thank you very much, Mr. Chairman.

I think the hearings today have great significance, not only because of the tragic cases which will be described here this morning but because it points up the question of which agency of the Government is responsible in situations like this. It occurs to me that this applies not only to this drug.

I hope that this morning's hearing will shed light not only on the responsibility that needs to be pinpointed in the Executive, but also the role Congress itself must exercise in this area.

I think that is the significance of the hearing today.

Thank you.

Senator KENNEDY. Thank you very much.

Carrying Senator Schweiker's point even further, I am sure, as we will hear during the course of the morning, we will hear that the drug companies may very well produce a drug that meets certain standards of the Food and Drug Administration, but once they do, how can we expect that they are going to bear a responsibility on the question of whether it is being used appropriately.

The Food and Drug Administration may approve a particular drug for certain use and, yet, how can they be assured that the drug is going to be used just for that particular purpose and not be used for other purposes by some doctors?

We have heard the representatives of the American Medical Association say that they do not want to be interfered with in how a particular drug would be used. And then we find it is the consumer, the patient, so to speak, that is left holding the bag.

These are some of the viewpoints that are going to be tested this morning.

It is quite clear that in this particular instance it has had tragic implications. I want to make sure that the responsibility and accountability is insisted upon, and we are looking forward to this hearing.

We will hear this morning Mrs. Malloy, Mrs. Green, and Mrs. Luder. We are interested in your stories. We know that this is a difficult experience—I know it is just from personal experience—to be talking about particular health difficulties.

But we want you to know how much we appreciate your presence here and how much we appreciate your sharing with us your own knowledge and understanding and experience of this particular drug.

Mrs. Malloy, would you be kind enough to start off?

STATEMENT OF MRS. JOHN MALLOY, SAN DIEGO, CALIF., ACCOMPANIED BY MRS. ALBERT GREEN, GLENCOVE, LONG ISLAND, N.Y., AND MRS. JANICE LUDER, LOS ANGELES, CALIF., A PANEL

Mrs. MALLOY. Yes, sir, Senator.

Senator KENNEDY. Tell us very briefly just about yourself for the moment and tell us how you came in contact with DES.

Mrs. MALLOY. My first experience with DES was back in 1955 when I was threatened to lose the baby, the doctor gave me a little white pill to take. This was a miracle that was going to save my child, and I lost that baby in 6 months.

I became pregnant about 3 months later and again started spotting. And about the third month, the doctor gave me a little white pill called diethylstilbestrol, and I took that during the course of my pregnancy.

In December 1955, Christmas Day, I had a baby girl.

When she was 14, I was reading the morning paper, and the morning paper had an article written by Dr. Herbst, describing the dangers of DES, and stating that several daughters of mothers who were taking DES had vaginal cancer.

Of course, I became alarmed, and I called my doctor immediately and brought my two daughters—I am sorry—first I had taken DES in 1949 with another daughter. I took the two daughters to the doctor, and during the course of examination, Marilyn was found to have cancer of the vagina.

Three weeks later, she had vaginal surgery in New York City. She was 4 weeks in the hospital. The doctors told me they had gotten all of it, there was no problem, everything was taken care of, the cancer had rarely ever spread beyond the female organs.

And so, reassured, we went back to Virginia. And then, a year later, she had cancer of the lung, and she had three tumors on her trachea and her bronchial tubes. And the doctors operated and removed the lung. They removed the tumors from the trachea and the bronchial tubes.

About 4 months later, she started having severe head pains. The cancer had spread into her head. She had whole head radiation, and her hip started to hurt, and she had hip radiation, and from hip radiation she went on to the arms and legs and, eventually, she went blind and died 2½ years after we had discovered the cancer.

Our other daughter, our middle daughter Patty, who is now 24, is under constant care. She is being watched every 3 months by the doctors because she had a condition known as adenosis. I am not sure of the medical description of adenosis but it is an abnormal condition in her vaginal tract. And she does have to be watched very carefully because of the DES I took during pregnancy.

Senator KENNEDY. What kind of strain has this placed on you and your family during this period?

Mrs. MALLOY. It is a little hard to describe the strain, Senator.

I myself went into a fairly deep depression after her first surgery. I got her back on her feet and, for no reason, no apparent reason, I went into a depression. I recovered, fortunately, without medical help, and I went on myself and realized what was happening and fought it. We are under constant pressure. It is a horrible, terrible thing, to

watch the child suffer and, eventually, when she dies, you think that this is a blessing, this is far easier to accept than the actual suffering.

Senator KENNEDY. Did you know at the time you took that drug it was generally recognized as to being an important drug in terms of miscarriages?

Mrs. MALLOY. That was the impression I had.

Senator KENNEDY. And it has been in recent times that these studies that you have mentioned, that had really detected in the daughters of women who had taken the drug, cancer of the cervix or vaginal cancer.

Now, it has been approved for a very limited use, but I think we will hear testimony this morning which will indicate it is much more broadly and widely used than what it has really been permitted for, the types of emergency of incest and rape.

What would you say to the young women of the country who are using it indiscriminately?

Mrs. MALLOY. Stay away from it, as far away as you can get.

Our middle daughter, just graduated from the University of Georgia, and even at the University of Georgia, it was handed out indiscriminately. This is, I think, the danger with a drug like this.

It is supposed to be for emergency cases only. But, is it?

This concerns me. I am also concerned deeply about its use in cattle. I am going to give up eating beef before I—

Senator KENNEDY. Well, we will come to this, but I suppose one of the important messages I hear from you this morning is that to the mothers who have taken this DES and do have daughters, the importance of followup procedure. That is, I think, an extremely important message that hopefully will go out from this hearing to the thousands and tens of thousands of people, even millions of people who may have taken this particular drug, that the importance of followup is something which is extremely essential.

Mrs. Green.

Mrs. GREEN. My case, I think, was a little different.

I had a son in 1948, and 2 years later decided we would like another child. No problem with the son. My period was very regular.

One month I was a little late, you know, and when my period came it was very heavy, and he said I think we ought to give you diethylstilbestrol, I think you have had a spontaneous abortion.

We went to the hospital. I never had a D. & C. I never had any other problems. And I started to take diethylstilbestrol. I am making a point of that because I feel it was given out that easily. This must have been 1950.

My daughter was born on February 9, 1951, and she was fine until she was 15. She hemorrhaged one day. I lived in a small town in New York called Glen Cove. And the doctors told me she had a very rare form of cancer. This was in 1966.

In my hometown, no one had ever treated it, no one had ever seen it, and they recommended a doctor in New York City which is about 25 miles away. The doctor who treated my daughter and was wonderful to her was treating one other case from California.

She was fine for awhile, and then the cancer spread. She died when she was 18, in March 1969.

About 2 years later, I guess, I received a call from Dr. Herbst, I think it was, asking about Susan, and telling me there was some con-

nection between diethylstilbestrol, DES, and my daughter's vaginal cancer.

I could not believe that something with any inherent danger would be given out as indiscriminately as that drug was given out in the 1950's.

The other thing that bothers me is that many friends contacted me when this became publicly known, and said they had taken it, what do I suggest they do, and I suggested the alternative you mentioned, they take their daughters and have them checked immediately.

And many of them were told by gynecologists, oh, do not worry. Your chances of your daughter contacting cancer—well, you can get hit by an automobile faster.

You know, that was another thing that bothered me, the attitude of some of the doctors in the field.

You know, if you take statistics, it is very meaningless unless that statistic is one of your own children.

I am acting dean of a school of education with many, many young women. We have about 1,200 majors in education, most of which are young women. I know that they do not use the pill, the morning after pill in just extreme cases. I know that it is used indiscriminately.

Senator KENNEDY. That is today?

Mrs. GREEN. Yes.

Senator KENNEDY. In 1975.

Would you be distressed or disturbed, given your own kind of understanding or awareness of personal experience, to find out that it is being widely used in many different situations in women's colleges and broadly distributed in many different parts of the country?

We are going to hear direct testimony to that effect this morning.

Mrs. GREEN. No; I am not surprised. I think it seems to me that before you would try any pill, there would be certainly a great deal of research with control groups, or longitudinal studies, or something, before you would give it out to the public.

I think that the drug companies have a responsibility when something comes out, realizing it may not be used for exactly the reason they are stating on the bottle of the pill and, in this case, where the pill has been proved to cause cancer, just do not feel that any condition is worth taking that kind of risk that you would prescribe this kind of pill.

I know it is being used, as I said before.

Senator KENNEDY. I think, in both your cases, that Dr. Herbst deserves great credit. He has been the real leader in research in this area, and I think to a great extent the fact that this particular problem has been flagged as significant as it has is to his credit.

Ms. Luder.

Ms. LUDER. First of all, I would like to say that my story is not going to be about any of my children that took the drug simply because I will never be able to have any children. It is the fact that my mother took the drug.

I first found out last summer. I went to a gynecologist for what I supposed was a routine exam. At that time he told me that he had found what he described as an irritation, and he made another appointment, and asked me to come back. So I did.

At that time I did not think too much about it. I was not really worried. I went back the second time, and they did a biopsy, and this time he told me that he thought I had adenosis, which as Mrs. Malloy said was some kind of irritation in the vagina.

He also mentioned, for the first time, on this visit that he would like me to go home and ask my mother if she had ever taken a drug called diethylstilbestrol.

I said all right. I went home, and I asked my mother, and her first reaction was that she was very positive that she had never taken any such drug. She claimed that during her pregnancy she had never taken anything more than a common vitamin.

So naturally she was alarmed thinking that perhaps she had taken the drug, so she called right away, and the doctors told her, no, she had not.

So I called my gynecologist on the phone and said my mother had found out she had not taken the drug. He did not say too much about it.

He said, all right. He said I would still like to see you again.

In the meantime the doctor called back and said they had found the records, and she had taken the drug after all.

So I would like to say here that there might be a chance that perhaps records are lost over a period of time, and certain women who do not think they have taken the drug should have their daughters go in for a test anyway, because the pap test is very important.

I went back, and he sent me to a hospital clinic to be examined by another doctor, who was a specialist in the field at this time, and he took another biopsy, and called me on the phone 2 days later, and confirmed the fact that as he put it, there was a tumor.

He did not like to use the word cancer, I guess too many people cannot handle that.

My husband was overseas at the time. The Red Cross brought him home, and together, 2 days later, we went down to the medical center and at that time my doctor told me I definitely did have cancer.

I was operated on last August. The repercussions of this operation are still strong in my life. It has only been 5 or 6 months since the operation. I think the most tragic thing in my life, assuming that I will live a long, full life, there is always that chance that the cancer will appear again, that it has rendered me sterile.

Family life is very important to me. It is the mental thing I am still trying to adjust to as a woman.

I have talked to many other women since then who have had hysterectomies, and I think it is common knowledge that you go through a transition period where you feel like you are not a woman, and this type of thing.

And added to this is the constant fear hanging over your head—the suspicion that the cancer will crop up again.

Not only has it affected me, naturally it has affected my family, but specifically my mother. Sometimes I can just cry when I see her. She feels very guilty.

Senator KENNEDY. There could be no reason that I could possibly imagine why your mother should feel in any way a sense of anything but a tremendous admiration for you, and for your bravery.

Ms. LUDER. That is true. She was a woman who was in danger of losing her child. Naturally you put your trust in your doctor, that is

all you can do, and at the time she did what he told her. He was merely saving a life.

It is true, in essence, that she should not feel guilty, but I am sure anyone can understand that she would.

Senator KENNEDY. Of course, there was not the information then that would ever suggest to the doctor that recommended that she take this drug that it was in any way going to be a danger to you or to the children.

That information has only been developed in recent times.

Ms. LUDER. Right.

Senator KENNEDY. But we have it now. That is the very major difference. We have that information now, and we are able to avoid the kinds of problems that have affected each of you. I think we can do that now. I think we must, and we have to, and we will.

I think your doctor deserves a great deal of credit, Ms. Luder, for following up and pursuing that.

I think in considering a variety of different issues, he ought to be recognized.

I think it shows the importance of continuing followup. This is something for those who have been affected by the drug. This is extremely important.

I think it is something that we cannot stress or emphasize enough.

I want to thank you.

Senator Schweiker?

Senator SCHWEIKER. Thank you, Mr. Chairman.

Mrs. Malloy, I am sure it was not an easy decision for you to make, to come here today and to testify. I am sure you probably decided to help other people who might be confronted with the situation you are confronted with.

What would you expect your Government to do about it? You have obviously come here hoping that we are going to do something, or certainly somebody will do something. I gather that you would feel that the Government does have a responsibility, and that certainly if no one takes it, probably Congress should.

What do you think we should be doing, and is that not why you are here?

Mrs. MALLOY. Yes, Senator. This is why I am here.

I feel rather strongly about DES, naturally. I feel someone has got to safeguard us some way or another from this kind of thing happening. It is inexcusable to me that a drug can be passed out so readily and so easily, and then for us to find out later on it really had no effect anyway. It did not really prevent miscarriages.

This is one of the very sad parts of it.

We were given the idea that this was going to help our miscarriages. I think something has to be done, as Mrs. Green said, there has to be more research done before these things are handed out indiscriminately.

I feel very strongly against DES in any way, shape, or form. I am sure all three of us do.

Senator SCHWEIKER. I certainly understand that.

Ms. Luder, what do you think your Government's responsibility is here? You certainly ought to be telling us, I think, in view of what has happened.

Ms. LUDER. I definitely think it should be taken off the market. I think any redeeming value it might have is outweighed by the tragedy it causes.

I think also not only should they try and remove it from the market, from using it in cattle, also, aside from the fact they are distributing it to humans, they should perhaps try and create some kind of campaign, mobile clinics, that can get into remote areas, and check people that might already have it, and keep a close watch on those that might yet contract the cancer.

That I would think would have to be Government funded in that type of situation.

Senator SCHWEIKER. Mrs. Green, would you care to add anything to that?

Mrs. GREEN. No; just that the gynecologist that took care of Susan said he felt we do not usually give young girls internal examinations, but he felt that in any case where there was any idea that DES had been taken, the young girl should be given internal examination so they can watch very carefully, because the earlier they can detect it, of course, the better the treatment.

That would be a followup to what Ms. Luder said, if we could get the mothers to either think back and check records, and have their daughters examined, even very young girls, it might save some lives.

Senator SCHWEIKER. Thank you, very much.

Senator KENNEDY. Again we want to thank you. We are very hopeful that this message will go out to all Americans. I think it really comes down to the risk-benefit ratio, and I suppose we will hear a good deal about that this morning. I think we have to measure certainly what it really means in terms of saving lives and the risking of the kinds of tragedies which your families have been exposed to. I think what you have certainly shown for us is what statistics really mean, and they mean human beings, and human tragedy and suffering.

I appreciate very much the fact that you are here and sharing with us your experience. I am sure I speak for all members of the committee in saying we are going to do everything in our power to see that this does not happen to any other Americans, or to any other people in this world, to the extent we can.

Thank you very much.

I hope you can stay for the rest of the hearing.

We will next hear from a panel of witnesses, all of whom have a great deal of expertise regarding the problems associated with DES.

Peter Greenwald, M.D., has been director of the Cancer Control Bureau of the New York State Department of Health since 1968. He is a clinical assistant professor of medicine at the Albany Medical School, and an assisting attending physician at the Albany Medical Center Hospital.

Robert H. Pantell, M.D., is a consulting pediatrician and clinical scholar at the Stanford University School of Medicine. Until June of 1974, Dr. Pantell was involved in an effort to persuade the medical boards in the State of Idaho to educate the physicians of that State on the risks of DES.

Ms. Belita H. Cowan is a college instructor of health care in Ann Arbor, Mich. Very recently, she conducted a survey on the use of DES in Ann Arbor and Detroit, and her findings will be of great interest and assistance to the subcommittee.

We will start off with Dr. Greenwald.

We want to welcome you back, Doctor. We heard you here on this committee, I think, on the same subject 2 years ago.

Since that time we have passed legislation in the Senate, but we were unable to get corresponding action in the House. We saw regulations passed by the FDA, which were then frustrated.

I know the information that has been developed even more recently substantiates your early observations 2 years ago, making the situation even more dangerous.

We want to welcome you. You have been a great help to our committee in the past.

STATEMENTS OF PETER GREENWALD, M.D., DIRECTOR, CANCER CONTROL BUREAU OF NEW YORK STATE DEPARTMENT OF HEALTH, CLINICAL ASSISTANT PROFESSOR OF MEDICINE AT THE ALBANY MEDICAL SCHOOL, AND ASSISTANT ATTENDING PHYSICIAN AT THE ALBANY MEDICAL CENTER HOSPITAL, ACCOMPANIED BY ROBERT H. PANTELL, M.D., CONSULTING PEDIATRICIAN AND CLINICAL SCHOLAR AT THE STANFORD UNIVERSITY SCHOOL OF MEDICINE, AND MS. BELITA H. COWAN, COLLEGE INSTRUCTOR OF HEALTH CARE IN ANN ARBOR, MICH., A PANEL

Dr. GREENWALD. Thank you.

I am Dr. Peter Greenwald, licensed physician in New York State, and director of the Cancer Control Bureau, New York State Department of Health.

I am here at your invitation to present the results of our own studies on diethylstilbestrol (DES) and human cancer, and my opinion about the use of DES as a morning-after pill.

In general, I feel that in this country we should be able to expect proof of safety before a new drug is released, or before an old drug is used in a new way, especially when there is almost no risk to not using the drug. The safety of DES as a morning-after pill has not been proven.

In fact, evidence to date suggests a probable severe cancer risk among at least some daughters born of pregnancies when DES contraceptive treatment failures occur.

The New York State Department of Health Cancer Control Bureau has conducted three studies bearing on the human cancer risk of DES. The first confirms the cause-and-effect relationship and provides some information on dosage and latency, the second assesses the possibility of maternal DES ingestion contributing to cancers other than vaginal or cervical in men or women, and the third evaluates current usage of DES as a morning-after pill in New York State. Results in brief are as follows:

I. VAGINAL CANCER ASSOCIATION

In 1971, five teenage girls reported to the New York State Cancer Registry as having vaginal cancer were investigated. DES therapy to prevent miscarriage had been given during pregnancy to the mothers of four patients, and the fifth took a similar synthetic estrogen, di-

enestrol. This was the first confirmation of the work by Dr. Herbst and his colleagues in Boston of the now widely accepted association between maternal use of DES and vaginal cancer.

At the present time, 23 teenagers and young adults have been reported to the New York State Cancer Registry, with this type of vaginal or cervical cancer. Eight have died of advanced disease. All mothers, where our investigations are complete, 20 of 23, are known to have taken DES to prevent spontaneous abortion.

Senator KENNEDY. Do you know what that figure is nationally?

Dr. GREENWALD. The last comprehensive registry report was 170 patients. These are patients that have been fully investigated. The number is actually over 200 cases occurring.

Senator KENNEDY. We have the latest figure from Dr. Herbst as being 220.

Dr. GREENWALD. Yes.

Senator KENNEDY. Do you think that this is really the tip of the iceberg, so to speak?

Dr. GREENWALD. Yes; I think I will mention it. I feel that the incidence is still going up. We know from our data, and there is a figure here, that the incidence of vaginal cancer diethylstilbestrol induced is increasing.

As long as it is increasing, we have no way of estimating the ultimate total risk, and there have been more and more patients die with these conditions.

Senator KENNEDY. Well, now, how do you explain that increase in total numbers—you are going to develop that during the course of your testimony?

Dr. GREENWALD. Yes.

Senator KENNEDY. OK.

Dr. GREENWALD. The cause and effect relationship between the use of DES by mothers and vaginal cancer in their daughters is suggested in our studies by the facts that all mothers took DES during the first trimester; all patients were born during the peak years of clinical use of DES to prevent miscarriages, by the similar age at diagnosis among patients; the time relationships; and the rather uniform microscopic pattern of these tumors.

The consistency of all of these observations supports the possibility of a common cause. These findings also are in keeping with the independent investigations of others, and are in accord with our biologic knowledge of DES, especially with the fact that DES can be shown to produce cancer in a variety of animals.

It should be noted that "cause-and-effect relationship" means to me that DES is a necessary factor and that the cancer will not develop without it. There are undoubtedly additional factors affecting susceptibility and resistance.

Approximate cumulative dosages of synthetic estrogens taken during pregnancy for 11 mothers of vaginal or cervical cancer patients and 21 mothers of patients whose children did not develop cancer are shown on table 1. Among mothers of patients, the mean dosage was 4,868 milligrams and the range 135 to 15,750 for those whose dosage was known.

Senator KENNEDY. What is the dose for the morning after?

Dr. GREENWALD. It would be 250 milligrams, usual dose; 50 milligrams a day for 5 days.

Senator KENNEDY. So that is greater than actually was being used in the cases——

Dr. GREENWALD. Yes. One patient here had an exposure lower than recommended dose for DES contraception, in uteral exposure, and she developed vaginal cancer.

Another point related to that—we found no significant difference in the main dosage for the group whose daughters got vaginal cancer and the other group.

Since very few women in either group received small dosages, we cannot be sure of a dose-response ingredient from this data. However, DES was used over a wide dose range and in the absence of differences it seems very possible that small doses as well as large may induce cancer.

The New York State patients were 8 to 23 years old at time of diagnosis. With prenatal carcinogenic exposures, age at diagnosis is often used to estimate the latent period for cancer development, although with DES the latent period may be influenced by menarchy.

Studies of various types of other human carcinogens indicate latent periods of less than 1 year to more than 50 years. While there clearly are differences between DES and other carcinogens in age at exposure, type of carcinogen and mechanism of exposure, this comparison suggests that we may well expect that some patients with longer latency periods will be diagnosed in future years as the interval since the peak years of DES exposure grows longer.

Next is the increase I mentioned before in the figures.

Senator KENNEDY. As I understand what you are suggesting, this amount of dosage, as you mentioned in the paper, it seems possible to you that it does induce cancer, is that right?

Dr. GREENWALD. Yes. In fact it seems likely. The fact that there is one young girl who developed cancer with a dose lower than the dose used, and the fact that we do not find a relationship of dose to risk of cancer, both mean to me that it is fairly likely that small dosages could produce cancer.

Senator KENNEDY. As you made the point earlier, the amount that they are actually taking in terms of the morning-after pill is higher than the amount which were detected in terms of those that actually contracted of——

Dr. GREENWALD. Well, for one of them. Most of them had a larger dose than contraceptive. But one patient did have a smaller dose.

On the basis of their study, the Mayo Clinic group estimated that the incidence of vaginal cancer or cervical cancer among DES exposed persons could be as high as 4 per 1,000. The 4 per 1,000 is an upper limit estimate for study subjects followed for up to 30 years, whose median age at last followup was 22 years. This estimate could be affected by studying more people.

I do not think we should pass off the incidence rates of this magnitude as trivial. Four per one thousand is equivalent to the annual death rate from heart disease in New York State, is 44 times higher than the annual incidence rate for leukemia, and considerably higher than the annual incidences of breast cancer and colon cancer.

In other words, this means that the DES risk could be as high as a risk for a person developing leukemia over a period of 44 years. That is another way of doing it.

If this is unimportant, then I think a number of researchers should seek other occupations.

Senator KENNEDY. Now, I think it is important for the public to understand what you really mean by the incidences, and also as a researcher, and what the significance of the incidences are.

Dr. GREENWALD. Right.

Senator KENNEDY. You are not talking about the whole kind of population—you are talking about the control group that is exposed?

Dr. GREENWALD. That is right.

Senator KENNEDY. What you are talking about is the group that is exposed, the possibilities of contracting this kind of cancer.

Dr. GREENWALD. That is correct.

Senator KENNEDY. And in that relationship, the types of percentage that you are talking about, are really astonishing, and outstanding, and have an extraordinary magnitude, as I understand it.

Dr. GREENWALD. That is right. For the exposed population we should not be willing to accept or tolerate a risk of even 4 per 1,000.

If you take the annual cancer incidence in the United States, it is really 2 per 1,000, over a population, of a couple of hundred million. That means 400,000 deaths. And the fact that there will be a large number likely exposed, plus this risk, means there will be quite a number of people that could develop cancer. I think an unacceptable number.

Now, I will go into other types of cancer. The DES association with vaginal cancer also has been demonstrated for a similar type of cancer of the cervix. We have studied extensively the prenatal DES experience of mothers of boys and girls with many other types of cancer, and thus far have not found an association of these other tumors with maternal drug use.

Again I should like to point out the great value of the New York State Cancer Registry, the largest such reporting system in the country, in this study. This episode serves as a good example of the value of such registries.

In 1973 and again in 1974 we surveyed 45 large hospitals, college health services, and planned parenthood organizations in New York State to see how DES was being used as a morning-after pill.

A 1975 resurvey is in progress. Use is fairly widespread, especially at the colleges and universities. Dosages generally are 25 to 50 milligrams of DES per day for 5 days and nausea is reported as a side effect of the drug.

Senator KENNEDY. Does the magnitude of that survey surprise you, or concern you?

Dr. GREENWALD. Yes; what we are finding currently is roughly equivalent to 1974. We did the survey again the past several days. Two-thirds of the responding institutions used DES as a morning-after contraceptive. It is more difficult now to give you figures about individuals who get it, because the answers are more guarded.

Senator KENNEDY. What are you talking about? Are they using it for rape, or incest, or are they using it more broadly?

Dr. GREENWALD. From the number, it is used much more broadly, the numbers are in the hundreds for different universities.

And in general there are several concerns. One, which we will get to, is if you say for emergency, most young people in the predicament of

having a potential unwanted pregnancy, can consider it an emergency, and it is used in that situation rather widely.

Senator KENNEDY. It is an emergency to them?

Dr. GREENWALD. Sure.

Senator KENNEDY. It is not the kind of emergency that the Food and Drug Administration puts in terms of rape or incest?

Dr. GREENWALD. Right. The interpretation of the Food and Drug Administration directive is much more broad, I think, than it was intended.

Senator KENNEDY. As I gather, the significance of this testimony, this part of it, is that in spite of the fact of the warnings of the FDA 2 years ago, that it only be used in emergencies, you are finding what I would consider a pretty broad range of use?

Dr. GREENWALD. That is right.

Senator KENNEDY. Both by numbers of universities, and within the universities, even with the kind of warnings that were put out 2 years ago?

Dr. GREENWALD. That is correct. In addition, some people have shifted to other estrogens, a drug called premarin, mainly because it is not as controversial, but we do not have any idea that it does not have the same risk. It just is not studied.

The absence of followup is of great concern. I must say in 1975 some of the universities have a plan to followup, which is better than they did last year, but it is a passive plan. They essentially give the students a clinic appointment for a month later. There is no assurance of followup, and often it does not occur.

Senator KENNEDY. How good is that plan?

Dr. GREENWALD. Well what happens is that a student comes in, and she is given a clinic appointment, and if she does not come back, that is it, nothing happens. Little effort is made to ascertain the effectiveness of treatment, or to recontact patients who might have been pregnant prior to, or in spite of the treatment.

Treatment failures might result from an already established pregnancy, from excessive lapse of time between unprotected intercourse and DES ingestion, from inadequate dosage, from vomiting of pills, from a second sexual exposure, or from the drug failure.

The many unanswered questions raise doubt about the wisdom of approving DES as a morning-after pill. A cancer risk is present for daughters born when treatment failed, but the extent of the risk is unknown. A high risk is present for an apparently benign but perhaps precancerous lesion (vaginal adenosis).

Senator KENNEDY. What is that?

Dr. GREENWALD. Abnormal gland tissue in the vagina.

Senator KENNEDY. As I understand it, this is a new side effect which has been discovered in the relative recent times?

Dr. GREENWALD. That is correct.

Senator KENNEDY. Beyond the other dangers of vaginal cancer and cancer of the cervix, this is a new development.

Can you tell us a little bit about it?

Dr. GREENWALD. It is abnormal gland tissue. Several concerns about it. First reports indicated that perhaps 90 percent of exposed young ladies have vaginal adenosis.

We are talking now about a very high frequency condition.

Senator KENNEDY. Ninety percent?

Dr. GREENWALD. Ninety percent of exposed women. A number of places are finding——

Senator SCHWEIKER. Regardless of dosage size?

Dr. GREENWALD. Regardless of dosage. These are patients who, because of concern by their mothers about them about exposure, go in for gynecological exam.

Senator KENNEDY. Is this 90 percent of the daughters that——

Dr. GREENWALD. Ninety percent of exposed daughters.

Senator KENNEDY. Exposed daughters.

Dr. GREENWALD. Another concern is that a number of cancers have been found in association with the adenosis. So this raises the possibility that the cancer developed out of the area of adenosis and not independent of it.

In other words, adenosis may be a precursor to the cancer. We are not sure of that. We do know that the cancer often occurs right in the same spot that the adenosis is occurring.

Senator KENNEDY. In sort of laymen's language, this is certainly a side effect, where they have not detected cancer in those particular areas, nonetheless it is a side effect, which if cancer appears, usually appears within this kind of climate, is that right?

Dr. GREENWALD. Yes; that is right. It seems that way.

Senator KENNEDY. And so from a clinical point of view, it is extremely serious, as I gather?

Dr. GREENWALD. Well, it indicates a possible higher risk, and indicates that certainly at the very least close followup is necessary.

I think the ladies that were here before me were correct in saying that it is important to have frequent exams of young women known to be exposed.

Senator KENNEDY. Certainly not the kind you have outlined earlier that takes place in many university centers; that is not adequate?

Dr. GREENWALD. I think it is not adequate.

Senator SCHWEIKER. Is there any link at all? I am not quite clear regarding the benign tumor. Are you saying there is, or there is not, or is it a question mark?

Dr. GREENWALD. A question mark. There is no definitive answer about whether there is a link between adenosis and cancer, vaginal cancer.

The only information we have is that the cancers frequently occur right in the area of adenosis. That raises the question. We are not sure.

Senator SCHWEIKER. Not the same tumor——

Dr. GREENWALD. Whether some of the adenosis cells have changed into cancerous cells or not is the question. We are not sure.

Senator KENNEDY. Carry it one step forward, do normal people have this?

Dr. GREENWALD. No; they do not. They have it, but many, many fewer have it. It sometimes occurs, vaginal adenosis, sometimes occurs——

Senator SCHWEIKER. What is the incidence of that compared to the incidence of people who have been exposed to DES?

Dr. GREENWALD. That is a variable. It might be up to 20 or 30 percent, but there is disagreement, I believe, among gynecologists that have done the exams. Those women without DES do not get cancer,

so it could be there is a different implication of the adenosinosis in the DES exposed.

Senator KENNEDY. I think that is important. It appears to be three or four times higher in incidence, and it is also more dangerous.

Dr. GREENWALD. Yes.

Senator KENNEDY. This is relatively new, a relatively new development, as I understand it?

Dr. GREENWALD. Yes.

Senator KENNEDY. At least discovered.

Dr. GREENWALD. Yes; a new observation for the past couple of years.

Senator SCHWEIKER. One other question.

You mentioned before the incidence was 4 in 1,000, as I recall.

Dr. GREENWALD. This is Mayo Clinic estimate of the upper level of patients where cancer has already occurred among those daughters with exposure; that is right.

Senator SCHWEIKER. Of people who do not take DES, what would be the incidence of cancer?

Dr. GREENWALD. Zero for this type of cancer. It was almost unheard of before the DES exposure occurred. We have studied 20 to 23 patients in New York State, and these are all the patients diagnosed since 1950 in a State of 18 million population, and only 23 occurred.

We completed our study on 20, and every single one of them, their mothers had taken DES.

Since the DES is approved as a morning-after pill, what will be done to assure ascertainment and followup of treatment failures?

It is recommended that a patient see a doctor in this situation, but what is the recommendation for the doctor? Is DES as a morning-after pill to be used as a controlled drug? Perhaps it should.

Several situations recently have come to light where we inadvertently may have produced cancer in ourselves. Let us not add another such situation to the list.

Finally, it should be noted that at times in the treatment of cancer DES may be a useful drug and its benefits outweigh its risks.

I hope that this DES controversy helps us to recognize further the importance of prevention and early detection in cancer, since both have a role here, and helps to direct our attention to the importance of prevention as a vital part of the health care in the United States.

Thank you.

Senator KENNEDY. Thank you very much.

Excellent, helpful testimony, and very important.

Are you aware of the Controlled Substances Act that goes into regulation, I understand, of morphine and heroin?

Dr. GREENWALD. I am aware of it in general, yes.

Senator KENNEDY. Are you suggesting that this ought to be a substance which is added to those?

Dr. GREENWALD. I think so.

There is the question that this is not really addicting, and they may have to change the rules. But I think that this should be a controlled substance if it is used at all.

Senator KENNEDY. Would you use it at all?

Dr. GREENWALD. I might conceive of an instance. In general, I would say no.

If I was absolutely certain that the woman was of a mind not to have completed pregnancy, I suppose there are conditions. I do not think so. I think even in that instance there are alternatives that do not have a carcinogenic risk.

Senator SCHWEIKER. Doctor, you say in your second to last paragraph, "Finally, it should be noted that at times in the treatment of cancer DES may be a useful drug and its benefits outweigh its risks."

Dr. GREENWALD. DES is sometimes used in the treatment of cancer and breast cancer, especially when the cancer has spread, because it stops pain and makes the patient much more comfortable.

It is doubtful, but it may limit the growth of the tumor. There is definite use for DES, cheap and effective, for some cancer patients.

Senator SCHWEIKER. You are not relating it to the treatment for preventing miscarriages?

Dr. GRUENWALD. No; I think that has been established as not effective.

Senator SCHWEIKER. That is all I have.

Senator KENNEDY. Dr. Pantell.

Dr. PANTELL. I am Robert Pantell. I am a pediatrician.

Let me state at the outset that I feel all drugs are potentially dangerous. In this respect, diethylstilbestrol is no different than any other drug.

However, I feel there are several characteristics peculiar to diethylstilbestrol which make it unique in the annals of hazardous drugs.

A number of drugs have been used in pregnancy with tragic consequences to the newborn. Thalidomide is a notable example of this.

In these instances, the family trauma was immediate, and appropriate planning was possible.

Furthermore, the drugs taken in the previous months could be readily identified and their risks investigated rapidly. Diethylstilbestrol is far more sinister. It strikes more than a decade later. Many persons will never know if they are at risk and if they should be seeking special early detection services. Other families will live in a perpetual state of anxiety, guilt, and fear.

The precise incidence of adenocarcinoma attributable to diethylstilbestrol is still not known, and the possibility of squamous cell carcinoma appearing in old women may extend the anxiety period to several decades. These are problems far less dramatic than the tragic child victimized by cancer but, nonetheless, far more common and extremely real to those many exposed individuals and their families.

In my experience as a practicing pediatrician in Idaho, there were a number of alarming events which have raised my concern over the continued widespread use of diethylstilbestrol.

In August 1972, I began work as a pediatrician for a clinic system in southwest Idaho. The clinics were established in 1971 to provide health care to migrant farmworkers and rural poor and isolated residents in southwestern Idaho.

We were the only medical facility available in Owyhee County and in the small towns of Homedale and Parma.

Residents of these communities often transferred their care from physicians in distant communities.

We routinely asked all women coming to us regularly whether they received drugs during pregnancy. It soon became apparent that the

recollection of drugs taken during pregnancy was poor. There are many reasons for this.

Uncomplicated prenatal care usually involves several oral preparations taken by expectant mothers. Patient knowledge of the names and purposes of these medications varies widely. Many individuals have been so accustomed to taking numerous pills, they do not even question the purpose and content of medications.

Many persons we cared for did not speak English. They had particularly poor comprehension of events and medications that had been supervised by non-Spanish speaking physicians. Finally, patient recall of events occurring many years ago is understandably extremely difficult.

It is, therefore, of the utmost importance that accurate written records of former care be obtained whenever offering medical care to patients.

In the winter of 1973, Mrs. A. G. came to our clinic. In 1971, she had received a medication from an obstetrician to help her maintain her pregnancy. Because of our concern that Mrs. A. G. had received diethylstilbestrol, a drug posing potential risks to her 3-year-old daughter, we requested her records be transferred from her obstetrician.

After several phone and mail requests, a note was received from the obstetrician stating that her pregnancy was normal. No mention of drugs was made.

Upon further questioning, Mrs. G. recalled the pharmacy where the drug was dispensed. Mr. George Murray, pharmacist in Homedale, Idaho, identified the drug as des-Plex, a preparation manufactured by Amfre-Grant, containing 25 milligrams diethylstilbestrol, as well as eight different items.

I might add, at this point, that combining potent drugs with vitamins needlessly obscures the purpose for which the preparation was given.

At the same time, another patient, Mrs. M. S., also came to our office for care.

Mrs. S. was currently being seen for prenatal care by the same obstetrician who formerly cared for Mrs. G. Mrs. S. was, at that time, taking des-Plex and had been on this medication continuously for the first 6 months of her pregnancy. Mrs. S. was unaware of the risks of diethylstilbestrol in pregnancy. She was taking this drug 2 years after the November 1971 FDA bulletin stated that diethylstilbestrol was contraindicated in pregnancy. Mrs. S. subsequently delivered a female child.

Because of our inability to establish an effective line of communication with the obstetrician who was prescribing diethylstilbestrol, a letter was sent, in conjunction with Dr. Thomas O. McMeekin, to Mr. C. E. Barnett of the Idaho State Board of Pharmacy, and to Mr. Armand Byrd, Secretary of the Idaho State Board of Medicine, on March 25, 1974.

We described our experience and suggested: (1) An independent party negotiate with the obstetrician to identify those patients at risk; (2) an effort be made by the board of pharmacy and/or medicine to educate this physician as to the dangers of diethylstilbestrol and current recommendations for its usage.

The reply from the State board of pharmacy was that this was not in their jurisdiction.

The secretary of the State board of medicine, at the time I left Idaho in the last week of June 1974, communicated to me that action had not yet been taken on the matter.

Neither Dr. McMeekin or I have received any further communication concerning this issue.

The physician under consideration, besides maintaining a private practice, was then, and to my knowledge still is, an obstetrical consultant for the State.

My concerns as a pediatrician are severalfold.

1. When a commonly used drug, such as diethylstilbestrol, is discovered to have new potential problems, there exists no formal effective mechanism to alert physicians to those problems short of withdrawing the drug.

The aforementioned physician is not unique. Notice of diethylstilbestrol toxicity appeared in the medical literature, the FDA bulletin, the package insert, and undoubtedly was discussed in medical meetings.

It is my experience that physicians cannot keep up with the voluminous medical literature. FDA bulletins are not universally read or received. Package inserts are seldom read, and are certainly less likely to be read for drugs which physicians have been using for many years without obvious side effects. Finally, medical meetings vary tremendously.

In a fall 1974 meeting of a county medical society in Idaho, a colleague of mine reported that the guest speaker claimed there had been only 14 cases of vaginal carcinoma reported and that the risk to female offspring is between 1/50,000-1/80,000. These statements are markedly at odds with figures published at that time.

2. It extremely difficult identifying those patients at risk. Because of this, it may become necessary to begin screening for adenocarcinoma by performing pelvic examinations in girls at far earlier than usual ages.

Indeed, one recent publication has advocated that daughters of DES pregnancies should be examined for abnormal cellular changes in the vagina every 6 months throughout their lives. The technical and traumatic implications of this recommendation require no further comment.

3. In a mobile society, many families, especially farmworkers, may be lost to medical followup before proper explanations and preventative approaches can be offered.

4. Despite our best efforts, many children and young women will inevitably be stricken with vaginal cancer and its consequences.

5. The most common and one of the most disturbing problems is the disruption of families in which there is a risk of a child developing adenocarcinoma of the vagina. Other carcinomas may eventually be found to occur in older women, prolonging the period of risk.

The hanging sword will be perched above the head of some children and their families for years. Tragically, we have no idea how many years.

In summary, I feel the current procedures for the regulation of diethylstilbestrol are ineffective. I strongly urge diethylstilbestrol be

gory if there is no drug felt to have less risks in identical clinical usage.

Senator KENNEDY. Thank you very much.

I think there are a number of important lessons learned from this experience. Certainly one of them is the difficulty in many rural communities, to be able to keep abreast of either the direct information that is being made available by the Food and Drug Administration. I think you commented on this. There is also the problem in following up situations. You mentioned migrant workers, and I was also thinking in the kinds of rural moving population, as well as difficulty in maintaining records and followup and misinformation that you become aware of.

You mentioned that a speaker claimed that the risk was 1 out of 80,000. We hear now that it is 1 out of 4,000. There is misinformation, difficulty in followup, failure to really get information out in the field. This is at least some insight as to what the situation is with regard to this particular problem in rural communities.

I think it points up the importance of responsible action in the distribution of this drug.

Quite clearly, when a drug is used for some legitimate purposes, and then the FDA puts out a bulletin indicating it should not be used for other purposes, doctors within a particular community are at least generally familiar with the use for one purpose and are quite reluctant to withhold it for the purposes outlined in that statement by the Food and Drug Administration.

I think, of course, that we constantly hear that from the spokesmen from organized medicine, that they feel they ought to be able to do it no matter what the Food and Drug Administration says. They feel, in spite of the overwhelming burden of medical evidence, scientific evidence, that they ought to be completely free to use any drug that is approved for any purposes they want.

We have heard that time and again by those who sat in the seat that you are sitting in. That raises, I think enormous problems in terms of providing adequate protection.

I do not know how you could expect drug companies to be able to reach out in that community and be able to protect the individuals, and how you would expect the Food and Drug Administration to be able to take some doctor—well, we have heard some examples of extraordinary conscientiousness of doctors who have performed a noble kind of service. We have heard of a lot of other areas where they have been extremely reluctant to equip themselves with the knowledge to really adequately protect their patients.

Dr. PANTELL. The sad thing seems to be unwillingness of anybody to assume the responsibility in protecting the consumer in these instances.

Senator KENNEDY. I think that is what your testimony reminds us.

You have outlined, what I think, makes eminently good sense—the suggestion that this be put on the controlled substance list. We have to do something in terms of a legislative effort on that to see if it could be.

Ms. Cowan, do you want to start?

Ms. COWAN. I am Belita Cowan, a college instructor who teaches health care to students enrolled in health occupation training pro-

grams. I have long been following women's health problems as they relate to drug use.

My purpose in being here today is to inform the subcommittee of several issues which may not have been brought to the subcommittee's attention.

The first concerns the prescribing habits of doctors who dispense DES—diethylstilbestrol.

The second relates to medical protocol in hospital emergency rooms where rape victims are treated.

The third issue concerns the possible legal liability on the part of emergency room doctors who prescribe DES.

Last summer, I conducted a survey of over 200 women, ages 18 to 31, who had taken DES as a "morning-after" pill in Ann Arbor, Mich., between 1968 and August of 1974. In addition, I interviewed many nurses, gynecologists, and emergency room doctors at two Ann Arbor hospitals, the University of Michigan Student Health Service, and a number of Detroit hospitals. The purpose of the study was to determine how and when DES was prescribed to women, and the precautions taken, if any, to insure the careful monitoring and followup of all patients.

What is occurring in Ann Arbor, Mich., is, I believe, indicative of what is happening in other cities, particularly those with university medical centers.

For purposes of statistical analysis, I excluded from the numerical tabulations all rape victims, persons already on contraceptives, and those who were not at midcycle at the time of the unprotected sexual encounter. That left 65 women.

The results of the study were published last September, and are included in table I which is attached to your copy of this report.

The study showed that far from being an emergency medication, DES is being used repeatedly as a contraceptive.

Twenty-nine percent of my sample stated that they had taken the "morning-after" pill at least twice within a year's time. The study showed that DES is being prescribed with carelessness and casualness. Forty-five percent were not given pelvic or breast exam. Fifty-six percent stated that the doctor did not take a personal and family medical history. Eight women said that they got the "morning-after" pill not for themselves but for a friend or roommate.

Senator KENNEDY. You mean actual patients did not even go to the doctor?

Ms. COWAN. That is correct.

Senator KENNEDY. This is after the Food and Drug Administration order that this type of drug could only be used in an emergency, and still you found that, at least in some instances, there were individuals who were able to obtain this DES through a friend or roommate?

Ms. COWAN. Yes.

A third of my sample received the morning-after pill in 1973 and 1974.

Senator KENNEDY. That is after—

Ms. COWAN. Yes.

Only 26 percent were followed up to see if they were pregnant.

The study also revealed that DES is being given to women for whom estrogens are contraindicated. Women who cannot take birth control

pills are being given the morning-after pill. They are not aware nor are they informed that the morning-after pill is estrogen.

Fifty-seven percent of the sample were unaware that the morning-after pill did not have FDA approval and that it had not been proven safe and effective.

Further, the study revealed that many women are not being told of the possible cancerous effects to the fetus if the woman is pregnant.

I could not find a single case where a pregnancy test was given prior to and after the DES regimen. Although, I must say, that there is no pregnancy test which can accurately detect a 2- or 3-week pregnancy.

In cases where patients are warned of the association between maternal stilbestrol ingestion and possible adenocarcinoma in the female offspring, patients are not usually counseled to seriously consider terminating the pregnancy should the morning-after pill not work.

Six percent of those in the survey stated that they themselves were DES daughters; that is, their mothers took stilbestrol when they were pregnant in the early 1950's.

Of all the doctors I interviewed, only one expressed hesitation about giving the morning after pill to DES daughters. Dr. Ann Pfreder of the University of Michigan Health Service stated that "We don't know the effects of the morning after pill on DES daughters, so I don't want to give it to them."

The most interesting finding of the study is that 24 percent of the women stated that they did not take all 10 pills in the series. As one woman put it, "I got so sick from the first pill that I never took the rest. I couldn't stand to be that ill." And, not surprisingly, 65 percent stated that if they had been fully informed about DES, they would not have taken it in the first place.

Since FDA has, unfortunately, gone ahead and approved DES for use in emergency situations such as rape, I should like to explain why DES ought not be given to rape victims by hospital emergency room personnel. Evidently, FDA has little understanding of emergency room procedures and the treatment of rape victims.

Informal studies done by Ann Arbor and Detroit rape crisis counselors have shown that emergency room doctors take only a cursory medical history. They often do not find out whether the woman has heart problems, impaired liver function, severe diabetes, a history of blood clots, or history of abnormal genital bleeding. The doctors do not, and indeed cannot, do a thorough enough medical history to find out if there are contraindications to estrogens.

Pregnancy is one contraindication. However, minors who are rape victims sometime give inaccurate contraceptives or sexual histories for fear that their parents may find out.

In most cases, the rape victim is not given adequate information on DES. In fact, she may not even be told what the drug is for or why she should come back for a followup.

For the first 3 or 4 days after the rape, most victims are in considerable pain and discomfort. It is not unusual for the woman to discontinue taking the morning after pill because she does not want the added discomfort of nausea or vomiting. Besides this, the victim may have already received large doses of penicillin or even valium, and may not wish to take more drugs.

Followup is essential when DES is given to the patient. However, followup of rape victims is virtually impossible for many reasons. After the rape, the victim may move out of town or move to another part of town; get an unlisted phone; change jobs; live with relatives.

Some rape victims initially give false names and addresses because they are afraid of harassment.

Many rape victims are brought to a county hospital, sometimes by the sheriff, from outlying parts of the county, and they will not travel that distance for a followup.

The rape victim wants to forget. The last thing in the world she wants to do is to return to the hospital.

When the rape victim comes to the emergency room, she may be disoriented or in a state of shock; she may not realize she needs to come back for a followup.

But the greatest deterrent to followup is the cost involved. Most victims simply cannot afford to pay another \$30 or \$40 for a hospital visit.

Finally, followup is not considered the responsibility of the emergency room personnel. According to Dr. George Fin, of St. Joseph Hospital in Ann Arbor, Mich., "Our policy is to refer rape cases as well as other emergency cases to follow up with their own family physician or at local medical facilities. Followup is not within our capacity. We do not have the setup, and we do not do it."

In reviewing the 1974 rape cases seen at Wayne County Hospital in Detroit, one doctor estimated that only about 25 percent of all rape victims come back for any kind of followup, even VD testing.

Senator KENNEDY. I want to put the rest of the statement in the record. I think the matter that we are primarily interested in and concerned about is the use of DES as a morning after.

With regard to rape and the implications of that, in terms of followup, which we have all heard about, is extremely important, but I would like to get back to this major point of consequence to us, and that is the use of the morning-after pill and your particular experience.

I understand this is a copy of the form which the University of Michigan uses [indicating]. On that form it says, it has "DES Initial Visit Form," the age, and a number of other items and questions on it.

And No. 14 on this says, "I understand that the use of diethylstilbestrol as a morning-after pill is an FDA-approved use of the drug and that it should not be taken if there are any chances of pregnancy from previous exposure this month."

Then it continues, "It might cause cancer years later in the offspring. I have been advised this is only emergency-type therapy for unprotected intercourse. No guarantee or promises have been made to me as a result of taking these pills."

I imagine those words in the early part of this statement that "I understand the use of the morning-after pill is an FDA-approved use of the drug" would at least create a climate and atmosphere in the mind of the student that it is going to cover the purpose and does not really present significant danger.

Ms. COWAN. I am acquainted with that form. I would like to say that words on a form are one thing, but doctors' prescribing habits are another.

The person signs that form. I think the form was drawn up for legal reasons rather than health services' interests in completely informing the students; despite the fact that students must now sign that form, they can still readily obtain the morning-after pill.

It is given to them more than once.

Senator KENNEDY. Well, there are a number of points.

One is that when the order went out almost 2 years ago, May 1973, it was a mistake because it was never approved. But, nevertheless, it was continued. As we will hear later on, there was no important effort to try to curb the possibility of abuse by the Food and Drug Administration.

Then, beyond that, it certainly seems to me to suggest to the students that the fact that it has been approved by the FDA would give it sort of a premature safety and efficacy which, obviously, is a dangerous situation.

Ms. COWAN. Continuing, in my statement, on emergency room procedures—

Senator KENNEDY. I think if you want to summarize just that aspect of it, this is of great importance and interest generally, but is it not to the point here, with regard to rape victims that may take DES because of the control situation, there is little followup for the reason you have outlined here, even in emergency situations?

Ms. COWAN [continuing]. I am recommending DES not be given to rape victims by emergency room personnel because the emergency situation associated with rape is because of trauma, both physical and psychological of the rape, and the emergency situation does not constitute the possibility of pregnancies and is really secondary to the emergency.

And I feel that even in rape cases DES should not be given out by the emergency rooms.

Senator KENNEDY. Can you see any use for it then?

It should not be used in an emergency and should not be used in other situations.

Is there any use for it?

Ms. COWAN. I believe it should not be used as a morning-after pill, and I think Dr. Greenwald has pointed out its legitimate uses.

Senator SCHWEIKER. One statistic I do not think you got to in your prepared statement, and I think it does have some relevancy; you say, "We know that statistically less than 5 out of every 100 single unprotected sexual encounters result in pregnancy. Therefore, we are subjecting 95 percent of women given DES to an unnecessary drug."

I think that is a very important point because we are exposing 95 percent of women needlessly to something where we are probably really only really concerned about 5 out of 100. So we have to get the problem in perspective.

Ms. COWAN. That is correct, which then leads into the final issue, which is the possible legal liability on the part of doctors who prescribe DES.

Recently, even the AMA has conceded that the doctrine of informed consent includes disclosure by the doctor of risks to the patient, including risk of failure of the drug, as well as disclosure of alternative treatments.

As far as I could tell, few doctors are suggesting any alternatives to DES. They could suggest menstrual aspiration or early abortion.

In conclusion, DES must be given only under the following conditions:

1. A thorough personal and family history must be taken.
2. Warnings as to risks to the patient and possible offspring must be discussed.
3. FDA must provide adequate information in a patient insert.
4. A pregnancy test must be given prior to and after DES therapy.
5. There must be followup.
6. The patient must be informed of alternatives, including menstrual aspiration and early abortion.

Unless all of these steps are taken, DES should not be prescribed to anyone.

Senator KENNEDY. Thank you very much.

Senator SCHWEIKER. I have one question for Dr. Greenwald.

Doctor, I am not clear on one point, and maybe you can clear it up.

If a woman had been taking DES preceding the time when she became pregnant, is there a connection, or must the administration of DES occur at the time of or immediately following to the actual pregnancy?

Dr. GREENWALD. As far as we know, DES is not not retained very long in the body, and it would have to be taken after the pregnancy started. That is our best information.

Senator SCHWEIKER. It must occur sometime during the pregnancy period?

Dr. GREENWALD. Yes; because it does not stay around in the body very long.

Senator SCHWEIKER. That is all I have.

Senator KENNEDY. Thank you very much.

Dr. GREENWALD. Thank you.

Senator KENNEDY. Our next panel of witnesses consists of two employees of the Food and Drug Administration who are testifying before us pursuant to subpoenas.

Dr. Marvin Seife is Director of the Generic Drug Division of FDA's Bureau of Drugs. He has been with FDA since 1965.

Dr. Vincent Karusaitis, an obstetrician and gynecologist, is a medical officer in the Generic Drug Division.

Dr. Seife, what is your position in the FDA, and when did you get involved with the morning-after drug?

STATEMENT OF DR. MARVIN SEIFE, DIRECTOR OF THE GENERIC DRUG DIVISION, BUREAU OF DRUGS, FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY DR. VINCENT KARUSAITIS, OBSTETRICIAN AND GYNECOLOGIST, MEDICAL OFFICER IN THE GENERIC DRUG DIVISION, FOOD AND DRUG ADMINISTRATION

Dr. SEIFE. At the present time I am Director of the Division of Generic Drug Monographs in the Office of Drug Monographs.

I have held many positions since I have been with the FDA, for the past, approximately 10 years, many supervisory positions. At the present time we are involved with generic drugs from the years 1938 to 1962.

In other words, we are implementing the Kefauver-Harris amendments as to safety and efficiency.

Prior to the Kefauver-Harris amendments drugs were passed only for safety. As a result of the 1962 amendments, efficacy had to be shown. The huge task of showing efficacy for all drugs from 1932 through the third week of October 1962, had to be undertaken after a 2-year period, that is the end of 1964, by FDA to show efficacy.

All the drugs we handle have been published in the Federal Register, and are declared effective, and the indications listed.

In some instances the actual labeling is given.

In this instance, for diethylstilbestrol, for 1971 the first publication in the Federal Register gave the usual indications for diethylstilbestrol. The indication for postcoital use was not listed.

In August of 1973 we received a submission from a small firm in New Jersey, August 6, 1973, asking for 25 milligram tablet of diethylstilbestrol for purpose of postcoital use.

We assigned it abbreviated new drug application number. On September 17, 1973, I sent them a letter stating that we could not accept it for this use since the Federal Register had not indicated it to be effective for this use.

Senator KENNEDY. Why did you do ANDA abbreviated instead of NDA?

Dr. SEIFE. At this point the previous diethylstilbestrol which was a generic drug used for many, many years was considered to be abbreviated, and listed accordingly in the Federal Register of November 10, 1971.

Now, the company, for some reason——

Senator KENNEDY. Is that true for postcoital use?

Dr. SEIFE. No; only for usual uses.

Senator KENNEDY. Is this procedure——

Dr. SEIFE. This is not procedure.

In all my years with the FDA, this is unique, this is the first time in my experience that a drug has been published for a new use in the Federal Register without any study, without any investigative new drug application for a totally new indication.

Senator KENNEDY. Was that the correct thing to do?

Dr. SEIFE. No.

Senator KENNEDY. Who made the decision to do it?

Dr. SEIFE. I have no idea.

Senator KENNEDY. Who told you to do it?

Dr. SEIFE. The Federal Register.

Senator KENNEDY. Who puts that out? Who put it in the Federal Register?

Dr. SEIFE. This goes up to the chain of command.

Senator KENNEDY. Give us the next one up.

Dr. SEIFE. Probably on the first document, the November 10, 1971, document, I was probably Acting Director of the Office of Scientific Evaluation, and I probably had my signature on the document, which declared it to be an abbreviated new drug application for the usual uses.

But later in the game——

Senator KENNEDY. Let me go back. Did your division approve or disapprove this?

Dr. SEIFE. No.

Senator KENNEDY. No, what?

Dr. SEIFE. We have never approved it, we never saw the document.

Senator KENNEDY. Did you protest this procedure?

Dr. SEIFE. Our group was unanimous in protesting this particular use.

Senator KENNEDY. Who was trying to get it approved, was it the drug companies, was it FDA, you?

Dr. SEIFE. No; FDA published—apparently the Division of Metabolic Endocrine Drug Products handled this application. Our unit had nothing to do with it.

And on September 26, 1973, a Federal Register statement came out stating that the 25-milligram tablet could be used for postcoital use.

Now, based on that, we resurrected this application, which came to us in August 1973. Now in December 1973, Dr. Karusaitis and Dr. Carroll, who represented me, attended a meeting, an in-house meeting at which many subjects were discussed, among which diethylstilbestrol for postcoital use.

I think Dr. Karusaitis can relate what happened.

Senator KENNEDY. Can you relate what happened?

Dr. KARUSAITIS. We were given a period of time which was sufficient to have our say, and the gist—

Senator KENNEDY. Tell us what your position is.

Dr. KARUSAITIS. My position, I am a practicing physician in New York State, work for FDA for the past 5½ years. My specialty is OBGYN.

The first submission that we received, I made this notation, the indication was new, the dosage was new, therefore this application was not acceptable, and would have to pursue a full NDA.

And I said it was a “no-go” period.

Senator KENNEDY. What happened to that?

Dr. KARUSAITIS. That went through channels, to Dr. Seife.

Dr. SEIFE. We sent them a letter on September 17, 1973, to the firm, saying that we cannot review their application since there was no appropriate Federal Register statement.

Now, September 26, almost 10 days later, a Federal Register statement appears calling for the use of the drug as a morning-after pill, and calling for abbreviated new-drug application, which means no studies.

Senator KENNEDY. Means no studies?

Dr. SEIFE. Which circumvents the usual procedures.

Senator KENNEDY. Quite clearly the usual procedures were not followed?

Dr. SEIFE. Right.

Senator KENNEDY. And the procedures which were outlined were objected to by those such as yourselves who have primary responsibility in these areas, and for some reason—the decision was made further up the line about these unusual procedures, and we will get back to the Commissioner a little later, for the reasons for it.

Can you tell me, at any time, did any of you feel there was a pressure for speeding up the application?

Dr. KARUSAITIS. Since the original was a proposal—therefore we would have finalization of that proposal, and we would have to have input, comment was invited, and people were asked to appear, and to give their viewpoints.

With this in mind, I would go down to the hearing clerk, look at the proposal sent in, the comments, and in June we sent a letter to Paul Bryan, Dr. Finkel, and Dr. Ortiz, with the question: What finalization, if ever, if when, would be made on the proposal which was the original proposal, September 26, 1973.

We felt that since it was a proposal, until you got a finalization, it was open.

Senator KENNEDY. What happened at the December 1973 meeting?

Dr. KARUSAITIS. I cannot say about the December meeting. I can say that there was a meeting in which I presented the fact that I did not understand the pregnancy bit, how would you determine the pregnancy of a woman who had just been raped, or was an emergency, what type of test would be taken.

I could not understand that we would approve this in a simplistic matter without a full NDA, which we asked for a year ago.

Senator KENNEDY. And was that advice heeded, or was it overruled?

Dr. KARUSAITIS. It was overruled. It stayed in our bailiwick, we were told we would keep the submission.

Senator KENNEDY. Would it be fair to say you were forced to approve it?

Dr. KARUSAITIS. No, sir.

Senator KENNEDY. It would not?

Dr. KARUSAITIS. My feeling was always the same. I would not approve it.

Senator KENNEDY. You would not approve it?

Dr. KARUSAITIS. No, sir.

Senator KENNEDY. What about you Dr. Seife?

Dr. SEIFE. I would not sign the letter. In fact, Dr. Crout called me recently and said he would sign the final approval letter if it were approved. The drug has not been approved for this use, and will not be until March 7, 1975. That is the date of the final order, the date of the effectiveness of the final order.

Senator KENNEDY. You mean as of today it is not approved?

Dr. SEIFE. That is right.

Senator KENNEDY. Even though the bulletin went out in May 1973?

Dr. SEIFE. Right.

Senator KENNEDY. As of today it is not approved?

Dr. SEIFE. Correct.

Senator KENNEDY. But on March 7 it will be?

Dr. SEIFE. Yes, sir.

Senator KENNEDY. For emergency purposes?

Dr. SEIFE. Postcoital use; yes.

Senator SCHWEIKER. I am trying to determine the sequence of events.

The first thing, which was an abnormal departure from pattern, was the letter to you which, as I understand it, was a variance from what the Federal Register said, is that correct?

Dr. SEIFE. Yes.

Senator SCHWEIKER. A letter of application which did not coincide with the Federal Register, abnormal situation, number one.

The second abnormal situation was the application submitted in abbreviated form, and since there was a new indicated use, this was also a departure from precedence, is that correct?

Dr. SEIFE. Yes.

Senator SCHWEIKER. Third, and I am not sure I have the sequence right, but third, a letter of approval was erroneously sent out.

Dr. SEIFE. No, no letter of approval has ever been issued for this use ever. I would be the one to sign it, until Dr. Crout relieved me of this burden.

Senator SCHWEIKER. The letter was sent out, I guess, a couple of years ago, what did it say then?

Dr. SEIFE. That was a bulletin to physicians, saying that this was an indication for the drug.

Senator SCHWEIKER. Now, explain to me what the Bulletin said. Did it approve the drug?

Dr. SEIFE. No, it just stated that 25 milligrams, taken twice a day for 5 days, 5 consecutive days, the morning after, or as soon after coitus as possible, would be effective in preventing pregnancy.

Senator SCHWEIKER. It did not approve the drug. But it said it would be effective, and it was an FDA bulletin?

Dr. SEIFE. Yes.

Senator SCHWEIKER. I have trouble comprehending exactly what you are telling me.

Senator KENNEDY. If the Senator would yield——

Senator SCHWEIKER. I will be glad to yield, because it is a very key issue.

Senator KENNEDY. This is the FDA Drug Bulletin, May 1973, and it says:

"In agreement with the * * *" FDA has approved under restrictive conditions postcoital use of diethystilbestrol.

So even though it was in error, it was sent out?

Dr. SEIFE. Yes. I imagine that is how the company that filed the ANDA received their information——

Senator KENNEDY. You did not approve it?

Dr. SEIFE. No.

Senator SCHWEIKER. It said FDA did approve it, and that is the question I asked, which you denied.

Dr. KARUSAITIS. He is not denying it. He is telling you he did not sign the approval, it goes through him.

Senator SCHWEIKER. You are saying you did not approve it, but it is pretty obvious that the Bulletin said FDA approved.

Dr. SEIFE. That is correct.

Senator SCHWEIKER. That was abnormality No. 3.

Dr. SEIFE. Yes.

Senator SCHWEIKER. Then just a few weeks ago the new indication for postcoital usage was approved in an abbreviated form procedure.

Dr. SEIFE. No.

Dr. KARUSAITIS. To be effective, Senator, the 7th of March.

Senator SCHWEIKER. What occurred then?

Dr. KARUSAITIS. It is coming, the 7th of March, to be.

Dr. SEIFE. Next month.

Senator SCHWEIKER. Under abbreviated procedure.

Dr. SEIFE. Yes.

Senator SCHWEIKER. This also, as you said earlier, is a departure from normal procedure?

Dr. SEIFE. Yes.

Senator SCHWEIKER. So we really have four abnormal occurrences here that differed from normal practice and pattern, that is all I tried to establish.

Thank you.

Dr. SEIFE. Yes.

Senator KENNEDY. On a drug that causes cancer.

Dr. SEIFE. Yes, that is true. That is why we felt very strongly about having this as an abbreviated new drug application.

Senator KENNEDY. I want to thank the both of you for your appearance here.

Let me just say that I think you have performed nobly in trying to do what I think the Congress had intended the Food and Drug Administration to do, and that is to pursue the public interest on this.

I think you deserve a great deal of credit. There have been times before this committee we have had our differences, and it has not been really with the employees in the Food and Drug Administration, who have been performing, I think, nobly. I think that ought to give the American people a great sense of confidence.

It is these other administrative decisions which I think we are questioning. That is a matter of great concern to us.

We want to commend you. I do. We want to thank you for performing the job.

Senator SCHWEIKER. I share those sentiments.

I have one more question.

Even though the fourth abnormality I cited indicated that some approval for March 7—

Dr. KARUSAITIS. Approval will be effective the 7th of March, 1975.

Senator SCHWEIKER. OK. Your Department has still not approved that?

Dr. SEIFE. Correct.

Senator SCHWEIKER. It is normal for your Department to approve procedures such as that?

Dr. SEIFE. That is right.

Senator SCHWEIKER. You are telling us, even though this future approval date has gone out, it still has not cleared your Department, is that right?

Dr. SEIFE. Right.

Senator SCHWEIKER. So that is abnormality No. 5.

Dr. SEIFF. We have to receive draft labeling, final printing labeling, we have to review the whole application before approval. This might take several months.

Senator KENNEDY. Well, the bottom line is you have been overruled, that is the way I read it.

Dr. SEIFF. On the abbreviated part.

Senator SCHWEIKER. About five times the way I count them.

Senator KENNEDY. Thank you very much. You have been very frank and very responsive to our questions, and very helpful, and we want to thank you.

Dr. SEIFF. Thank you.

Dr. KARUSAITIS. Thank you.

Senator KENNEDY. Our next panel of witnesses appear here as representatives of companies which have marketed or still market a product with a 25-milligram dosage of DES.

Robert H. Furman, M.D., is vice president of Lilly Research Laboratories, Eli Lilly & Co. In late 1973, Lilly deleted the 25-milligram dosage forms of DES from its product line.

Robert L. Pillarella is president of Tablicaps, Inc., of Franklinville, N.J. Tablicaps is presently marketing a 25-milligram dosage form of DES, in accordance with FDA regulations regarding the emergency usage of this drug.

Mr. Pillarella, I want to indicate that Mr. Williams wanted me to extend a word of welcome to you and regret that he is unable to be here.

He wanted me to indicate to you that he looks forward to reading your testimony and wanted to thank you for coming.

Dr. Furman, please proceed.

STATEMENT OF ROBERT H. FURMAN, M.D., VICE PRESIDENT, LILLY RESEARCH LABORATORIES, ELI LILLY, INC., ACCOMPANIED BY ROBERT L. PILLARELLA, PRESIDENT, TABLICAPS, INC., FRANKLINVILLE, N.J.

Dr. FURMAN. Mr. Chairman, I am Robert Furman, a physician, vice president, Eli Lilly Research Laboratories.

Eli Lilly & Co. is pleased to respond to the invitation of the chairman to appear today. As requested, our statement will include comments on Lilly's decision not to market a 25-milligram dosage form of diethylstilbestrol for postcoital contraception. It also will discuss Lilly's suggestions for the proper use of prescription pharmaceuticals.

Diethylstilbestrol, DES, is a synthetic compound capable of producing feminizing effects similar to those of the naturally occurring feminizing hormones—estrogen.

It was synthesized by Dodds in 1938. DES was added to the Lilly product line in 1941 "at a time when the natural products were scarce and expensive." It was regarded as a milestone in the development of effective hormone therapy, and it is used today in the treatment of a number of conditions.

The four principal conditions in which DES is most often employed are the following:

(A) As replacement therapy in states of estrogen deficiency, for example, the menopause or the absence of ovaries.

(b) For the prevention of post partum breast engorgement.

(c) Cancer of the prostate.

(d) Breast cancer in postmenopausal women.

Since 1951, studies in animals and humans have indicated that high doses of estrogen, administered after the ovum (egg) had been released from the ovary—determined by body temperature rise—prevent pregnancy.

In 1966, and subsequently, reports by Morris and Van Wageningen and by Kuchera demonstrated that DES prevented pregnancy when administered in large doses—25 milligrams twice daily for 5 days—beginning no later than 72 hours after sexual contact.

Precisely how DES acts to prevent pregnancy when administered after sexual contact is not known. It probably interferes with the attachment of the fertilized ovum to the lining of the uterus (implantation).

The term "interceptives" has been suggested for agents which interfere with implantation. We are not aware of any evidence that DES will interrupt an already implanted ovum.

Lilly had provided a 25-milligram dosage form of DES for use in patients with carcinoma. In February of 1973, a spokesman for the FDA indicated to the Senate Subcommittee on Health that DES had been approved as a postcoital contraceptive. In the May 1973 FDA Drug Bulletin, the provisions of the newly approved indication were delineated.

Senator KENNEDY. That was the bulletin referred to and was not approved until for this coming March?

Dr. FURMAN. Yes, sir.

In the Federal Register for September 26, 1973, the FDA gave notice to the effect that it was proposing to withdraw its approval of 25 milligram dosage forms of DES for all indications except postcoital contraception. Industry was invited to submit abbreviated new drug applications for the use of the 25-milligram DES dosage for this indication.

Senator KENNEDY. Do you think it would have been appropriate for new drug application, ANDA, an abbreviated new drug application—

Dr. FURMAN. I will point out a little bit later in my testimony, Mr. Chairman, it is our feeling that under circumstances such as this that the company has the responsibility to carry out studies of its own or support studies which demonstrate not only efficacy but safety as well.

Senator KENNEDY. Well, then, I guess your answer would be, no, you think not abbreviated application, but ought to be new drug application, is that correct?

Dr. FURMAN. Yes, sir.

In the Federal Register for February 5, 1975, the final labeling, patient package information and package size are set forth. The notice indicates that only one abbreviated new drug application has been received.

After the Federal Register notice of September 26, 1973, Eli Lilly & Co. deleted the 25-milligram dosage forms from its product line. These items had been made available to physicians for other uses, such as carcinoma.

We elected not to submit an abbreviated NDA for the use of DES as a postcoital contraceptive. This decision was arrived at after careful review and evaluation of the medical and scientific aspects of the situation.

After prior review by FDA, a letter was mailed to over 230,000 physicians and approximately 55,000 pharmacists in March of 1974, discussing the use of DES, including its use as a postcoital contraceptive. The letter informed them as follows:

Although postcoital contraception is recognized by some authorities as an indication for diethylstilbestrol, Eli Lilly and Company has neither conducted nor supported laboratory or clinical investigations to establish efficacy and safety of its product for this indication. Therefore, diethylstilbestrol supplied by Eli Lilly and Company is not recommended for postcoital contraception, and we are deleting from our product line the 25 milligram dosage forms. We continue to endorse diethylstilbestrol for the indications included in our current literature.

Although diethylstilbestrol is supplied by many manufacturers, Eli Lilly and Company believes it important to acquaint the medical profession with this information.

Senator KENNEDY. Is this fair to say the Lilly Co. was concerned about the safety of DES for this purpose?

Dr. FURMAN. Yes; it was.

Senator KENNEDY. In other words, you reviewed the material that had been developed and you made a medical and scientific decision not to move ahead because of the questions of safety, as I understand it?

Dr. FURMAN. Principally safety.

On the basis of the information that was available to us, we did not feel that we could responsibly go ahead and market the 25-milligram dose for this purpose.

Senator KENNEDY. Well, can you indicate to us why, based upon the information that you had, you made a decision not to move ahead, and why the Food and Drug Administration would move ahead based on the information that they had?

After all, you were the principal producer of the drug.

Dr. FURMAN. Well, Mr. Chairman, the Commissioner has had available to him a number of consultants. He had OB-GYN advisory committee. We were not privy to all the information that he had. So I do not feel that I can editorialize on that judgment.

All I can say is, based on the information we had, the judgment we arrived at, was not to go ahead with the 25-milligram tablets for this purpose.

Senator KENNEDY. Well, he would certainly have access to the kind of information that you pointed out.

But, evidently, I think it could be fair to assume that your standards were higher than the FDA standards.

Dr. FURMAN. Well, I would hate to say they were necessarily higher, Mr. Chairman, but the Commissioner and the decision he has to make is one situation. Eli Lilly & Co. and the product responsibility aspects of the issue, our responsibility to the physician and as manufacturer, put a somewhat different task on the situation.

Senator KENNEDY. We will let the record speak for itself, but it would certainly appear to me that the standards which your company developed, as one that is producing this drug, are more strenuous than that which was developed in this particular case by the FDA. That would be a conclusion I would draw unless you want to make a comment on it.

Dr. FURMAN. I accept your judgment in that regard.

Well, as stated in the Lilly letter to physicians, the primary basis for Lilly's decision was lack of its own clinical or laboratory information regarding efficacy or toxicity.

This decision is consistent with our policy to secure adequate clinical information on safety and toxicity prior to introducing a new drug.

Let me turn now to the problem of minimizing the misuse of prescription drugs. You have asked for our suggestions.

There is regrettably no certain way to assure proper drug usage. We believe the only realistic way to insure against the misuse of drugs is through a continuing effort to develop and disseminate information on drug usage.

The development of information necessary for the proper use of a drug must begin prior to the filing of an IND. It must continue through clinical investigations and after marketing as increasing clinical experience is developed.

To have maximal effect, the educational process should involve several components—the industry, the university, the Government, the physician, the pharmacist, and the patient.

The foregoing process produces a vast amount of complex information which must be effectively made available to the physician in order for him to make sound therapeutic judgments. This process of communication is an essential part of our responsibility to assure proper drug usage.

For this reason, we at Eli Lilly & Co. examine very closely the information sent to health professionals. Company literature is reviewed to insure that only medically and scientifically valid statements are made and that the necessary warnings and contraindications are provided.

Of equal importance in the dissemination of scientific information is a balanced, accurate discussion of the available data by a competent, well-educated, and well-trained responsible sales representative. Most of our salesmen have pharmacy degrees, and all are university graduates.

The ultimate responsibility for the care of the patient rests with the physician. His ability to evaluate and to utilize new drug information depends on his knowledge of fundamental clinical pharmacology, the basis for all drug therapy.

There is agreement that greater emphasis needs to be placed on clinical pharmacology training in our medical schools as well as in programs of continuing education for practicing physicians.

The pharmacist can help the patient understand the physician's instructions regarding his medical problem and its management. The clinical pharmacist, in the hospital or clinic setting, is an important member of the health care team. He is an important source of drug information in particular clinical situations.

The patient plays a role in the proper use of drugs. Lack of understanding on his part can spell therapeutic failure.

As we seek to insure that all drugs are properly used we must not forget that, unfortunately, there is no risk-free drug, and inherent in every therapeutic situation is the matter of risk versus benefit. Adequate knowledge, however, can diminish the risk.

Let me conclude by offering the following specific recommendations which Eli Lilly & Co. believes will help insure that drugs are properly used:

1. A company should assume responsibility for its own independent evaluation of the safety and efficacy of the products which it offers the medical profession. This is essential if the company is to meet today's professional responsibility.

2. A more intensive training in clinical pharmacology is needed for medical students and physicians.

3. Measures should be developed to enhance consumer protection, such as product coding systems, expiration dating, and identification of the manufacturer of the dosage form on the product label.

4. Ethical practices and high standards of training for sales representatives on the part of all manufacturers should be a priority for all manufacturers.

We believe that it is in the context of these areas of concern that recommendations for better safeguards can be developed. Eli Lilly &

Co. is committed to and stands ready to assist in the accomplishment of these suggestions.

Senator SCHWEIKER. Thank you, Dr. Furman.

You mention in your statement the usage on page 1, four principal uses of DES.

You did not mention preventing miscarriages or some definition such as that.

Would that fall under "A" or not?

Dr. FURMAN. No.

The use of DES in threatened miscarriage or threatened abortion was abandoned and removed from the literature.

Senator SCHWEIKER. About when was that, roughly?

Dr. FURMAN. My recollection is a little uncertain at the moment. I believe it was 1968.

Senator SCHWEIKER. That is the only question I had.

Mr. Pillarella, we are pleased to have you here.

Mr. PILLARELLA. I am Robert L. Pillarella, president of Tablicaps.

We are pleased to appear before this joint session of the Subcommittees on Health and Administrative Practices and Procedures.

We are delighted because a small company, such as Tablicaps, rarely has the opportunity to show the role small companies can play in this great country of ours. Probably more important, the reassuring anticipation that this joint subcommittee recognizes the same concern as Tablicaps. That is, in providing Government approved medical therapy for rape victims.

For the first time, a rape victim may have the opportunity to receive approved medication. A medical therapy which would provide the proper warnings, as noted in the Food and Drug Administration policy published in the Federal Register, dated February 5, 1975.

We are presenting a brief and concise statement addressed to the following specific requests: a short Tablicaps biography, how Tablicaps became involved with diethylstilbestrol, where we feel this dosage form belongs in medical therapy, what constitutes appropriate and inappropriate use, minimizing the potential for misuse.

Tablicaps was incorporated in the State of New Jersey in 1969, and is located in Franklinville, Gloucester County, N.J.

Tablicaps was incorporated with the intent to establish a line of quality generic pharmaceutical products.

We felt that a steadily aging population and the demand for higher standards of health would increase the need for drug products throughout the world, further increasing the number of third party payment plans and anticipated Government interest in drug programs for the elderly would create a greater demand for generic drugs. Therefore, Tablicaps began to form a product line which would be the basis to implement our corporate philosophy.

Among the products selected was the widely used generic estrogen, diethylstilbestrol.

Tablicaps began manufacturing various strengths of diethylstilbestrol tablets in 1970.

The Food and Drug Administration, in November 1971, issued a drug efficacy implementation report affecting diethylstilbestrol. In accordance with this report, Tablicaps submitted to the Food and Drug Administration a request for the approval of diethylstilbestrol in the 0.5 milligram, 1 milligram, and 5 milligram tablet dosage forms.

At a later date, we submitted an application for the 25 milligram dosage form of diethylstilbestrol for routine estrogen indications.

The Food and Drug Administration notified us that:

This application would not be reviewed until the appropriate Federal Register for this therapeutic indication, requiring higher dosages than those normally recommended, is published.

I would like to add one thing.

Up to this point, we did not apply for an abbreviated new drug application for postcoital use. All we had applied for, and what we were notified, is that at this time there was no use for 25 milligram diethylstilbestrol.

To continue with my statement, in September 1973, the Food and Drug Administration published in the Federal Register the proposed patient labeling for the use of diethylstilbestrol 25 milligrams as a postcoital contraceptive. It was stated herein that drug applications would be entertained under the conditions proposed.

In January 1974, Tablicaps submitted an application for the postcoital use of diethylstilbestrol, 25 milligrams, which we call DESMA.

The DESMA application was submitted by Tablicaps because we considered the restricted market for this emergency medical therapy to be the right size for us. Whereas, a market void might develop due to the limited and restricted potential.

Another consideration was the rape victim who is entitled to the opportunity of receiving approved medication. Lately, DESMA complements the diethylstilbestrol family of products for the corporation.

Tablicaps believes that DESMA has a place in medical therapy because it is the first product approved by the Food and Drug Administration as a postcoital contraceptive. Its use is important in cases such as rape and in those emergency situations determined by a patient and her physician, and is not to be used as a routine or premeditated contraceptive.

Senator KENNEDY. Just on this point, and excuse me for being out of the room, I want to add a word of welcome to you. I gather you think it ought to be used under extremely limited circumstances?

Mr. PILLARELLA. Absolutely.

Senator KENNEDY. Could you develop this point?

Mr. PILLARELLA. Well, if we take a look at problems as we see them right now, the first case you have is rape.

Whether we as citizens or as Government would like to recognize it or not, rape is increasing. We do have an incest problem. It does exist. There is no hiding from it.

These are two of the cases where it has a definite known need.

One of the biggest questions that I have heard so far in all of my discussions, and it has come up here a few times, is the emergency definition.

The emergency definition becomes a very difficult thing to define, simply because, as you said earlier, emergency is interpreted at a given time, a given place, and if that emergency should be for the patient's well-being, or something like that, as defined by the physician, then I think it is applicable.

However, I am not a physician. I cannot make that determination. I cannot practice medicine. I cannot make a prognosis.

I think further in my statement, in fact the next paragraph, I think, would really tell you what you are asking for, Mr. Chairman, if I may continue.

Senator KENNEDY. OK.

Mr. PILLARELLA. As to what constitutes appropriate or inappropriate use of this product, Tablicaps emphasizes that DESMA is not to be considered for a routine method of birth control, nor for family planning, nor for premediated contraceptive use, but for emergency treatment only.

Tablicaps recognizes the potential for the misuse of DESMA, and we believe it will best be minimized by providing the physician with adequate information and properly educating the patient. This is accomplished by the physician and patient package insert which is phrased in frank and specific language.

I would like to stop here.

I have a package of our product, which we intend to submit to you, without the tablets. I would like for the committee to have it and add it to the record, without the tablets.

To further minimize the potential for misuse, Tablicaps suggests two measures in addition to the Food and Drug requirements, the first of which we have already implemented:

1. Tablicaps states, as an introduction to the patient package information, the following in bold print: "Dear Patient: It is important that you read the following information so that you will understand the nature of this product."

2. In addition, since the potential misuse is dependent upon the availability of the product to the patient, Tablicaps also recommends adding to the labeling requirement the following: "This prescription is not renewable."

We fully realize our responsibility in making DESMA available to the medical community, and we will exert our best effort to assure its restricted use.

Now, I would like to add to this statement one thing.

We realized that this is a very controversial product. We, as a corporation, will do everything within our power to participate in the solution to a national problem.

Mr. Chairman, that is all.

Senator KENNEDY. Thank you very much.

I want to make sure that you understand that there has been nothing that has been suggested in terms of this hearing that has any implication or reflects certainly upon you or your company in attempting to develop this particular drug. I do not know whether you felt that because of the nature of the testimony that you would have felt any kind of discomfort on.

As I understand, you did not suggest, or your company, that there be an ANDA, did you?

Mr. PILLARELLA. No, we did not.

Senator KENNEDY. That was FDA?

Mr. PILLARELLA. This came out by Federal Register predicated on studies which had been submitted to whoever advised the Commissioner of Food and Drug.

Senator KENNEDY. You were prepared to meet whatever requirements were placed upon you by the Food and Drug Administration, were they not?

Mr. PILLARELLA. We were prepared to evaluate that requirement.

Senator KENNEDY. I have no further questions.

Senator SCHWEIKER. I have no questions.

Senator KENNEDY. Thank you very much.

Mr. PILLARELLA. Thank you.

Senator KENNEDY. Finally, we will hear from two old friends of the Senate Health Subcommittee.

Frank J. Rauscher, Ph. D., is Director of the National Cancer Institute of the National Institutes of Health.

Alexander Schmidt, M.D., is Commissioner of the Food and Drug Administration.

I want to welcome you gentlemen back to the Senate Health Subcommittee.

Dr. Rauscher, do you want to start?

STATEMENT OF FRANK RAUSCHER, PH. D., DIRECTOR, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH, ACCOMPANIED BY ALEXANDER M. SCHMIDT, M.D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION; J. RICHARD CROUT, M.D., DIRECTOR, BUREAU OF DRUGS; PETER BARTON HUTT, GENERAL COUNSEL; AND ROBERT C. WETHERELL, JR., DIRECTOR, OFFICE OF LEGISLATIVE SERVICES

Dr. RAUSCHER. Thank you, Mr. Chairman.

Mr. Chairman and members of the subcommittees, I am pleased to appear before you today to present findings concerning the use of diethylstilbestrol, DES, as an "emergency" postcoital contraceptive and to provide information on the use of DES as an animal feed additive.

I will address the latter use first and point out that the National Cancer Institute remains fully supportive of legislation, regulation, and activities which serve to reduce or eliminate environmental exposures to chemical carcinogens.

Specifically, if DES were used as an animal feed additive and if residues of the drug were left in edible portions of animals, the result would be long-term exposures to virtually the entire population of the United States.

It should be recognized that there is no health advantage to the exposed individual as is the intent when the drug is used therapeutically. The law prescribes that substances like DES which have been shown to be carcinogenic can be used as feed additives providing no residues appear in any of the edible portions of the animal at the time of slaughter.

The NCI remains fully supportive of these requirements.

Senator KENNEDY. Residues are now appearing.

Dr. RAUSCHER. That is correct.

Senator KENNEDY. You want to end that?

Dr. RAUSCHER. Indeed.

Senator KENNEDY. You want DES out of beef?

Dr. RAUSCHER. That is our recommendation.

Senator KENNEDY. All right.

Dr. RAUSCHER. Concern that the newly approved use of DES as a postcoital pill for emergency situations may cause cancer in treated

patients is to be viewed in light of present-day knowledge and information on human subjects.

Since the intended use of DES is, as a postcoital contraceptive for emergency use, following unprotected intercourse, the primary concern over dangerous side effects, assuming the treatment is effective, would be for the patient.

Secondarily, however, concern for the embryo must be addressed since treatment might be ineffective and a child might be born despite these efforts.

First, I will speak to the concern for the treated patient.

Among the women treated with DES for threatened abortion, no increase in the incidence of cancer at any organ site has been detected to date. The dosage of DES and the duration of treatment varied widely from 2.5 to 150 milligrams per day and from 3 to 212 days.

Most of these women were treated with as much as 50 milligrams per day for 150 days or longer. These observations date back to the late 1940's. They show no evidence that such use may be cancer causing.

It should be pointed out, however, that such observations are in contrast to those attendant to the use of DES for treatment of what is term "gonadal dysgenesis." Gonadal dysgenesis in the female implies defective and incomplete development of the ovaries, and DES has been used in an attempt to correct that condition.

Among those patients who have been treated for 5 or more years with an average treatment time of 12 years, evidence exists which suggests an increased risk of an unusual type of cancer. In fact, in a recent study performed by Bruce S. Cutler in 1972, 3 cases of cancer of this unusual type were discovered among a group of 24 females who had been treated for gonadal dysgenesis over a period of 5 or more years.

Because this form of cancer is so rare, it has been assumed that such treatment puts the patient at increased risk as regards this disease.

The contrast between the cancer experience of women treated for threatened abortion and those treated for defective development of the ovaries can reasonably be assumed to be the result of differences in total dosage and duration of treatment.

As indicated earlier, the risk associated with the use of DES as treatment for threatened abortion was so low that it could not be demonstrated. Only at the higher exposure levels to the drug does evidence exist which suggests an increased cancer risk.

On this basis it can reasonably be assumed that the postcoital use which involves 50 milligrams per day for a period of only 5 days would represent far less risk to the patient than did treatment for threatened abortion where, indeed, no increase in risk could be demonstrated.

Senator KENNEDY. Could I ask you why you are so interested in banning it in animal feed, and yet you do not mind the additional amounts being taken under these controlled conditions—

Dr. RAUSCHER. As you mentioned earlier in the hearing, Senator, it is a matter of risk-benefit. We feel that under a very limited circumstance the American woman should have an option in her treatment for threatened pregnancy with respect to this particular drug.

I continue to be very concerned, as you know, about its use in animals because American women who may be pregnant at the time may eat

DES-contaminated meat products, leading to the possible increased cancer risk to their female offspring.

That is why I would be very concerned about its continued use in animal feed.

Senator KENNEDY. What are these extreme cases?

Dr. RAUSCHER. Rape, incest, and any disease that could be life threatening following pregnancy. Severe juvenile diabetes is one example in which pregnancy could constitute a definite risk to life.

Senator KENNEDY. What is your reaction to the testimony we have heard today about the widespread use of DES? Does this present a health hazard of important consequences?

Dr. RAUSCHER. I think it is very important. If widespread use were to continue, I would recommend to you, in the strongest terms possible, that its use be discontinued.

Senator KENNEDY. Why?

Dr. RAUSCHER. Because of the potential danger to the fetus, where DES did not work as a postcoital drug.

Senator KENNEDY. But the bulletin that went out, even the 1973 bulletin that went out, indicated that it only should be used for emergency purposes, along the lines, I think, that you have outlined here, for incest, rape; so is that going to provide sufficient protection to the American woman, or does something more have to be done?

Dr. RAUSCHER. I believe Dr. Schmidt will describe new procedures that he thinks will control the indiscriminate use of DES. I would agree with him that if proper monitoring, proper restriction of a drug cannot be assured as being applied only to these emergency situations, I would recommend very strongly that it not be used at all.

Senator KENNEDY. Given the kind of general testimony about the widespread use, are we going to wait another year, 2 years, while we develop some kind of procedures? And who are the people that are going to be at risk in the meantime?

Dr. RAUSCHER. In March the new procedures will go into effect. May I comment on that after we hear what procedures will be introduced?

Senator KENNEDY. All right. That would be fine. But let me gather, at least from what you have stated here, that over the period of the last 2 years, even with the statement in the FDA Bulletin, that it only be used and restricted for emergency purposes, would not the reality of the situation, in terms of the wider distribution, as we have heard this morning, that this is the case—can we afford to go any longer period of time without getting a real handle and control on this?

Dr. RAUSCHER. I would agree with you. We cannot afford to go any longer, if we cannot agree, ourselves, that safeguards can be introduced immediately.

Senator KENNEDY. The safeguards we have heard are not adequate.

Dr. RAUSCHER. Evidently that is correct.

Senator KENNEDY. So we will hear from Commissioner Schmidt on what he thinks would be adequate safeguards. But would you proceed?

Dr. RAUSCHER. Thank you.

Concern for the daughters exposed immediately following conception also needs to be addressed, since the effectiveness of treatment

is unlikely to be 100 percent, and the possibility exists that some daughters may be born to treated mothers.

Since 1971 there have been extensive studies which document that the daughters of women treated with DES for threatened abortion during the first 17 weeks of pregnancy have a low but demonstrably increased risk for cancer of the vagina and cervix. These cancers appear around the time of puberty but in some case do not come to clinical attention until several years after puberty. Currently, the incidence is estimated to be no greater than three to four per thousand daughters at the 95 percent confidence level; but the incidence may very well increase as the daughters grow older.

It should be pointed out, however, that all of these exposures occurred in mothers who were demonstrably pregnant at the time of treatment. This, then, differs markedly from postcoital treatment which is recommended to begin within 24 to 72 hours following unprotected intercourse.

The significance of this statement lies in the fact that it is considered unlikely that treatment at such an early time and for such a short period would create risks comparable to those associated with treatment for threatened abortion. The period during which the drug is administered precedes the critical stages of tissue and organ development and differentiation.

It therefore seems improbable that the effects of DES administered at such an early time would produce effects similar to those induced by treatment for threatened abortion. One can only speculate as to what the former effect might be, if any, and how such effects would translate into human risks such as congenital diseases or cancer.

In summary, Mr. Chairman, I believe that current evidence suggests that the risk of causing cancer in the treated patient, the adult female, is extremely small.

Considered against the emotional trauma experienced by a rape victim, including the fears and anguish over the possibility of pregnancy or of intervention procedures such as uterine scraping and frank abortion, the benefit would appear to greatly outweigh the minimal risks involved.

It is my feeling that physicians who have responsibility for treating emergency pregnancies should not be deprived of what may be a useful medical tool, particularly so since there is a considerable accumulation of evidence which indicates the risks to the patient are small and, to date undetected despite the long and wide use of DES.

And, finally, Mr. Chairman, if I may just comment in synopsis, I recommend and the National Cancer Institute recommends that DES not be used in animal feed if residues result, that DES not be used routinely as post coital drug, and that its use be confined to victims of rape, incest, or illnesses which could be life-threatening following pregnancy.

Finally, that its use for this purpose be withdrawn if it continues to be used for nonemergency purposes.

Thank you, Mr. Chairman.

Senator KENNEDY. Well, you have heard the testimony about the use of nonemergency purposes, where there are incidences where roommates were picking up these pills for their friends, and very little follow-up procedures. This is the kind of abuse that would be of great concern to you?

Dr. RAUSCHER. Of much concern, yes.

Senator KENNEDY. As I understand from your testimony, unless you are given absolute assurances that that kind of use was to be terminated and ended, and ended now, that you would be for banning the use of the drug?

Dr. RAUSCHER. I agree. That is correct.

Senator SCHWEIKER. Dr. Rauscher, one thing that I am concerned about is, how often our Government makes a decision based on theoretically what should happen, or what might happen, because of the guidelines it publishes, whether in the Federal Register or through instructions to the pharmaceutical manufacturers. If everybody followed such instructions to the letter, there is no question that the safeguards would be there.

But I do not think the witnesses here, who we heard this morning, are really untypical or atypical. I think in the field it is a different world than we envision down here, whether it is in the Senate, in the executive department, on the regulatory agencies.

I wonder how realistic it is to presume that these instructions are going to be followed to the letter.

My question, I guess, is: If the reality of the "field" is really somewhat different from what we hope it would be, or wish it would be, or regulated it to be, then do we not have a responsibility to maybe not prescribe or not issue the drug approval, particularly we in fact know that we can never obtain the theoretical control? It is so important in a drug like this, to prevent people from getting cancer.

Dr. RAUSCHER. I agree with what you said. I do not think we can presume that out in the field we are going to be able to control the situation. It must be monitored. If the FDA cannot set up adequate means for effective monitoring, then we would not know to what extent use has been controlled. Under those circumstances, I would again recommend that its use be withdrawn.

Senator SCHWEIKER. I think your summary is a fair summary. You were talking about weighing the risks. You suggest the risk of causing cancer is extremely small, and perhaps four people in a thousand may well be in that category. It may be less because you are talking about a different usage of it. I realize it may be less than that.

But I ask the basic question: Is not 1 in 1,000 too many?

Dr. RAUSCHER. One in 1,000 is a very high risk. You are talking now about mothers treated with DES.

Senator SCHWEIKER. What figures can you give me, do you have, or did you base your statement on, then, that I do not have concerning the risk being extremely small? What do we say the risks are?

Dr. RAUSCHER. Here I was talking about mothers who were treated, not the daughters. We have been following the daughters, and most of these are NCI-supported studies you heard about this morning.

We have also been following the mothers that were exposed. There is no increased risk to these. Cancers are virtually nonexistent in the adult female following exposure during their first trimester pregnancy to DES. I am talking about mothers here, not the daughters.

Senator SCHWEIKER. Let us talk about the daughters.

Dr. RAUSCHER. The risk 4 per 1,000 is a very high risk. It could never be tolerated. That is 400 per 100,000.

Senator SCHWEIKER. I understand you were talking about mothers, but I do not understand why we are not talking about daughters.

Dr. RAUSCHER. I am talking about daughters when I say if DES continues to be used in uncontrolled or indiscriminate conditions, then that risk, in my judgment, would be so high as to make me recommend its use not be continued.

Senator SCHWEIKER. Because you admit under certain conditions, such as a woman being pregnant prior to usage, there are certain risks. Even a good doctor, following every regulation that FDA prescribes, cannot eliminate certain risks.

I'll get back to the question: Is not causing one person cancer a little too great of a risk to take?

Dr. RAUSCHER. It certainly is too great a risk. What I am trying to do is balance that risk against the greater risk, in our judgment, of the real diseases that occur during the traumas of rape, of possible pregnancy, of worrying about pregnancy, of a possible abortion and of guilt associated with that, throughout the rest of your life because of the abortion. That is also a serious problem.

We think by at least making this available under controlled conditions to these emergency cases, we might be able to do something about those problems, as well as limiting the number of cancers—

Senator SCHWEIKER. I, as a father, would have a great deal of difficulty after hearing the witnesses this morning telling my daughter to take that minimal risk. I certainly would have great personal reservations about my own family, if such a decision had to be made by me as a father, whether to take that risk.

I know it is great to talk in terms of percentages of who we help and who we hurt, but after hearing the witnesses this morning, I would really have trouble telling my wife and children to go ahead and take that risk.

I think it is a pretty tough decision to make. The problem I see is when an FDA approval is given, or when a letter saying that a drug is FDA approved for certain things, people do not assume those risks are there and they think somebody assessed that risk for them, and came down in their favor.

I think that is the presumption that we in the Government, who work with these problems, have to make. I am not really, Doctor, directing my comment specifically to you; I am rhetorically asking the question of what our responsibility is here. As a father I would have real trouble saying, notwithstanding all the risks, go ahead and use DES after hearing the testimony this morning.

Well, let us hear from Dr. Schmidt, unless you want to say something. I really did not ask you a question.

Senator KENNEDY. Dr. Schmidt, we welcome you here this morning, and look forward to your testimony.

Dr. SCHMIDT. Thank you, Mr. Chairman.

I would ask that I be able to submit my testimony, because I think it is important.

Senator KENNEDY. Sure.

Dr. SCHMIDT. Second, I have listened very carefully and sympathetically to all of the testimony this morning, and I think it has been very important testimony.

To me, in a very real sense, what we have heard this morning is that the issue we are talking about, basically, is the widespread use of an approved drug for nonapproved use. I am very concerned about

this problem, and I want to work with Congress and with the medical profession to solve it.

If the issue is that the Food and Drug Administration should not approve a safe and effective drug because of the possibility of or the demonstration of its misuse by a certain number of physicians, then I think that we will need the help of Congress to work through this problem.

As you have heard this morning already, diethylstilbestrol is a synthetic female hormone, and it is one member of the class of estrogens. It has achieved wide use in medicine and animal husbandry because it was the first estrogen compound active after oral administration to become available.

Diethylstilbestrol has the usual properties of all estrogens. This is an important point, and I think one that has not been addressed by a number of witnesses this morning, but we may well be coming back to this point.

DES, with other estrogens, is a feminizing hormone and used in medicine as replacement therapy in estrogen-deficient states, and for the treatment of cancer of the breast in certain patients and for cancer of the prostate in the male.

Senator KENNEDY. As you point out, here, DES has usual property of all estrogens. Have other estrogens been associated with the same cancers as DES?

Dr. SCHMIDT. Yes. Well, a qualified yes. The studies that have been done in animals show that DES is no different than other estrogens in being the kind of carcinogenic—

Senator KENNEDY. What about humans?

Dr. SCHMIDT. Because of the unique uses of DES in certain human conditions, studies have been done in persons that have been exposed to DES. Other estrogenic preparations have not been used to the extent that DES has, so we simply do not know with the other estrogens, as we do with DES, whether or not they would have the same potential hazards. It is my belief they would.

As you have heard this morning, other estrogens have been and can be used for the purposes of DES. One of the difficult questions then posed for me is: If one takes action against one member of a class of drugs, one must logically take that action against the entire class of drugs.

Senator KENNEDY. What does this say about birth control pills?

Dr. SCHMIDT. This says that in all probability, any hazard that is associated with the use of DES as a morning-after contraceptive, would be associated with the use of other estrogens as a morning-after contraceptive.

Senator KENNEDY. Dr. Rauscher, can you accept that?

Dr. RAUSCHER. Yes, I can. I think other estrogens would have the same effect in humans, postcoital, certainly based upon our model systems in animals.

Senator KENNEDY. Well, can you leave birth control pills on the market?

Dr. SCHMIDT. Well, again, no one has spoken this morning to the estrogens that are essential ingredients in oral contraceptives or in the pill. I believe that this is another type of benefit-risk judgment that is a good one to examine.

Senator KENNEDY. Dr. Rauscher, what about it? You have expressed the gravest kind of concern about DES, advocate it to be banned in terms of animal feed, only to be used in the most dire sources of emergencies. You have heard Dr. Schmidt, with which you have agreed, that other estrogens have similar properties, and that birth control pills have those particular properties.

Yet I do not hear you suggesting that we ought to ban birth control pills.

Dr. RAUSCHER. One thing we are doing is identifying populations very carefully throughout the world, for that matter, to see whether there is any increased risk to cancer from using birth control pills.

Senator KENNEDY. After the fact, this is after it is being used?

Dr. RAUSCHER. Again, estrogens, when used in the adult, young adult or older adult, female, even DES, as I pointed out in my testimony, we can detect—when they are used that way—we can detect no increased risk in the female. And based on that, at least in part, it has been felt that the birth control pills were safe.

Senator KENNEDY. But you do not know what the impact of birth control pills would be on daughters of mothers who are taking it?

Dr. RAUSCHER. We do not know. Because of the very low dose, I think it is on the order of 2 or 3 milligrams, it varies, we would expect the risk to be small. But we do not know.

Senator KENNEDY. But present?

Dr. RAUSCHER. Yes, indeed.

Senator KENNEDY. Do you think we will be back here 10 years from now on another hearing on this?

Dr. RAUSCHER. I pray we will not. This is one of the reasons we are doing our monitoring now.

Senator KENNEDY. We will not know until another 10 or 12 years, so when people get it—

Dr. RAUSCHER. We will not know.

Dr. SCHMIDT. A point that Senator Schweiker spoke to, a risk we are now talking about, is the risk to the female offspring in the event of a failure of the oral contraceptive to prevent pregnancy or the risk to the female offspring in the instance in which DES fails as a morning-after pill. The group in which the risk has been identified is that of the female offspring. No risk has been identified to those taking diethylstilbestrol with that one exception. So, the failure rate then is of great significance here.

Senator SCHWEIKER. What you are saying, then, if I understand it, is if the birth control mechanism fails, no one has determined the possibility that the same incidence of cancer among the female offspring could occur for people using birth control pills as have been given the DES for treatment in preventing miscarriages. That could be a possibility. Obviously we do not know. You are confirming we do not know?

Dr. SCHMIDT. Yes, we addressed this very specifically in both the patient labeling and physician labeling of diethylstilbestrol, and it is also the reason we are requiring that it be packaged in a special way, for use as a morning-after contraceptive.

Another thing that has not been discussed this morning in a balanced way is the number of times that the physician would be put in a position of recommending abortion, or that the patient would have to

choose either abortion or carrying the child that resulted from the unprotected intercourse as an alternative to diethylstilbestrol.

If one then wished to avoid this risk to the female offspring, then the choice you are posing to your daughter or to the patient is to have an abortion or to carry the child and that is something that is, as Dr. Rauscher said, a very significant factor in this equation.

We have evidence from psychiatrists and others that the trauma of the rape is in good part the fear of the pregnancy in what is being carried in the womb of the woman.

Senator SCHWEIKER. That is true, Doctor. But I am not sure, given a known fear of cancer in their female offspring, if they would make that same choice, and the tragedy is they do not know.

And there is another factor they do not know.

Dr. SCHMIDT. The issue is whether or not a woman should have, and the American physician should be able to counsel with the woman, the options of carrying the child to term, having an abortion, or taking relatively small doses of diethylstilbestrol for 5 days, when there has been no risk identified to the lady taking the pill. When she is fully informed that were she to have a failure and we have some idea of the failure rate, which is low, then she would be faced with, again, the decision as to whether or not to have an abortion.

That is the basic question that was put to the Food and Drug Administration to answer.

Senator SCHWEIKER. I was commenting on the fact that many people taking the pill I do not think are fully aware of what happens if they make a mistake. Given the choices because of an error with the risk that their offspring may have cancer; I just wonder how many people will really make the judgment they have been making.

I think it is the duty of our Government to inform people of their choices, even though they may not be making the very choice that you say is to their benefit.

My question is: Do we have any research ongoing on this very question? Do we have to wait for Dr. Herbst to tell us 10 years from now, as Senator Kennedy said?

Dr. SCHMIDT. As I understand it, the question you are posing would be answered by a survey of women. Faced with this series of choices, would they wish to have, as a choice, diethylstilbestrol.

Senator SCHWEIKER. The last question I asked was: Do we have any research now under the Government's direction to determine whether, when somebody misses with the pill, that their offspring may have cancer like these ladies here before us experienced? That is my question, and I think, in view of what you are saying now, it is a pretty important question.

Dr. SCHMIDT. Yes. And Dr. Rauscher spoke to that. It is a terribly important question, and one that should be answered.

Senator SCHWEIKER. I think FDA has the responsibility to answer it.

Dr. SCHMIDT. Sir, I have been fighting for more research funds for the Food and Drug Administration. I would love to take this opportunity to agree with you; but basically I think that the research question you pose is NCI.

Senator SCHWEIKER. Is that not a question we should answer before we widely disseminate a product? Is that not something we should do before we put a drug on the market that says FDA approved?

I think that is a very fundamental question.

Dr. SCHMIDT. You are making a terribly important point, one I tried to make, and that is, that the issue of unapproved use of an approved drug, and the issue of the rarely occurring adverse reaction is a terribly important one, and one that we have not addressed in this country well.

There are certain things that one can find out about a drug only with widespread use of that drug.

The last time I appeared here we were talking about the Dalkon shield, and there are certain things that can be learned only after insertion of a few million medical devices.

There are only things you can learn after, in effect, commercial distribution of a drug.

One of the issues that is before all of us, Congress most particularly, because I think it will take legislation, is the issue of the system of adverse-reaction drug reporting, and how the Food and Drug Administration can move to take regulatory actions.

We will probably be talking at some point this morning about formal evidentiary hearings and due process. The Food and Drug Administration is operating under the law as passed by Congress, and this includes what I consider to be due process types of actions. With diethylstilbestrol and animal feed additives, this is, in fact, the issue right now.

But the basic problems we are addressing this morning, to me are problems that go to the heart of the drug approval process in this country and to the way physicians practice medicine.

Hopefully, we realize that and can address these problems.

Senator SCHWEIKER. Do we currently have any research going on to answer the question? I just keep coming back to that.

Dr. SCHMIDT. Yes.

Dr. RAUSCHER. Yes.

Senator SCHWEIKER. In that specific area, female offspring of people using estrogens and something goes wrong?

Dr. RAUSCHER. We have on the order of \$20 million per year in what we call our demography or epidemiologic surveillance programs in various parts of the country. This kind of exposure or possible cancer effects on women taking the pill or of unusual cancers in the offspring of women taking the pill, where it is a failure, would be picked up through these programs.

But these things take up on the order of 5 years or more to accumulate enough unusual cancers, as Dr. Herbst found.

Senator SCHWEIKER. It is going on now, but will take 5 years to get an answer?

Dr. RAUSCHER. It has been going on for 10 years. It could well take more time to get the answer. Our entire population is under constant surveillance.

Dr. SCHMIDT. I cannot refrain from adding one point—

Senator KENNEDY. Could I, just on this point, in response to Senator Schweiker's comments, I think you have framed one of the issues, and that is, when the Food and Drug Administration approves the drug for a particular use and it is not approved for other uses, how are we going to prevent use for purposes for which it was not approved?

I gather from your response, you have neither the manpower or authority to do it. If we in the Congress prohibit you from saying

that you approve for certain reasons and not others, and we say obviously we find risk on the one side, that may be used for certain purposes, and those are the wrong purposes, and therefore we are going to ban it completely, when it may be used for some legitimate purposes; then that is the wrong kind of legislation in terms of trying to assure decent health. When we do come down, I think that it is the responsibility of the medical profession to insure that they are not going to be using the drugs for the purposes for which they are not approved, a very, very heavy responsibility in this area; and we cannot legislate that particular kind of sense of judgment nor do I think we should.

When we hear the principal spokesman for organized medicine appear before the committee and say: Senators, we do not care what are going to say or do, if we think it is in the best interest, no matter what the Food and Drug Administration or no matter what the National Cancer Institute or no matter what scientific opinion has been expressed, we want to be able to use that, we are going to.

This is the position which is taken by organized medicine and by a great many of the practicing doctors and physicians.

Any kind of suggestion that they ought to do otherwise is always sort of used as a flag to say: Well now, you are talking about interfering in the orderly processes and practices of medicine.

I think what we are seeing here this morning, obviously we are looking at a variety of different factors, but obviously on this particular drug, that is what we want to get back to.

I think, Dr. Rauscher, you have outlined the general kind of approaches you have taken to deal with the possibilities of estrogens and the implications that they can have for future kind of generations, and you have outlined that you are watching that and are going to be on top of that. We are thankful for that and hope you are going to be extremely effective.

But in this particular instance, what we have seen here is—whether procedures were right, for development of a particular kind of approval, the fact that it was approved at the time when it really was not approved, and the fact that it came to the attention of the Food and Drug Administration, the publication of the Bulletin over a year ago—was it 2 years ago—and that there was not anything done to correct it, and the fact that we get what I think has been an extremely valuable testimony in terms of the widespread use of it and misuse of it, and are still unable to deal with it and cope with it.

This brings us right back to where we were at the outset of the hearing this morning, when those three witnesses testified in terms of the tragedy it brought to them.

So these matters are closely related.

I want to try to get back on the track of the purpose of this hearing today, and the reason for it, and what FDA is doing.

You indicated you wanted to go through your statement, and we are well into it. In any event, and I will be glad to go along with whatever way you would like to proceed.

Dr. SCHMIDT. I would like to go through my statement, because there are very important points in it, and I will try to do it quickly.

DES has two important properties of particular interest to today's subject: DES prevents pregnancy if administered at or shortly after

intercourse, even if the woman is at her most fertile period, midway in the menstrual cycle. Also DES is known to produce cancer in several animal species.

I think in view of this information, very understandable concern has been expressed as to whether or not the use of DES for postcoital contraception in emergencies is justified.

We have considered these issues in great detail and we have concluded that under the conditions that we have described and established, our approval is both justified and in the best interest of the public.

Our decision to approve DES for use in emergencies carries with it very specific conditions. First of all, the one-time course of 10 tablets necessary for this use will be put up in a single package unit and dispensed as such to the patient by prescription only.

Second, the package will contain, in addition to the tablets, a patient leaflet and this leaflet is forthright in stating the potential hazards of the treatment and the conditions essential for its use.

The patient leaflet and package inserts for the physician both stress the importance of limiting the use of DES to emergency situations, as for example rape or incest. The patient leaflet emphasizes, and I quote: "If you find it necessary to use this treatment more than once, you should consult with your physician to obtain an adequate means of routine contraception."

Senator KENNEDY. Now, just before leaving that, how is that really going to be any different from your pamphlet of 1973? I mean, what you have outlined there as terms of procedures, how is that going to really be any different from what was outlined in 1973 and we have heard during the course of the morning's hearings and otherwise—

Dr. SCHMIDT. Well—

Senator KENNEDY. If I can just finish—that we are still getting very broad misuse of the drug in spite of all of these points that have been made.

Dr. SCHMIDT. What was printed in the drug bulletin is a description of what has not yet happened.

Our thesis is that when there are no other forms except this special package and when the package itself includes patient insert, and the patient gets and reads that, and when the labeling to the physician states that it should be used only once and for emergencies, and so on, and this is explained by the physician in obtaining the patient's informed consent, then these factors will control in a reasonable way the use of the drug.

Recently, we have talked with some universities, and its use has been decreasing as a result of, No. 1, the drug bulletin, and second, the publicity that is being given to the patient package insert, and so on. But up until now, there has not been a patient package insert given to the patients, so there is a difference.

Senator KENNEDY. You mean you are putting an awful lot of faith in a patient package insert. Is that going to be satisfactory, Dr. Rauscher, giving the package insert on this?

It seems to me what you were warning in your 1973 bulletin, you talked about emergency measures, the agency considered the use of DES to be safe only as an emergency measure, rape and incest. You used those very same kinds of things you are talking about in here now. And then we have Dr. Greenwald—and it also indicated that

the FDA had approved it. Now we hear from Dr. Greenwald and others about the expansion of the use of this drug. You say it is contracting. They say it is expanding, in New York State certainly. And it seems to me that that puts a very substantial burden on the insert.

I think that to think that is going to remedy the situation is not satisfactory in terms of the nature of this whole—

Dr. SCHMIDT. As I say later in my testimony, one of the things that this approval will do is to give us the means to find out how much is being manufactured and sold for this purpose. And we will be able to answer some use-type questions that we have not been able to answer before.

Also, we are labeling other dosage forms, "not for use as a morning-after contraceptive." We think that this will also have an impact.

Senator SCHWEIKER. I admit the wording is clear on the insert, no question about that. The problem I foresee, though, is a person in for treatment after rape and so emotionally upset, that I think the last thing she will be doing is reading the insert. She starts taking the pill. She either reads the insert after taking it or gets sick and discontinues it. Do you not have the worst of both worlds? You have exposure with the possibility it would not be effective because of discontinued usage.

The insert, while laudable, read under normal conditions, might act as a deterrent; under emotional conditions I wonder if it really does?

Dr. SCHMIDT. Well, for this reason we have also urged physicians to be sure that they explain to the patient the conditions under which we consider its use to be safe. And you know, the basic question, I am sorry, but I must come back to the basic question that is underlying your questions, and that is, should the Food and Drug Administration take estrogens off the market?

Senator KENNEDY. That is not the issue. That is a red herring. That is a red herring, Mr. Commissioner.

Dr. SCHMIDT. What are our legal options then?

Senator KENNEDY. Why can you not just not approve it?

Senator SCHWEIKER. For this particular use.

Senator KENNEDY. I mean, here you had it approved for these purposes, even though it was not limited to those purposes, you have already indicated. Then you say because you are going to have a package insert, that is going to change the behavioral pattern.

Have you got any indication in the Food and Drug Administration that at any time that you have included such a package insert for patient guidance that it has changed or altered or affected the favored or best use of a particular drug?

Dr. SCHMIDT. We have some information from surveys that women read and pay attention to the package insert in the oral contraceptives. We also have—

Senator KENNEDY. Can you submit that to us? And has it changed the pattern of usage?

Dr. SCHMIDT. No; I cannot say that.

Senator KENNEDY. That is what we are talking about here.

Dr. SCHMIDT. Well, that type research is beyond our capability and budget.

Senator KENNEDY. Well, it is beyond, then—why do you believe that is going to meet the problems we have heard here today about

continued use, expanded use? You say on the one hand we are going to have a package insert, the patient is going to be able to read it; then we ask what evidence do you have to show that really achieves or accomplishes anything. You say, "Well, we have evidence that they read it, but we do not have any evidence that changes it,"

Here Dr. Rauscher says given the kind of usage we are having today, it presents a serious health hazard.

Dr. SCHMIDT. You heard testimony this morning that 75 percent of the women who had taken DES said that had they known of its recommended use and hazard, they would not have taken it.

I think that that is information that informed consent is important and would be meaningful.

The options that were available to us, as I discussed in the testimony—perhaps it is best that I go on with the statement.

Senator KENNEDY. Well, could you not recommend that this kind of substance only be approved under a controlled substance basis?

Dr. SCHMIDT. Well, it is my understanding of the act that it would have to be changed before we could do that.

Senator KENNEDY. Has anybody suggested it? Has anybody come up to talk to any Member of the Congress and say, "We have got an item here. These are the results that we found. We believe if it is going to be used it ought to be a controlled substance; we recommend this kind of change in the legislation"?

Do you think it would take 1 hour or 2 hours to bring about that kind of a change when it offers this kind of a health hazard, and you have got the overwhelming kind of evidence that has been presented here?

Dr. SCHMIDT. Overwhelming kind of evidence about what?

Senator KENNEDY. The overwhelming evidence that the daughters of mothers that used this kind are in a high incidence of having either vaginal cancer or cancer of the cervix.

Dr. SCHMIDT. All right. And we made a benefit-risk decision and that is that the diethylstilbestrol as a morning-after contraceptive is remarkably effective.

Studies that were presented to our advisory committee stated that not a single pregnancy resulted in 1,000 cases.

The number at risk is the number of failures, which is something around, say, in 1,000, and half of that for the female children. And then you still have the option of abortion.

So, you should not imply that large numbers of people will be at risk of cancer of the vagina. And there is no evidence of risk in those who take the pill.

So that is the risk to her equation, and the benefit side of the equation is whether or not American women subjected to rape and incest, institutional types of rape, and so on, and the physicians caring for them should be able to make an informed judgment, knowing the risk, to use diethylstilbestrol.

It was my judgment that given strictly limited conditions, this benefit-risk decision came down to the side of the benefit. And we have, therefore, approved it.

Senator KENNEDY. Are you satisfied with the uses of DES as a morning-after pill in this country at this time?

Dr. SCHMIDT. No; I am not.

Senator KENNEDY. Why not.

Dr. SCHMIDT. Because the evidence that I have before me is that it is overused.

Senator KENNEDY. Why? What is the danger of overuse?

Dr. SCHMIDT. The danger of overuse is small, very small.

Senator KENNEDY. What is the danger?

Dr. SCHMIDT. Finite.

Senator KENNEDY. What is it?

Dr. SCHMIDT. It is, basically, that some very few numbers of female offspring in the failures—because the girl did not complete the course, or for whatever reason, maybe carried to term, and these female offspring may be at risk. This should be minimized.

I do not think that this is an easy route to a lot of partying. I mean, this must be the subject of very tough decisions on the part of the parties involved in tragic situations. Now, we—

Senator KENNEDY. What about—

Dr. SCHMIDT. We are saying in the testimony that we are admittedly doing several things to address the problem of this widespread unapproved use of an approved drug. The use of the ANDA—

Senator KENNEDY. If I could go back to part of your answer, is not one of your problems, also, adenoses? That we heard testimony about here today as well? Ninety percent—

Dr. SCHMIDT. Again, that is in the offspring.

Senator KENNEDY. What?

Dr. SCHMIDT. Again, that is in the offspring.

Senator KENNEDY. That is right, in 90 percent of the offspring.

Dr. SCHMIDT. But it is 90 percent of what? Ninety percent of the failures of the drug to act as a contraceptive, and it is remarkably effective.

When it is effective, there is no risk, because there is no offspring and there is no adenoses and there is no adenocarcinoma of the vagina.

Senator KENNEDY. Well, Dr. Rauscher, we are talking about the real world here, or what are we talking about? Should we be worried? Concerned? Or what?

Dr. RAUSCHER. We should be worried if we cannot monitor the use of this drug.

If it is used for the purposes as we describe it, that is emergencies, the number at risk must be exceedingly small. But unless that can be assured, I would fall back on my statement that—

Senator KENNEDY. Well, we are talking about the real world here, we are talking about doctors and the use of this particular drug. What kind of assurances can you give to us, in terms of the attitude of doctors in this country, that they are going to do something different in terms of the use of this drug which both of you have indicated is being widely overused or misused? What are they going to do today, given the kind of orders put out by the FDA, they did not do 2 years ago. We find the same drug, the same kind of warnings about the dangers, the same kind of indication that it should be used only for rape or incest. Why are we going to have other than a continuation of what I think Dr. Rauscher has indicated is a health hazard and as you, Dr. Schmidt, have indicated, poses a health problem? And which Lilly says itself is unsafe to market.

Dr. SCHMIDT. The point I am trying to make is that the circumstances after the approval will be different than the circum-

stances before approval in the very real sense, that approval of this indication with conditions is a means of controlling the use of the drug. If it is not, we will contemplate other action.

That is a very important point. Our options are to ignore the situation, or to try to control the situation by taking the initiative to say, "Look, people, look American physician, this is when it should be used. You have got to inform your patient." And for us to say, "Look, patient, this is what you should know."

Now, if the option is ignoring it, ignoring and not trying to come to grips with the use that has been going on, I say I want to try what we are doing.

Senator SCHWEIKER. Is it not——

Dr. SCHMIDT. If it does not materially affect the circumstances that are now around the country, we will contemplate other action.

Senator KENNEDY. Well, the point is, Mr. Commissioner, that you put the bulletin out 2 years ago. It was out there 2 years ago, and I do not find anything that you have done in the meantime which would indicate any kind of followup or any kind of a policing of the particular program.

You did not either recall the bulletin or send a flash bulletin out, or anything else. You sent one out at a time when it was not approved. Was it approved at the time you sent it out?

Dr. SCHMIDT. No, sir; it was not.

Senator KENNEDY. Well, it was not approved. You sent it out. It was out for 2 years. And we do not find either withdrawal of the bulletin or an attempt to police it during that period of time.

Now, you say, well, things are going to be different. Things are going to be different.

Dr. SCHMIDT. That is true.

Senator KENNEDY. Well, why should we have any sense of confidence that things will be any different when we find out nothing was done for 2 years when the bulletin was out, that the bulletin says it was approved when it was not approved; when we find out that the regular procedures that were followed in the FDA in getting a new drug approval in any event, circumventing what had been the established procedures of the Food and Drug Administration. Why should we feel there is going to be anything more done on this?

And given the fact of this being a serious health hazard, why should we be any more salutary that the interest of the consumer is going to be protected in this way?

Dr. SCHMIDT. No. 1, the drug bulletin has had some effect.

No. 2, there is a difference of fact——

Senator KENNEDY. In what respect?

Dr. SCHMIDT. Sir?

Senator KENNEDY. In what respect has it had some effect?

Dr. SCHMIDT. We learned from calling some college campuses that the statements in the drug bulletin, namely that the Agency considers the use of DES for this purpose to be safe only as an emergency measure, such as rape or incest, that physicians are urged to inform patients, and so on and on, that that had an impact on some physicians' use of the drug. And further, the drug bulletin did not put into the hands of patients the information provided by the package insert.

What will be different in the future is that, No. 1, DES will be in a special package with a package insert, it will have the special physician

warning; no other 25 milligram-dose sizes other than 25 milligrams will be out. All other dose sizes will be labeled not for use as a morning-after contraceptive.

These are differences that will occur when an ANDA is approved.

You keep coming back to saying that a drug associated with a huge risk has been approved; in actuality, were there a huge risk involved with this, I would not have approved it. There is not a huge risk involved in this use.

Senator KENNEDY. Well, Dr. Rauscher calls it unacceptable.

Dr. SCHMIDT. I am sorry, he can speak for himself, but that is not the way I interpret it.

Senator KENNEDY. Well, he is speaking for the head of the Cancer Institute, he is speaking for a lot more than himself.

Dr. SCHMIDT. Dr. Rauscher's testimony said that he agreed with the benefit-risk judgment that I made.

Senator KENNEDY. For the limited use.

Now, why you believe that a package insert is going to do very much is just amazing to me when you are unable to give us any kind of assurances, other than general comments, that it would.

The University of Michigan program, they had a package insert. You would have an insert, talking about it as a morning-after pill with a lot of the different kinds of explanations about taking it and some of the risks, and evidently we heard from the testimony here that it did not reduce the amount of use.

And here you say that you are going to go ahead now and do the same thing all over again, because you are going to have a package insert you can expect some change.

Dr. Rauscher, would you be satisfied with a package insert?

Dr. RAUSCHER. Not only a package insert, I certainly would not be satisfied if it did not work.

Senator KENNEDY. Pardon?

Dr. RAUSCHER. I said not only with a package insert, and I certainly would not be satisfied with that if it did not work.

Senator KENNEDY. What else do you think could be done?

Dr. RAUSCHER. I do not know.

Senator KENNEDY. Well, that is a pretty tough comment, is it not? When you have the danger that is out—we have listened to the witnesses that we heard earlier today. We cannot say, we do not know what we can do to those three people who testified this morning.

I think we know what we can do and if that is to have to change the control substance act, we ought to do it this afternoon. And if it takes legislative change, we ought to do that right away. And insure that we are not going to have that.

It seems to me, that we ought to stop the use of it until we do know what we are doing.

Dr. SCHMIDT. Where is, would you control 'benthol?

Senator KENNEDY. Yes.

Mr. SCHWEIKER. Dr. Schmidt, you ask what options do you have. It seems to me there is one option you are overlooking. When you have conditions for misuse and evidence of blatant misuse, it would seem to me you would have to crank into the risk/benefit equation a misuse factor.

You have apparently taken the position that until you find there is a misuse factor a year or two from now, it will not be cranked into

the equation. It just seems to me that one of the things FDA ought to consider is the misuse factor. It just seems to me it is a very key factor that ought to be accounted for before the fact, rather than after the fact, particularly in light of historical evidence.

Dr. SCHMIDT. Mr. Chairman, I think, you know that we are very concerned about this basic problem with methadone now in court and, in a sense, depending on the decision of the judge, or judges, in the methadone case, we will have a better case of what is considered legal and illegal for us to do in controlling distribution and use of the drug.

In the testimony this morning, you heard it said that 65 percent of the girls who had taken DES had stated that had they been fully informed about DES, they would not have taken it in the first place.

Now, this is admittedly soft data. And yet, I think it fair to accept that informed consent might cut the use down by 65 percent.

We will do everything we can to find out if informed consent takes place which I think is terribly important. The package insert is not the same thing. Nor is it the same as the Michigan situation.

Senator SCHWEIKER. To answer my question, you are saying, in this situation you have not taken into account the factor of misuse before your decision regarding DES, is that not a fact?

Dr. SCHMIDT. Yes, sir; I have taken the action because of potential misuse and in my testimony I say and I am saying right now that we will monitor the use. And if the premise of our argument is proven to be false and that is that misuse continues or increases we will then contemplate and take some other action.

Senator SCHWEIKER. Well, how could a bulletin that erroneously indicated FDA approval for 2 years not be withdrawn? And you are saying here you would monitor it.

How do you account for 2 years nonwithdrawal?

Dr. SCHMIDT. All the drug bulletin did is specify the conditions under which it would be marketed as a postcoital contraceptive. None of that has taken place yet, so one cannot say whether or not informed consent would diminish its misuse.

Senator SCHWEIKER. But it is on the market now for other purposes, is it not?

Dr. SCHMIDT. That is correct, and so are other estrogens.

Senator SCHWEIKER. Dr. Schmidt, you certainly could take the next logical step.

Dr. SCHMIDT. Should we take tremin off the market? Is that what you suggest?

Senator SCHWEIKER. My whole point is how are you going to monitor, safeguard, or supervise, the use of DES, when for 2 years you have had an erroneous published statement not withdrawn? That is the inconsistency I have trouble understanding.

Dr. SCHMIDT. The statement that appeared in the drug bulletin, in my view, is clearly in error.

Senator KENNEDY. What did you do about it?

Dr. SCHMIDT. However, the only thing that is in error about it is the statement that we had approved it. It seems—

Senator SCHWEIKER. That is pretty key; is it not?

Senator KENNEDY. Do you think of two more important words?

Senator SCHWEIKER. Yes; what else are we talking about? Whether it is approved, whether it is safe?

Dr. SCHMIDT. It says that we and our advisory committee, consider it safe and effective—under these conditions. And we listed those conditions.

And that is true. It was premature in saying that we had approved it in the sense that the Federal Register publication, and so on, had quite clearly not taken place.

The advisory committee meeting had been held and, as you can read, the statement that appeared described the strict conditions for use quite accurately. And I will not sit here and defend that being in there. But I would point out that it would be unfair to say that the drug bulletin article was in error other than its being before-the-fact approval.

Senator SCHWEIKER. That is sort of the bottom line; is it not, Dr. Schmidt?

Senator KENNEDY. It is the bottom line.

Dr. SCHMIDT. I think the bottom line—

Senator SCHWEIKER. The article is right, but the bottom line is wrong.

Dr. SCHMIDT. For the people you know, the significant thing is the safety and efficacy—

Senator KENNEDY. The bottom line, Commissioner, is in, I am sure, thousands of sheets printed, this one at the University of Michigan that says FDA approved use of the drug.

It does not have all the other words of your bulletin. It has those particular use of words and those are the bottom line.

Dr. SCHMIDT. That is precisely the importance of requiring a package insert and informed consent.

Senator KENNEDY. They had a package insert. They had this.

Dr. SCHMIDT. No; I will not accept that, that was an information sheet by the university. That is not a patient package insert.

Senator KENNEDY. I see.

Well, we covered most of this.

I had just one other area I was interested in, and that was on the use of DES in feed, in cattle.

Do you want to just talk to this?

We will, of course, include it, but that is really the only other area I want to touch on.

Dr. SCHMIDT. All right.

As I think most people know, we banned the use of DES in animal feed January 1, 1973, and we later banned the use of DES implants in livestock.

In January of last year, the U.S. Court of Appeals for the District of Columbia overturned our decision. The reason for the court's decision was that we had denied the sponsors of the new animal drug applications for these uses an administrative hearing.

We did not believe that there was an issue of fact on which to base approval of a hearing request, but the court disagreed.

While we disagree with the court's decision, we nevertheless now must hold the hearing as directed.

Senator KENNEDY. When was that issue? That was over a year ago?

Dr. SCHMIDT. The court of appeals decision was in January of 1974; yes, sir.

Senator KENNEDY. It is 1 year now. You still have not held a hearing?

Dr. SCHMIDT. That is correct.

Senator KENNEDY. Why is that?

Dr. SCHMIDT. I go on to explain; perhaps the best thing to do is to go through this testimony.

Senator KENNEDY. All right.

Dr. SCHMIDT. The issues for the hearing will include whether DES is safe within the meaning of section 512, which is the animal drug amendment of the Federal Food, Drug, and Cosmetic Act.

The hearing may also consider whether the methodology currently approved, or available for detection of DES in tissue, is sufficiently sensitive or suitable as a regulatory tool.

Now, the F.D. & C. Act exempts from the Delaney clause carcinogenic substances if, under conditions of use specified in labeling and reasonably certain to be followed in practice, no residue of such substances is found in edible tissues of animals after slaughter, using methods of examination prescribed by regulation.

Such methods were published in 1963 and have not since been modified.

To insure that methods appropriate to current scientific knowledge are used to assure the safety of our food supply today, we published in the March 1974 Federal Register a proposal to revoke existing methods for DES.

Final order on that proposal is being held in abeyance until the major issue of the level of sensitivity for an adequate method of analysis for a carcinogen in edible tissue is resolved.

In the Federal Register of July 19, 1972, we published a proposal setting forth the principles by which any method for analysis of an animal drug for which a zero tolerance is established would be determined. That proposal has resulted in substantial scientific discussion and disagreement.

Resolution of the scientific issues raised by that proposal has involved personnel in several bureaus of the Agency, as well as in my office. It is unquestionably one of the most important, as well as one of the most complex, proposals ever issued by this Agency.

I have concluded that it is absolutely essential that a final order be published with respect to this proposal before any hearing on DES is announced.

Certainly, a major issue with DES is the required sensitivity of the analytical method, and that issue must be resolved through the scientific principles to be included in this final regulation.

To try to put it in plain everyday language, I understand that under the Delaney clause, the important thing is that the Secretary or the Government approve a method, a regulatory method or method by which residues are measured.

As time has gone by, as you know, methods have evolved that are more and more and more sensitive. So that we have gone from parts per millions, to parts per billions, to parts per trillion, in our ability to measure, and I suppose someday we will get down and try to find one molecule.

The question is at what level should the sensitivity of the test approved by the Government be set. And this is an issue not only of

diethylstilbestrol, but with other chemicals and it is my judgment this issue must be resolved before we can have that hearing.

Senator KENNEDY. Well, there is no reason that you cannot abandon it during that period of time under your power as an imminent health hazard; is there?

Dr. SCHMIDT. We banned it and the ban was overturned.

Senator KENNEDY. As an imminent health hazard?

Dr. SCHMIDT. As an imminent health hazard? I do not have before me any evidence that would support any recommendation that it is an imminent health hazard, in the levels being found in liver of beef cattle, at this time.

Senator KENNEDY. You do not have the power to do that? The basis of the residues that are showing up now?

Dr. SCHMIDT. We have no evidence of there being a health hazard.

Senator KENNEDY. A carcinogen—you have not got the evidence? You did not think even though we have direct evidence, it is a human carcinogen, you do not feel under the statutory authority that you have now either sufficient evidence or power to ban it while you develop the criteria?

Mr. HUTT. Senator, this was the subject of discussion in 1972 in hearings before your subcommittee. At that time Dr. Rauscher and Dr. Edwards testified that, from a medical standpoint, they could not justify a medical determination to invoke the statutory requirement of a finding of imminent hazard.

Without the finding of an imminent hazard, we must hold a hearing before DES can be taken off the market.

This is probably one of the things in the statute that is most in need of revision.

Today the Food and Drug Administration, whether we are talking about an animal drug or a human drug, must consider, and deny or hold a full evidentiary hearing before it can remove a drug from the market.

Senator KENNEDY. We understand you did not hold the hearing and that was a mistake. And as I understand the difference, we had, as you pointed out, this hearing 2½ years ago, we are back to ground zero. At that time Dr. Edwards would not indicate it was a human carcinogen.

Dr. Rauscher, you say it is?

Dr. RAUSCHER. It is a human carcinogen based on—

Senator KENNEDY. What else do you need, Mr. Commissioner?

What else do you need?

I think under the Delaney language, under it, that you have got the complete authority and power to do it. What else do you need?

You have the head of the Cancer Institute saying it is human carcinogen. You have evidence it is showing up in increasing parts—

Dr. SCHMIDT. I think it is only fair for Dr. Rauscher to continue to talk, because there is more to say than what he said.

Dr. RAUSCHER. We believe, Mr. Chairman, that it is a human carcinogen, when administered to the female, carcinogen in the first trimestral of pregnancy.

It is not like many other carcinogens which, under certain circumstances, are not carcinogens.

Senator KENNEDY. Should pregnant women eat meat that has estrogen in it?

Dr. RAUSCHER. Certainly not.

Senator KENNEDY. You have the head of the Cancer Institute saying that.

What do you say? You do not have the power to put a temporary ban on this in order to develop?

Mr. HUTT. We have the legal authority if the Secretary—and this is nondelegatable—declares it is a imminent health hazard. At least up to now, the medical scientific determination has been that the small amounts of residues in the rare circumstances where they occur and with the unlikely event that anyone would eat enough of the particular organ of the animal in which it is found—namely, only the liver or kidney—are not sufficient that this could be declared an imminent health hazard.

If that medical and scientific determination were changed, then there would be a sufficient legal basis to take action.

I would suggest, Senator, that it is terribly important that Congress change the law and remove this restriction so that we could eliminate from the marketplace animal and human drugs which we believe unsafe or ineffective for any reason, whether or not there is an imminent hazard, before determining whether a hearing is justified.

Senator KENNEDY. Yes. We have had 3 years that we have been talking about this. We passed it in the Senate and basically because for one reason or another you did not follow your rules over there, in holding an evidentiary hearing, and your administrative ruling got knocked out. That was over a year ago. You have not had a hearing since.

I agree with you that we are going to act and we certainly are. But I do not see any reason why you people cannot. You are both in the same Department of HEW. Mr. Rauscher is the head of the Cancer Institute, Dr. Rauscher says it is completely inadvisable for a pregnant mother to eat any of the meat that has DES. You say you are not quite sure it is imminent hazard. The Secretary of HEW, you both work for him. I do not think we ought to make that decision, determination.

It seems to me it only makes sense to make that determination, to ban it, then to develop the procedures, and then go ahead. If they are going to reapprove it under certain control circumstances, do it that way, rather than just let it continue to be—

Dr. SCHMIDT. Senator, I believe a misleading statement has been made, or at least a misleading impression.

To my knowledge diethylstilbestrol residues identified in liver and perhaps kidney, and so on, but not in meat. I would not like the impression to be left that residues of diethylstilbestrol have been identified in meat unless one defines liver as meat.

Senator KENNEDY. Are you sure of that, Dr. Rauscher?

Dr. RAUSCHER. I believe that is correct; yes.

Senator KENNEDY. That there is none in the residue?

Dr. SCHMIDT. That is the whole point of the sensitivity, Senator. This is why I feel so strongly about holding a hearing on the important issue. Because if you said to me, if there is diethylstilbestrol in liver of a cow, do you think if you had a method sensitive enough you might be able to find a molecule floating around in a blood vessel some place, in striated muscle tissue? I would say probably you could.

The sensitivity of the method one uses is basic to the regulatory actions that we take and this has to be an issue in the hearing that we hold.

Senator KENNEDY. When are you going to have the technique?

Dr. SCHMIDT. We will hold the hearing as soon as we can after finalization of the order that sets the sensitivity of the matter.

Senator KENNEDY. When is that? Are you talking about a date?

Dr. SCHMIDT. No, we are not.

Senator KENNEDY. Months? Weeks? What?

Dr. SCHMIDT. The issue of setting of the sensitivity of the method is one of the most difficult ones that has ever been put before the Agency.

We published a proposal. We are through the comments. We are on probably the sixth or eighth final draft.

Senator KENNEDY. Will you support emergency legislation now until you get that through? Would you support emergency legislation now? Banning—

Dr. SCHMIDT. On what basis?

Senator KENNEDY. Banning it in animal feed.

Dr. SCHMIDT. On what basis?

Senator KENNEDY. As a health hazard.

Dr. SCHMIDT. No.

Senator KENNEDY. How about you, Dr. Rauscher?

Mr. HUTT. Senator.

Dr. RAUSCHER. Let me make one other point here. I think it is important to put on the record that most people feel it is unlikely that doses which are now in liver or in meat would induce cancer in people. On the other hand, my position has to be that we do not know.

Senator KENNEDY. That is right.

Dr. RAUSCHER. And that is the thing I have problems with.

Senator KENNEDY. Yes.

Dr. RAUSCHER. But the dosage is exceedingly low when it is present, but we do not know what that low dose is going to be.

It is my job to get that kind of information.

Senator KENNEDY. You can still eat meat without it, can you not? There are other countries that have abandoned it.

We are not banning meat here, are we? So you would support it?

Mr. HUTT. Senator, can I clarify one point?

When the Senate passed the legislation banning DES, it was limited to DES, which in my judgment was an error.

The problem is broader than DES. We have hundreds of drugs today that are on the market that the National Academy of Sciences has found to be ineffective, but that remain on the market because of the statutory prohibition against our taking them off the market until we have ruled on a request for an evidentiary hearing.

Legislation that would remove that barrier would allow us to act on DES without deciding the issue whether it is a health hazard.

When the Commissioner answered your question, he was answering that it should not be banned as a health hazard.

But it should be banned for other reasons; namely, the lack of assurance that it is safe.

We have no evidence it is a health hazard, but the burden should not be on the government to prove it is a hazard. The burden should be on the industry to prove it is not a hazard. Until they have satisfied that, then the drug should be banned even before an evidentiary hearing.

Dr. SCHMIDT. I thought you were going to ask me another question, at least I—

Senator KENNEDY. If we can get support for legislation, you can put it under whatever reasons you would like.

Dr. SCHMIDT. I am asking what basis—I asked what basis you would be banning it, and I would have a problem supporting legislation on the basis of a demonstrated health hazard.

Then I thought you were going to say, well, would there be any other basis?

Senator KENNEDY. Why do you not answer that one?

Dr. SCHMIDT. I would say probably, yes.

Senator KENNEDY. What would that basis be?

Dr. SCHMIDT. Well, there are several.

I am very interested in Lilly's testimony because it is good to hear that it is the responsibility of the industry to prove safety. I firmly believe that that is true.

I also believe that it is proper for Congress, in the name of the people, to make a benefit-risk judgment of a certain kind, and I would support the right and responsibility.

I have said many times that there are certain kinds of benefit-risk decisions that must be made by the people or by the people's representatives; these decisions are appropriate for Congress. And as I have said many times, I welcome working with Congress, resolving some of the problems that affect everybody in this country, that are a kind of basic benefit-risk questions.

Senator KENNEDY. Well, can you support legislation to ban?

Dr. SCHMIDT. Yes.

Senator KENNEDY. You can, Dr. Rauscher, and the only question is the reasons, the basis for it.

We are going to sit down with your people, starting this afternoon and work out the rationale so that we can introduce it at the earliest time possible.

Let me just as a final question, Commissioner, do you ever talk to Dr. Rauscher about this matter at all? The morning-after pill?

Dr. SCHMIDT. I am sorry?

Senator KENNEDY. Did you ever talk to Dr. Rauscher, given these various health issues that have been raised in terms of a cancer-causing agent, did you ever talk to the head of the Cancer Institute prior to the time you made the decision to approve the drug?

Dr. SCHMIDT. Because NCI has been involved all along in our discussions, in testifying before our advisory committee, in holding a seminar on the safety issue as a result of—

Senator KENNEDY. On this particular issue, DES?

Dr. SCHMIDT. Yes, sir.

Senator KENNEDY. As morning after?

Dr. SCHMIDT. I have known NCI's feeling all along, and I did not specifically talk to Dr. Rauscher. But I reviewed the NCI's position, their testimony, and their actions, and so on, as part of our approval process.

Senator KENNEDY. I want to thank you very much for coming up here. We will make sure the record is complete, Dr. Rauscher.

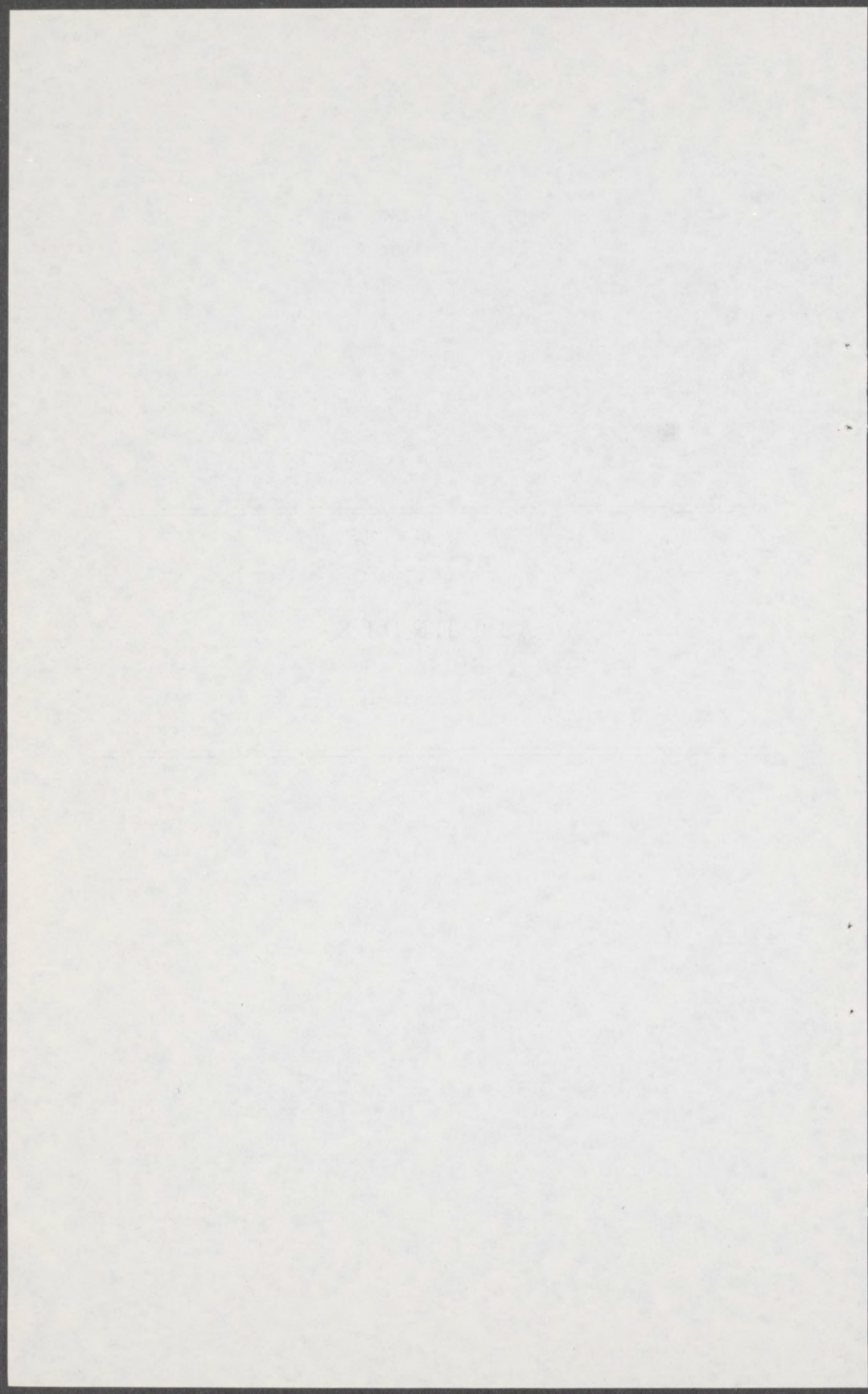
Thank you very much.

Dr. SCHMIDT. Thank you, sir.

Senator KENNEDY. The subcommittee stands in recess.

[Whereupon, at 1:23 p.m., the subcommittee recessed.]

APPENDIX



STATEMENT

BY

ALEXANDER M. SCHMIDT, M.D.

COMMISSIONER

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

BEFORE THE

SUBCOMMITTEE ON HEALTH

COMMITTEE ON LABOR AND PUBLIC WELFARE

AND

SUBCOMMITTEE ON ADMINISTRATIVE PRACTICE AND PROCEDURE

COMMITTEE ON THE JUDICIARY

UNITED STATES SENATE

FEBRUARY 27, 1975

Mr. Chairman and Members of the Subcommittees:

We are pleased to appear before your Subcommittees today to summarize our recent actions regarding the use of diethylstilbestrol (DES) as an "emergency" postcoital contraceptive and to provide a status report on the control of DES as an animal growth promotant.

Background

As you know, DES is a synthetic female hormone, one of the class known as estrogens. It was originally synthesized in 1938 and has achieved wide use in medicine and animal husbandry because it was the first cheap estrogenic compound active after oral administration to become available.

DES has the usual properties of all estrogens. It is a feminizing hormone and is used in medicine as replacement therapy in estrogen-deficient states, for the treatment of cancer of the breast in certain patients and for cancer of the prostate in the male. Although DES is not used in oral contraceptives, other estrogens are essential ingredients in the standard oral contraceptives known as "the pill."

Like all estrogens, DES also has two important properties of particular interest to today's subject:

- DES prevents pregnancy if administered at or shortly after intercourse, even if the woman is at her most fertile period midway in the menstrual cycle.

- 2 -

- DES is known to produce cancer in several animal species.

In view of this carcinogenic effect, it is understandable that concern has been expressed as to whether the use of DES for postcoital contraception in emergencies is justified. The Food and Drug Administration (FDA) has considered these issues in great detail and concluded that, under the conditions we have established, approval is both justified and in the best interest of the public.

Approval as an Emergency Postcoital Contraceptive

Our decision to approve DES as a postcoital contraceptive for use in emergencies carries with it certain conditions:

- The one-time course of ten 25 mg. tablets necessary for this use will be packaged in a single unit and dispensed as such to the patient, by prescription only.
- The package will contain, in addition to the tablets, a patient leaflet. This leaflet is forthright in stating the potential hazards of the treatment and the conditions essential for its effective use.
- The patient leaflet and the package insert for the physician both stress the importance of limiting the use of DES to emergency situations, as, for example, rape or incest. The patient leaflet emphasizes:

"If you find it necessary to use this treatment more than once, you should consult with your physician to obtain an adequate method of routine contraception."

- Since DES has no other approved indications requiring doses of 25 mg., all tablets of this size must be packaged in this special way or be removed from the market.
- All other tablets of DES, i.e., those containing 0.1 mg. to 5 mg. of the hormone, will carry a warning on both the container and in the package insert stating:

"This drug product should not be used as a postcoital contraceptive."

We believe these conditions are appropriate to assure the safe and effective use of DES as an emergency postcoital contraceptive, and I will discuss our reasons for this judgment in subsequent sections of my statement.

Carcinogenicity of DES

The evidence seems clear that DES can cause benign and malignant tumors in various organs of experimental animals. Similar tumors are produced by natural estrogens, and we are not aware of evidence demonstrating that DES is in any way unique among estrogens in regard to carcinogenicity. This carcinogenic effect has been shown in rodents (e.g., rats, mice, and hamsters) subjected to prolonged

- 4 -

periods of administration of the hormone (i.e., 25 percent or more of the lifetime of the animal). Usually, large doses are also required, but in some instances, this is not the case. Interestingly, the male hormone testosterone can also produce tumors in rodents if tested under similar conditions.

A subject of great interest, of course, is whether any evidence has appeared from human studies to indicate that DES or other estrogens pose a significant carcinogenic risk to the woman who takes them. While there is continuing scientific inquiry on this matter, the available data permit us to make the following observations:

- ✓ With respect to the long-term use of estrogens in oral contraceptives or as replacement therapy, the important epidemiological studies by Vessey et al., by Arthes et al., and by the Boston Collaborative Drug Surveillance Program indicate that such use is not associated with an increased risk of breast cancer.
- ✓ With respect to the use of DES itself in high doses, the recent work of Herbst et al. shows no significant difference in the subsequent incidence of cancer between women who received DES for threatened abortion 17-28 years ago and a matched control group.

Cutler et al. have reported a rare form of endometrial carcinoma in women with gonadal dysgenesis given DES for five years or more. We do not believe the findings are reasonably applicable to a five-day course of DES in normal women.

In regard to the association between the administration of DES to pregnant women and the occurrence of vaginal adenocarcinoma in their daughters, I would make the following points:

- When DES is used as an emergency postcoital contraceptive, risk to the fetus does not arise when the treatment is effective, since no fetus results. The patient leaflet and the package insert emphasize that effective use depends on starting the treatment within 72 hours of sexual exposure and continuing it for a full five days.
- A patient given DES as an emergency postcoital contraceptive must be evaluated to determine whether she has a preexisting pregnancy, in which case the use of DES is contraindicated. In the event of failure of DES to prevent pregnancy either because of treatment failure or because the patient does not take the full five-day course, the patient leaflet and the physician's labeling advise consideration of voluntary termination of pregnancy.

We believe that the combined measures of (a) evaluation for prior pregnancy, (b) careful instructions to assure a high degree of effectiveness, and (c) the option of abortion in the event of treatment failure will result in few children being born after exposure to DES as an emergency postcoital contraceptive. And even in such children the risk of vaginal cancer is low by comparison with the former use for threatened abortion, in view of the short course of DES and the fact that administration does not occur during the period of organogenesis.

Approval of DES as a Postcoital Contraceptive

The Food and Drug Administration addressed the problem of widespread use of DES as a postcoital contraceptive on its own initiative without an application before us from any drug firm. It must be understood that DES is a generic drug made by many manufacturers, none of whom came forward with data to support the use of DES for this indication. We, therefore, handled the problem through established procedures for public decisions, namely, public discussion before our Obstetrics and Gynecology Advisory Committee and the publication of regulations in the Federal Register.

The basic information relating to safety and effectiveness for this use was reviewed and presented to the advisory committee by representatives

- 7 -

of the National Institute of Child Health and Human Development. The regulatory action eventually adopted was developed in collaboration with the advisory committee, was published for comment in the Federal Register on September 26, 1973, and was modified appropriately on the basis of these comments. The final order, which becomes effective on March 8, 1975, permits marketing of DES for this use by any applicant who obtains an approved abbreviated new drug application. This kind of application is used for generic drugs when no additional data on clinical safety and effectiveness are necessary as part of the application. One such application has been received and is expected to be approved whenever it meets the conditions in the final order.

In addressing the problem of DES for emergency postcoital contraception, which was an important example of widespread use of a generic drug for an unapproved use, we considered four options:

1. Do nothing. i.e., ignore the use of DES as a postcoital contraceptive on the grounds that no application was presented to us. We considered this option as irresponsible in view of the widespread use and the safety issues involved.
2. Withdraw approval of DES as a drug. While some persons favor this position, no convincing case was ever developed by the responsible FDA staff or the advisory committee,

and this option was not exercised. An important consideration in this regard has been the prevailing opinion of experts that the safety issues related to DES properly apply to estrogens in general. There is therefore no current scientific basis for withdrawing DES per se from medical usage unless we are prepared to do so for all estrogens.

3. Contraindicate the use of DES for emergency postcoital contraception. We were, and are, prepared to exercise this option whenever the scientific facts justify it. However, we regard the use of DES for this indication as effective and safe under the conditions of approval.
4. Approve the indication with specific limitations and conditions which would bring this use of DES under proper regulatory control. We consider the scientific evidence in support of this option to be in accord with statutory standards of safety and effectiveness. This is also the most responsible option as it will allow reasonable control of this use of the drug as outlined below.

✓ The conditions of approval for DES as an emergency postcoital contraceptive have been adopted by regulation and are intended to accomplish the following:

- The patient leaflet assures that the essential information necessary for appraising risks, and for using the treatment effectively, is directly available to the user.
- The special packaging assures that only the number of tablets necessary for a single patient are dispensed with the patient leaflet in a single package.
- The elimination of all other 25 mg. tablets of DES assures that no other source of tablets for this indication is available.
- The warning on all other dosage forms of DES is a deterrent to their being prescribed for this use.
- The limitation of this use to a single dosage form in special packages will provide the FDA with an accurate estimate of the number of women being treated with DES, so that the national prescribing trend can be followed. This has not been possible in the past.

We recognize a concern that the use of DES for postcoital contraception might increase beyond the "emergency" category to include all circumstances of unprotected coitus. While this is theoretically possible, we believe it unlikely for the following reasons:

- 10 -

- The treatment itself is neither pleasant nor inexpensive. It requires the patient to visit a physician, have a pregnancy test, buy a special package of tablets, and continue to take the tablets for five days, frequently in spite of nausea and vomiting.
- The labeling for the physician and the patient makes it clear that the use of DES as a postcoital contraceptive is indicated only in emergencies and the patient leaflet provides a clear statement of the issues. We doubt that women, when properly informed, will have any incentive to choose this method of contraception over those which are simpler, cheaper, safer, and more convenient.

In summary, we consider our approval of DES as an emergency postcoital contraceptive, under the conditions outlined, to be a responsible solution to a complex problem. Our regulatory approach is in accord with statutory standards, good medical practice, and the public interest. It offers to women faced with an anguishing problem a safe and effective alternative to abortion.

DES as a Growth Promotant in Livestock

As you know, Mr. Chairman, we banned the use of DES in animal feeds on January 1, 1973. Further, we banned the use of implants of DES in livestock on April 27, 1973.

On January 24, 1974, the U.S. Court of Appeals for the District of Columbia, overturned our decision. The reason for the Court's decision was that we had denied the sponsors of the New Animal Drug Applications for these uses an administrative hearing. While we disagree with the Court's decision, we will hold the hearing as directed. The issues for the hearing will include whether DES is safe within the meaning of section 512 (e)(1)(B) (the Animal Drug Amendments) of the Federal Food, Drug, and Cosmetic Act.

The hearing may also consider whether the methodology currently approved or available for detection of DES in tissue is sufficiently sensitive or suitable as a regulatory tool.

The Federal Food, Drug, and Cosmetic Act exempts from the Delaney Clause (section 512 (d)(1)(H)) carcinogenic substances if, under conditions of use specified in labeling and reasonably certain to be followed in practice, no residue of such substances is found in edible tissues of animals after slaughter, using methods of examination prescribed by regulation.

Such methods were published in the February 16, 1963 Federal Register and have not since been modified. To insure that methods appropriate to current scientific knowledge are used to assure the safety of our food supply today, we published in the March 27, 1974 Federal Register a proposal to revoke the existing test methods for DES.

- 12 -

A final order on that proposal is being held in abeyance until the major issue of the level of sensitivity necessary for an adequate method of analysis for a carcinogen in edible tissue is resolved. In the Federal Register of July 19, 1972 (38 FR 19226), we published a proposal setting forth the principles by which any method for analysis of an animal drug for which a zero tolerance is established would be determined. That proposal has resulted in substantial scientific discussion and disagreement. Resolution of the scientific issues raised by that proposal has involved personnel in several Bureaus of the Agency, as well as in my office. It is unquestionably one of the most important, as well as one of the most complex, proposals ever issued by this Agency.

I have concluded that it is absolutely essential that a final order be published with respect to this proposal before any hearing on DES is announced. Certainly, a major issue with DES is the required sensitivity of the analytical method, and that issue must be resolved through the scientific principles to be included in this final regulation.

I will be pleased to answer any questions you or members of your Subcommittees may have.

Statement Presented before the United States Senate
Committee on Labor and Public Welfare, Subcommittee on
Health. Diethylstilbestrol (DES) Hearings.

Senate Health Subcommittee

United States Senate

Washington, D.C.

I am Peter Greenwald, M.D., a licensed physician in New York State, and Director of the Cancer Control Bureau, New York State Department of Health. I am here at your invitation to present the results of our own studies on diethylstilbestrol (DES) and human cancer, and my opinion about the use of DES as a morning-after pill.

In general, I feel that in this country we should be able to expect proof of safety before a new drug is released or before an old drug is used in a new way, especially when there is almost no risk to not using the drug. The safety of DES as a morning-after pill has not been proven. In fact, evidence to date suggests a probable severe cancer risk among at least some daughters born of pregnancies when DES contraceptive treatment failures occur.

The New York State Department of Health Cancer Control Bureau has conducted three studies bearing on the human cancer risk of DES. The first confirms the cause-and-effect relationship and provides some information on dosage

and latency, the second assesses the possibility of maternal DES ingestion contributing to cancers other than vaginal or cervical in men or women, and the third evaluates current usage of DES as a morning-after pill in New York State. Results in brief are as follows:

I. Vaginal Cancer Association

In 1971 five teen-age girls reported to the New York State Cancer Registry as having vaginal cancer were investigated. DES therapy to prevent miscarriage had been given during pregnancy to the mothers of four patients, and the fifth took a similar synthetic estrogen, dienestrol. This was the first confirmation of the work by Dr. Herbst and his colleagues in Boston of the now widely accepted association between maternal use of DES and vaginal cancer.

At the present time, 23 teen-agers and young adults have been reported to the New York State Cancer Registry with this type of vaginal or cervical cancer. Eight have died of advanced disease. All mothers where our investigations are complete (20 of 23) are known to have taken DES to prevent spontaneous miscarriage.

The cause-and-effect relationship between the use of DES by mothers and vaginal cancer in their daughters is suggested in our studies by the facts that all mothers took DES during the first trimester; all patients were born during

the peak years of clinical use of DES to prevent miscarriages, by the similar age at diagnosis among patients; the time relationships; and the rather uniform microscopic pattern of these tumors. The consistency of all of these observations supports the possibility of a common cause. These findings also are in keeping with the independent investigations of others and are in accord with our biologic knowledge of DES, especially with the fact that DES can be shown to produce cancer in a variety of animals. It should be noted that "cause-and-effect relationship" means to me that DES is a necessary factor and that the cancer will not develop without it. There are undoubtedly additional factors affecting susceptibility and resistance.

Approximate cumulative dosages of synthetic estrogens taken during pregnancy for 11 mothers of vaginal or cervical cancer patients and 21 mothers of patients whose children did not develop cancer are shown on Table 1 (appended). Among mothers of patients, the mean dosage was 4868 mg. and the range 135 to 15,750 for those whose dosage was known. The dosage taken by mothers of cancer patients was compared to mothers of the non-ill daughters on whom data are available. (Mothers of sons were excluded from the significance test on the means because the sons would have no possibility of developing the tumors of concern.) There is no significant difference in the mean dosages for the two groups of mothers.

Since very few women in either group received small dosages, we cannot be sure of a dose-response gradient from these data. However, DES was used over a wide dose range and in the absence of differences it seems very possible that small doses as well as large may induce cancer. It should be noted that one mother received only 1.5 mg. per day with a total dose of only 135 mg. This is less than the amount recommended for DES contraception. In addition, animal studies have shown that the carcinogenic effect is retained at low levels of administration.

The New York State patients were 8 to 23 years old at time of diagnosis. With prenatal carcinogenic exposures, age at diagnosis is often used to estimate the latent period for cancer development, although with DES the latent period may be influenced by menarchy. Studies of various types of other human carcinogens indicate latent periods of less-than-one to more-than-fifty years. While there clearly are differences between DES and other carcinogens in age at exposure, type of carcinogen and mechanism of exposure, this comparison suggests that we may well expect that some patients with longer latency periods will be diagnosed in future years as the interval since the peak years of DES exposure grows longer.

The incidence of DES-induced cancer is increasing each year. Figure 1 shows the number of patients diagnosed

each year in New York State, exclusive of New York City. New York City patients are excluded from the figure because we are not sure of the completeness of reporting for the earlier years. As long as incidence still is on the increase, the magnitude of risk from DES cannot be determined.

On the basis of their study, the Mayo Clinic group estimated that the incidence of vaginal or cervical cancer among DES-exposed persons could be as high as 4 per 1,000. I don't think we should pass off incidence rates of this magnitude as trivial. This is equivalent to the annual death rate from heart disease in New York State, is 44 times higher than the annual incidence rate for leukemia, and at least 10 times higher than the incidences of breast cancer and colon cancer. If it is trivial, a number of heart and cancer researchers should perhaps seek other occupations.

II. Other Types of Cancer

The DES association with vaginal cancer also has been demonstrated for a similar type of cancer of the cervix. We have studied extensively the prenatal DES experience of mothers of boys and girls with many other types of cancer, and thus far have not found an association of these other tumors with maternal drug use. Again, I should like to point out the great value of the New York State Cancer Registry, the largest such reporting system in the country, in this

study. This episode serves as a good example of the value of such registries.

III. DES Usage

In 1973 and again in 1974, we surveyed 45 large hospitals, college health services and planned parenthood organizations in New York State to see how DES was being used as a morning-after pill. A 1975 resurvey is in progress. Use is fairly widespread, especially at the colleges and universities. Dosages generally are 25 to 50 mg. of DES per day for five days and nausea is reported as a side effect of the drug.

The absence of follow-up is of great concern. It generally is assumed that patients will return when treatment fails. No effort is made to ascertain the effectiveness of treatment or to recontact the patients who might have been pregnant prior to or in spite of treatment. Treatment failures might result from an already-established pregnancy, from excessive lapse of time between unprotected intercourse and DES ingestion, from inadequate dosage, from vomiting of pills, from a second sexual exposure, or from the drug failure.

Our surveys suggest that the use of DES as a morning-after pill probably increased between 1973 and 1974. Although the total estimated number of patients reported to have been treated by the respondents has declined, the practice of

referring patients to a physician or agency which would prescribe hormones as contraceptives has increased. Table 2 summarizes the results of these surveys.

The many unanswered questions raise doubt about the wisdom of approving DES as a morning-after pill. A cancer risk is present for daughters born when treatment failed, but the extent of the risk is unknown. A high risk is present for an apparently benign but perhaps precancerous lesion (vaginal adenosis). The psychological impact of DES exposure is unstudied; for example, I have spoken to a number of mothers of teen-age girls who now visit gynecologists several times a year because of DES exposure and wonder each time if this is the visit at which cancer may be found.

DES is recommended only in an emergency. But many women with unwanted potential pregnancies would consider this predicament to be an emergency.

Since DES is approved as a morning-after contraceptive, what will be done to assure ascertainment and follow-up of treatment failures? It is recommended that a patient see a doctor in this situation, but what is the recommendation for the doctor? Is DES as a morning-after pill to be used as a controlled drug? Perhaps it should. Several situations recently have come to light where we inadvertently may have produced cancer in ourselves. Let's not add another such situation to the list.

-8-

Finally, it should be noted that at times in the treatment of cancer DES may be a useful drug and its benefits outweigh its risks.

I hope that this DES controversy helps us to recognize further the importance of prevention and early detection in cancer, since both have a role here, and helps to direct our attention to the importance of prevention as a vital part of health care in the United States.

TABLE 1

Amount of Synthetic Estrogen Taken During Pregnancy by Mothers
of Vaginal or Cervical Cancer Children and Non-ill Children
Reported to the New York State Cancer Registry

Non-ill Children Maternal Synthetic Estrogen					Vaginal or Cervical Cancer Children Maternal Synthetic Estrogen			
No.	Sex of Child	Average daily Dose (mg)	Number of Days	Total Dose (mg)	No.	Average daily Dose (mg)	Number of Days	Total Dose (mg)
1.	Male	4	120	480	1.	5	90	450
2.	Male	5	120	600	2.	7	90	630
3.	Female	30	30	900	3.	8	180	1,440
4.	Male	8	120	960	4.	25	90	2,250
5.	Male	10	120	1,200	5.	11	270	2,970
6.	Female	12	120	1,440	6.	15	240	3,600
7.	Male	10	150	1,500	7.	65	75	4,875
8.	Male	10	150	1,500	8.	Unknown	110	-
9.	Female	12	180	2,160	9.	Unknown	180	-
10.	Male	15	150	2,250	10.	Unknown	Unknown	-
11.	Male	18	150	2,700	11.	Unknown	Unknown	-
12.	Female	16	180	2,880	12.	Unknown	Unknown	-
13.	Female	16	180	2,880	13.	Unknown	Unknown	-
14.	Male	16	180	2,880	14.	Unknown	Unknown	-
15.	Female	19	180	3,420	15.	1.5	90	135
16.	Male	20	180	3,600	16.	Unknown	Unknown	-
17.	Female	21	180	3,780	17.	75	160	12,000
18.	Male	40	150	6,000	18.	75	210	15,750
19.	Female	50	120	6,000	19.	42	225	9,450
20.	Female	50	120	6,000	20.	Unknown	90	-
21.	Male	50	150	7,500	21.	Unknown	30	-
					22.	Unknown	Unknown	-
					23.	Unknown	Unknown	-
Mothers of Female Children Only (N=9)						(N=11)	(N=15)	(N=11)
Mean		25	143	3,273 mg		30	147	4,868 mg
S.D.		15	51	1,792 mg		29	72	5,234 mg

t tests - $p > .05$ for differences between means.

TABLE 2

Survey of Contraceptive Use of D E S by Agencies in New York State
1973 and 1974

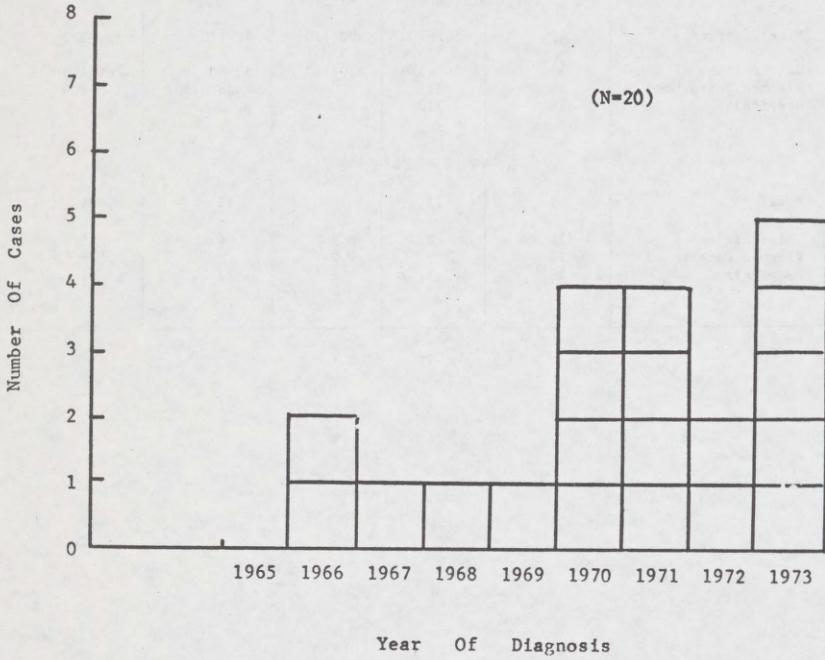
Type of Agency	Number Responding	Use D E S		Refer for D E S	
		1973	1974	1973	1974

Estimated Number of Patients					
Total (approx.)	45	685-700	500-530	75-130	235-320
Universities	15	340-350	130-160	20-30	80-110
Planned Parenthood	14	35+	30	Under 100	145-200
Hospitals	16	310	340	2	10

Number of Agencies					
Total	45	13	16	11	14
Universities	15	8	8	4	5
Planned Parenthood	14	2	2	5	8
Hospitals	16	3	6	2	1

Figure 1.

Vaginal and Cervical Cancers in Young Females
New York State, Exclusive of New York City
1965 - 1973



STATEMENT GIVEN BEFORE THE SENATE HEALTH SUBCOMMITTEE

Robert H. Pantell, M.D.
Consulting Pediatrician and Clinical Scholar
Stanford University School of Medicine
February 27, 1975

All drugs are potentially dangerous. In this respect, diethylstilbestrol is no different from any other drug. However, I feel there are several characteristics peculiar to diethylstilbestrol which make it unique in the annals of hazardous drugs. A number of drugs have been used in pregnancy with tragic consequences to the newborn. In these instances the family trauma was immediate and appropriate planning was possible. Furthermore, the drugs taken in the previous months could be readily identified and their risks investigated rapidly. Diethylstilbestrol is far more sinister. It strikes more than a decade later. Many persons will never know if they are at risk and if they should be seeking special early detection services. Other families will live in a perpetual state of anxiety, guilt and fear. The precise incidence of adenocarcinoma attributable to diethylstilbestrol is still not known, and the possibility of squamous cell carcinoma appearing in older women may extend the anxiety period to several decades. These are problems far less dramatic than the tragic child victimized by cancer, but nonetheless far more common and extremely real to those many exposed individuals and their families.

In my experience as a practicing pediatrician in Idaho, there were a number of alarming events which have raised my concern over the continued widespread use of diethylstilbestrol.

In August, 1972, I began work as a pediatrician for Community Health Clinics in Nampa, Idaho. Community Health Clinics was established as a non-profit organization in 1971 to provide health care to migrant farmworkers and rural residents in Southwestern Idaho. We were the only medical facility available in two of the four communities we served, Homedale (pop. 1,100) and Parma (pop. 1200). Residents of these communities often transferred their care from physicians in distant communities. It was routine practice to send for records of medical care for those persons who decided to obtain care regularly at our Clinics. All requests for transfer of information was done by mail on forms

signed by both patient and clinician.

A routine history and physical examination was performed on all patients coming to us regularly. One of the questions asked routinely of all women was whether they received drugs during pregnancy. In all pediatric histories, a question about the use of drugs in pregnancy was also present. It soon became apparent that the recollection of drugs taken during pregnancy was poor. The reasons for this are several fold. Routine prenatal care usually involves several oral preparations taken by expectant mothers. These include vitamins, anti-nausea pills and often pain pills. Patient knowledge of the names and purposes of the medications taken during pregnancy varies widely. With the population we were serving many women spoke no English making communication with non-Spanish speaking physicians additionally difficult. Finally, patient recall of events occurring many years ago is especially difficult.

Patients who presented with histories suggesting potentially serious medical conditions often required additional time spent in uncovering the precise nature of former diagnostic procedures and treatments.

In the winter of 1973, Mrs. A.G. came to our clinic. In 1971 she had received a medication from an obstetrician to help her maintain her pregnancy. Because of our concern that Mrs. A.G. had received diethylstilbestrol, a drug posing potential risks to her three year old daughter, we requested her records be transferred from her obstetrician. After several phone and mail requests a note was received from the obstetrician stating that her pregnancy was normal. No mention of drugs was made. Upon further questioning, Mrs. G. recalled the pharmacy where the drug was dispensed. Mr. George Murray, pharmacist in Homedale, Idaho identified the drug as des-Plex, a preparation manufactured by Amfre-Grant, containing 25 mg. diethylstilbestrol, ascorbic acid, thiamine, riboflavin, pyridoxine, calcium, niacin, folic acid and B12.

At the same time, another patient, Mrs. M.S., also came to our office for

care. Mrs. S. was currently being seen for pre-natal care by the same obstetrician who formerly cared for Mrs. G. Mrs. S. was at that time taking des-Plex and had been on this medication continuously for the first six months of her pregnancy. Mrs. S. was unaware of the risks of diethylstilbestrol in pregnancy. She was taking this drug two years after the November, 1971, FDA bulletin stated that diethylstilbestrol was contraindicated in pregnancy. Mrs. S. was sent to Dr. F. Birkeland of Nampa, Idaho for further obstetrical care. She subsequently delivered a female child.

Because of our inability to establish an effective line of communication with the obstetrician who was prescribing diethylstilbestrol, a letter was sent in conjunction with Dr. Thomas O. McMeekin to Mr. C.E. Barnett of the Idaho State Board of Pharmacy and to Mr. Armand Byrd, Secretary of the Idaho State Board of Medicine on March 25, 1974. We described our experience and suggested 1) an independent party negotiate with the obstetrician to identify those patients at risk, 2) an effort be made by the Board of Pharmacy and/or Medicine to educate this physician as to the dangers of diethylstilbestrol and current recommendations for its usage. The reply from the State Board of Pharmacy was that this was not in their jurisdiction. The secretary of the State Board of Medicine, at the time I left Idaho in the last week of June, 1974, communicated to me that action had not yet been taken on the matter. Neither Dr. McMeekin or I have received any further communication concerning this issue. The physician under consideration, besides maintaining a private practice was then, and to my knowledge still is, an obstetrical consultant for the State.

My concern as a pediatrician are several fold. 1) When a commonly used drug such as diethylstilbestrol is discovered to have new potential problems, there exists no formal effective mechanism to alert physicians to those problems short of withdrawing the drug. The aforementioned physician is not unique. Notice of diethylstilbestrol toxicity appeared in the medical literature, the FDA bulletin,

the package insert and undoubtedly was discussed in medical meetings. It is my experience that physicians cannot keep up with the voluminous medical literature. FDA bulletins are not universally read or received. Package inserts are seldom read, and are certainly less likely to be read for drugs which physicians have been using for many years without obvious side effects. Finally, medical meetings vary tremendously. In a fall 1974 meeting of a county medical society in Idaho, a colleague of mine reported that the guest speaker claimed there had been only 14 cases of vaginal carcinoma reported and that the risk to female offspring is between 1/50,000 - 1/80,000. These statements are markedly at odds with figures published at that time. 2) It is extremely difficult identifying those patients at risk. Because of this it may become necessary to begin screening for adenocarcinoma by performing pelvic examinations in girls at far earlier than usual ages. 3) In a mobile society, many families, especially farmworkers, may be lost to medical follow-up before proper explanations and preventative approaches can be explained. 4) The most serious problem is the disruption of families in which there is a risk of a child developing adenocarcinoma of the vagina. Other carcinomas may eventually be found to occur in older women, prolonging the period at risk. The hanging sword will be perched above the head of some children and their families for many years. Tragically, we have no idea how many years!

In summary, I feel the current procedures for the regulation of diethylstilbestrol are ineffective. I strongly urge diethylstilbestrol be withdrawn, or at the least be placed in the controlled substance category if there is no drug felt to have less risks in identical clinical usage.

Testimony of Belita H. Cowan
on the use of diethylstilbestrol as a "morning-after" pill

Senate Subcommittee on Health
Washington D.C.

February 27, 1975

I am Belita Cowan, a college instructor who teaches health care to students enrolled in health occupation training programs. I have long been following women's health problems as they relate to drug use.

My purpose in being here is to inform the Subcommittee of several issues which may not have been brought to the Subcommittee's attention. The first concerns the prescribing habits of doctors who dispense DES (diethylstilbestrol). The second issue relates to medical protocol in hospital emergency rooms where rape victims are treated. The third issue concerns the possible legal liability on the part of emergency room doctors who prescribe DES.

Last summer I conducted a survey of over 200 women, ages 18 to 31, who had taken DES as a "morning-after" pill in Ann Arbor, Michigan between 1968 and August of 1974. In addition, I interviewed many nurses, gynecologists, and emergency room doctors at 2 Ann Arbor hospitals, the University of Michigan Student Health Service, and a number of Detroit hospitals. The purpose of the study was to determine how and when DES was prescribed to women, and the precautions taken, if any, to ensure the careful monitoring and follow-up of all patients. What is occurring in Ann Arbor, Michigan is, I believe, indicative of what is happening in other cities, particularly those with university medical centers.

For purposes of statistical analysis, I excluded from the numerical tabulations all rape victims, persons already on contraceptives, and those who were not at mid cycle at the time of the unprotected sexual encounter. That left 65 women. The results of the study were published last September, and are included in Table I which is attached to your copy of this report.

The study showed that far from being an emergency medication, DES is being used repeatedly as a contraceptive. Twenty-nine percent of my sample stated that they had taken the "morning-after" pill at least twice within a year's time. The study showed that DES is being prescribed with carelessness and casualness. Forty-five percent were not given a pelvic or breast exam.

Fifty-six percent stated that the doctor did not take a personal and family medical history. Eight women said that they got the "morning-after" pill not for themselves, but for a friend or roommate. And only 26% were followed-up to see if they were pregnant.

The study also revealed that DES is being given to women for whom estrogens are contraindicated. Women who cannot take birth control pills are being given the "morning-after" pill. They are not aware nor are they informed that the "morning-after" pill is estrogen. Fifty-seven percent of the sample were unaware that the "morning-after" pill did not have FDA approval and that it had not been proven safe and effective. Further, the study revealed that many women are not being told of the possible cancerous effects to the fetus if the woman is pregnant. I could not find a single case where a pregnancy test was given prior to and after the DES regimen. Although, I must say that there is no pregnancy test which can accurately detect a 2 or 3-week pregnancy.

In cases where patients are warned of the association between maternal stilbestrol ingestion and possible adenocarcinoma in the female offspring, patients are not usually counseled to seriously consider terminating the pregnancy should the "morning-after" pill not work. Six percent of those in the survey stated that they themselves were DES daughters, that is, their mothers took stilbestrol when they were pregnant in the early 1950's. Of all the doctors I interviewed, only one expressed hesitation about giving the "morning-after" pill to DES daughters. Dr. Ann Pfreder of the U of M Health Service stated that "We don't know the effects of the morning-after pill on DES daughters, so I don't want to give it to them."

The most interesting finding of the study is that 24% of the women stated that they did not take all 10 pills in the series. As one woman put it, "I got so sick from the first pill that I never took the rest. I couldn't stand to be that ill." And not surprisingly, 65% stated that if they had been fully informed about DES, they would not have taken it in the first place.

Since FDA has, unfortunately, gone ahead and approved DES for use in emergency situations such as rape, I should like to explain why DES ought not be given to rape victims by hospital emergency room personnel. Evidently, FDA has little understanding of emergency room procedures and the treatment of rape victims. Informal studies done by Ann Arbor and Detroit

rape crisis counselors have shown that emergency room doctors take only a cursory medical history. They often do not find out whether the woman has heart problems, impaired liver function, severe diabetes, a history of blood clots, or history of abnormal genital bleeding. The doctors do not, and indeed cannot, do a thorough enough medical history to find out if there are contraindications to estrogens. Pregnancy is one contraindication. However, minors who are rape victims sometimes give inaccurate contraceptive or sexual histories for fear that their parents may find out.

In most cases, the rape victim is not given adequate information on DES. In fact, she may not even be told what the drug is for or why she should come back for a follow-up. For the first 3 or 4 days after the rape, most victims are in considerable pain and discomfort. It is not unusual for the woman to discontinue taking the "morning-after" pill because she does not want the added discomfort of nausea or vomiting. Besides this, the victim may have already received large doses of penicillin or even Valium, and may not wish to take more drugs.

Follow-up is essential when DES is given to the patient. However, follow-up of rape victims is virtually impossible for many reasons. After the rape, the victim may:

- move out of town or move to another part of town
- get an unlisted phone
- change jobs
- live with relatives
- some rape victims initially give false names and addresses because they are afraid of harassment
- many rape victims are brought to a county hospital, sometimes by the sheriff, from outlying parts of the county, and they will not travel that distance for a follow-up
- the rape victim wants to forget; the last thing in the world she wants to do is to return to the hospital
- when the rape victim comes to the emergency room she may be disoriented or in a state of shock; she may not realize she needs to come back for a follow-up

But the greatest deterrent to follow-up is the cost involved. Most victims simply cannot afford to pay another \$30 or \$40 for a hospital visit. Finally, follow-up is not considered the responsibility of the emergency room personnel. According to Dr. George Fink of St. Joseph Hospital in Ann Arbor, Michigan, "Our policy is to refer rape cases as well as other emergency cases to follow up with their own family physician or at local medical facilities. Follow-up is not within our capacity. We do not have the set-up, and we do not do it."

In reviewing the 1974 rape cases seen at Wayne Co. Hospital in Detroit,

one doctor estimated that only about 25% of all rape victims come back for any kind of follow-up, even VD testing.

Emergency room personnel neither have the time nor the desire to counsel rape victims about alternatives to DES, risks associated with DES, and carcinogenic effects to the offspring. Many ER doctors feel uneasy about prescribing DES for rape victims because they are unable to determine whether or not the victim is already pregnant.

What FDA fails to realize is that the emergency aspect of treating rape victims has to do with the trauma of the assault. According to the Women's Crisis Center of Ann Arbor, problem pregnancy is secondary. The assault itself -- both physical and psychological -- is what constitutes the emergency. According to Catherine McClarey, a Washtenaw County Commissioner and rape crisis counselor, "DES is too drastic a measure for the problem."

By its failure to regulate the use of DES, the FDA has created a drug abuse problem. We know that statistically less than 5 of every 100 single, unprotected sexual encounters result in pregnancy. Therefore, we are subjecting 95% of women given DES to an unnecessary drug. In dispensing DES to rape victims, we are unnecessarily exposing the majority of them to carcinogenic risks. If DES is to be given out at all, then the very least FDA can do is to ensure that the patient is fully informed of all the risks to herself as well as to potential offspring. There should be a patient insert which includes animal test data, all known side effects, contraindications, and alternatives to DES.

FDA should define what it means by "emergency." According to one Ann Arbor doctor, an emergency can be anything from a ripped condom to a forgotten birth control pill. According to another doctor, Judy Pagano of Wayne Co. Hospital, "If the FDA were to strictly define emergency, and specify the indications for DES, it would affect our prescribing habits because it would be legally important." According to a resident at University Hospital, "We are all very concerned about lawsuits. If I were in private practice, I might think differently about DES. As it is, I am covered through the hospital."

Which brings me to the final issue -- the possible legal liability of doctors who prescribe DES. Recently, even the AMA has conceded that the doctrine of informed consent includes disclosure by the doctor of risks to the patient, including risk of failure of the drug, as well as

disclosure of alternative treatments. As far as I can tell, few doctors are suggesting any alternatives to DES. They could suggest menstrual aspiration or early abortion.

In conclusion, DES must be given only under the following conditions:

- 1) a thorough personal and family history must be taken
- 2) warnings as to risks to the patient and possible offspring must be discussed
- 3) FDA must provide adequate information in a patient insert
- 4) a pregnancy test must be given prior to and after DES therapy
- 5) there must be follow-up
- 6) the patient must be informed of alternatives, including menstrual aspiration and early abortion

Unless all of these steps are taken, DES should not be prescribed to anyone.

**SURVEY OF 65 WOMEN WHO TOOK THE MORNING-AFTER PILL
1968-74.**

	Once	Twice	3 times	more
How many times did you take DES?	70.8%	20 %	7.7%	1.5%
Are you a DES daughter?	Yes 6.2%	No 75.4%	Don't know 18.4%	
Did the doctor take a personal and family medical history?	Yes 26.2%	No 44.6%	Personal, but not family history already on file 29.2%	
Were you given a pelvic and breast exam?	Yes 20%	No 46.2%	Only pelvic exam 33.8%	
Were you told you were taking an experimental drug?	Yes 43%	No 41.5%	Not Sure 15.5%	
Did you take all 10 pills?	Definitely Yes 75.4%	Definitely No 4.6%	Uncertain of number 24%	
Did you experience nausea?	Yes 81.5%	No 18.5%		
Did you experience vomiting?	Yes 33.8%	No 66.2%		
Was there a follow-up to see if you had a period?	Yes 26.2%	No 61.5%	Uncertain 12.3%	
Would you take the morning-after pill today if you were in the same situation?	Yes 7.7%	No 64.6%	Uncertain 27.7%	

CURRICULUM VITAEMARVIN SEIFE, M.D.

Date of Birth: April 18, 1924

Place of birth: Brooklyn, New York

EDUCATION:

1. B. S., Wake Forest University, Winston-Salem, North Carolina, 1945.
2. M.D., Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina, 1946.

TRAINING:

- ** 1. City Hospital, (New York), Welfare Island, New York 17, New York; January 1, 1947 to June 30, 1947; Intern, Internal Medicine (6 months).
2. City Hospital, (New York), Welfare Island, New York 17, New York; July 1, 1947 to June 30, 1948; Intern, Rotating (12 months).
3. City Hospital, (New York); Welfare Island, New York 17, New York; July 1, 1948 to June 30, 1949; Assistant Resident, Internal Medicine (12 months).
4. City Hospital, (New York), Welfare Island, New York 17, New York; July 1, 1949 to June 30, 1950; Chief Resident, Internal Medicine (12 months).
- ++ 5. Municipal Sanatorium, Otisville, New York; July 15, 1950 to October 15, 1950; Resident, Chest Diseases (3 months).
6. University of Colorado Medical Center (Colorado and Denver General Hospitals), Denver 20, Colorado; November 1, 1952 to March 31, 1953; Resident, Internal Medicine (5 months).

SERVICE:

Commissioned Captain, U.S.A.F.R. (MC), October, 1950.

1. Chief of Medical Services, U.S. Air Force Hospital, Lowry Air Force Base, Denver, Colorado; October 30, 1950 to June 30, 1951.
2. Chief of Medical Services, U.S. Air Force Hospital, James Connally Air Force Base, Waco, Texas; July 1, 1951 to October 29, 1952.
- ** (City Hospital rebuilt and now known as City Hospital Center at Elmhurst, 79-01 Broadway, Elmhurst, New York 11373).
- ++ (Municipal Sanatorium, part of New York City system of hospitals, is now closed).

Recipient of the James R. Lisa Award presented by Franklin Hanger, M.D. at the December 12, 1951 meeting of the Society of the Alumni of City Hospital for research in hepatic diseases.

EXPERIENCE:

1. Staff physician (internal medicine) and assistant medical director of the American Medical Center at Denver, Spivak, Colorado--(a 250 bed chest disease and cancer hospital for the medically indigent); August 1, 1953 through November 27, 1955.

2. Medical Director and Superintendent of the American Medical Center at Denver, Spivak, Colorado; November 28, 1955 through January 7, 1958.

3. Clinical Assistant in Medicine, University of Colorado School of Medicine, January 1, 1955 through December 3, 1955. (Resignation of position was necessary by increased professional responsibilities).

4. Private practice of internal medicine in Denver, Colorado, 1958 to 1963; Houston, Texas 1964 to 1965.

Member of Colorado State Medical Society Subcommittee on Tuberculosis Control, September 27, 1958 to September 26, 1959.

Attending Staff Denver General Hospital, Division of Medicine 1959-1962
St. Anthony Hospital, Denver, Colorado, Courtesy Staff 1958-1963
General Rose Memorial Hospital, Denver, Colorado, Courtesy Staff, 1958-1963
Memorial Baptist Hospital, Houston, Texas, Courtesy Staff, 1964-1965

5. The City of New York, Department of Health assigned to Department of Correction Clinician July, 1965

Chief Medical Officer for Riker's Island (N.Y. City Penitentiary)
August 1, 1965 to September 3, 1965.

6. FDA, Bureau of Medicine (Surveillance) September 7, 1965 to present

LICENSE:

North Carolina #7811 (June, 1947)
New York #48657 (April, 1949)
Colorado #12348 (October 13, 1953)
(Colorado Basic Science Certificate 1953)
Texas #D1491 (June 22, 1964)

MEMBER:

American College of Cardiology

FDA, Bureau of Medicine (#6 continued)

1. Medical Officer (Internal Medicine), Drug Surveillance Branch, September, 1965 to October, 1966.
2. Acting Deputy Director, Division of Supplement Review, Division of Supplement Review, Office of Drug Surveillance, October, 1966 to January 1966.
3. Acting Director Cardiopulmonary Renal Division/Office of Drug Surveillance, January 1966 to November 1967.
4. Acting Director, Cardiopulmonary Renal Division/Office of Marketed Drugs, November 1967 to October 1968.
5. Director, Cardiopulmonary Renal Division/Office of Marketed Drugs, October 1968 to November 1968.
6. Acting Associate Director for Marketed Drugs, November 1968 to June 30, 1970.
7. Acting Director, Office of Scientific Evaluation, Bureau of Drugs, July 1, 1970 to April 19, 1971.
8. Deputy Director for Medical Activities, Office of Scientific Evaluation, Bureau of Drugs, April 19, 1971 to January 18, 1972.
9. Director, Generic Drug Staff, Office of Scientific Evaluation, Bureau of Drugs, January 19, 1972 to present.

MARVIN SEIFE, M.D.

BIBLIOGRAPHY

1. Seife, M.: Primary Atypical Pneumonia, Etiology Unknown; review of current etiological concepts, J. Bowman Gray School Med. 5:1, (Jan.) 1947.
2. Seife, M.: Heartburn of Pregnancy, J. Bowman Gray School Med. 5:48, (March) 1947.
3. Seife, M., and Reich, C.: The Effect of Vitamin B12 Administered Subcutaneously, N. Y. State J. Med. 50:1401-1402 (June) 1950.
4. Seife, M., and Lisa, J.R.: Diabetes Mellitus and Pylephlebotic Abscess of the Liver Resulting From Schistosoma Mansonii Infestation, Am. J. of Trop. Med. 30:769-772 (Sept.) 1950.
5. Seife, M.; Kessler, B.J.; and Lisa, J.R.: Clinical, Functional and Needle Biopsy Study of the Liver in Alcoholism, Arch. Int. Med. 86:658-670 (Nov.) 1950.
6. Kessler, B.J.; Seife, M.; and Lisa, J.R.: Use of Choline Supplements in Fatty Metamorphosis of the Liver; Needle Biopsy Investigation, Arch. Int. Med. 86:671-681 (Nov.) 1950.
7. Seife, M.; Kessler, B.J.; Hoffman, J.; and Lisa, J.R.: A Clinical, Functional, and Needle Biopsy Study of the Liver in Pulmonary Tuberculosis, Am. Rev. of Tb. 63:202-209 (Feb.) 1951.
8. Reich, C.; Seife, M.; and Kessler, B.J.: Gaucher's Disease: A Review and Discussion of Twenty Cases, Medicine 30:1-20 (Feb.) 1951.
9. Seife, M.; Reich, C.; and Lisa, J.R.: Chronic Lymphatic Leukemia Associated with Hodgkin's Disease, Acta Haemat. 5:65-74 (Feb.) 1951.
10. Seife, M., and Reich, C.: Sick Cell Anemia in Pregnancy, N.Y. State J.M. 51:769-771 (March) 1951.
11. Shopfner, C.E., and Seife, M.: Rheumatic Carditis and Hemorrhagic Pneumonitis Treated with ACTH: Report of a Fatal Case, U.S. Armed Forces Med. J. 3:819-824 (June) 1952.
12. Shopfner, C.E., and Seife, M.: Treatment of Acute Rheumatic Fever with ACTH, U.S. Armed Forces Med J. 3:1153-1174 (August) 1952.
13. Seife, M., and Leon, J.L., Camphor Poisoning Following Ingestion of Nose Drops, J. A. M. A. 155:1059-1060, July 17, 1954.



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

STATEMENT BY

FRANK J. RAUSCHER, JR., PH.D.

DIRECTOR, NATIONAL CANCER PROGRAM, NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTES OF HEALTH

BEFORE

THE SUBCOMMITTEE ON HEALTH

SENATE COMMITTEE ON LABOR AND PUBLIC WELFARE

AND

THE SUBCOMMITTEE ON ADMINISTRATIVE PRACTICE AND PROCEDURE

SENATE COMMITTEE ON THE JUDICIARY

FEBRUARY 27, 1975

Mr. Chairman, and Members of the Subcommittees:

I am pleased to appear before you today to present findings concerning the use of diethylstilbestrol (DES) as an "emergency" post coital contraceptive and to provide information on the use of DES as an animal feed additive. I will address the latter use first and point out that the National Cancer Institute remains fully supportive of legislation, regulation and activities which serve to reduce or eliminate environmental exposures to chemical carcinogens. Specifically, if DES were used as an animal feed additive and if residues of the drug were left in edible portions of animals, the result would be long-term exposures to virtually the entire population of the United States. It should be recognized that there is no health advantage to the exposed individual as is the intent when the drug is used therapeutically. The law prescribes that substances like DES which have been shown to be carcinogenic can be used as feed additives providing no residues appear in any of the edible portions of the animal at the time of slaughter. The NCI remains fully supportive of these requirements.

Concern that the newly approved use of DES as a post coital pill for emergency situations may cause cancer in treated patients is to be viewed in light of present day knowledge and information on human subjects. Since the intended use of DES is as a post coital contraceptive for emergency use following unprotected intercourse the primary concern over dangerous side effects, assuming the treatment is effective, would be for the patient. Secondly, however, concern for the embryo must be addressed since treatment might be ineffective and a child might be born despite these efforts. First I will speak to the concern for the treated patient.

Among the women treated with DES for threatened abortion no increase in the incidence of cancer at any organ site has been detected. The dosage of DES and the duration of treatment varied widely from 2.5 - 150 milligrams per day and from 3 to 212 days. Most of these women were treated with as much as 50 milligrams per day for 150 days or longer. These observations date back to the late 1940's. They show no evidence that such use may be cancer causing. It should be pointed out, however, that such observations are in contrast to those attendant to the use of DES for treatment of what is

termed gonadal dysgenesis. Gonadal dysgenesis in the female implies defective and incomplete development of the ovaries, and DES has been used in an attempt to correct that condition. Among those patients who have been treated for 5 or more years with an average treatment time of 12 years, evidence exists which suggests an increased risk of an unusual type of cancer. In fact, in a recent study performed by Bruce S. Cutler in 1972, three cases of cancer of this unusual type were discovered among a group of 24 females who had been treated for gonadal dysgenesis over a period of 5 or more years. Because this form of cancer is so rare, it has been assumed that such treatment puts the patient at increased risk as regards this disease.

The contrast between the cancer experience of women treated for threatened abortion and those treated for defective development of the ovaries can reasonably be assumed to be the result of differences in total dosage and duration of treatment. As indicated earlier, the risk associated with the use of DES as treatment for threatened abortion was so low that it could not be demonstrated.

Only at the higher exposure levels to the drug does evidence exist which suggests an increased cancer risk. On this basis it can reasonably be assumed that the post coital use which involves 50 milligrams per day for a period of only 5 days would represent far less risk to the patient than did treatment for threatened abortion where indeed no increase in risk could be demonstrated.

Concern for the daughters exposed immediately following conception also needs to be addressed since the effectiveness of treatment is unlikely to be 100%, and the possibility exists that some daughters may be born to treated mothers. Since 1971 there have been extensive studies which document that the daughters of women treated with DES for threatened abortion during the first 17 weeks of pregnancy have a low but demonstrably increased risk for cancer of the vagina and cervix. These cancers appear around the time of puberty but in some cases do not come to clinical attention until several years after puberty. Currently, the incidence is estimated to be 3-4 per thousand daughters but this value may increase as the daughters grow older. It should be pointed out, however, that all of these exposures occurred in mothers who were demonstrably pregnant at the time of treatment. This, then, differs markedly from post coital treatment which is

5

recommended to begin within 24-72 hours following unprotected intercourse. The significance of this statement lies in the fact that it is considered unlikely that treatment at such early time and for such a short period would create risks comparable to those associated with treatment for threatened abortion. The period during which the drug is administered precedes the critical stages of tissue and organ development and differentiation. It therefore seems improbable that the effects of DES administered at such an early time would produce effects similar to those induced by treatment for threatened abortion. One can only speculate as to what the former effect might be, if any, and how such effects would translate into human risks such as congenital diseases or cancer.

In summary, Mr. Chairman, I believe that current evidence strongly suggests that the risk of causing cancer in the treated patient is extremely small. Considered against the emotional trauma experienced by a rape victim, including the fears and anguish over the possibility of pregnancy or of intervention procedures such as uterine scraping and frank abortion, the benefit would appear to greatly outweigh the minimal risks involved. It is my feeling that physicians who have responsibility for treating

emergency pregnancies should not be deprived of what appears to be a useful medical tool, particularly so since there is a considerable accumulation of evidence which indicates the risks to humans are so small as to be undetectable.

I will be glad to respond to any questions that you may wish to ask.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service, National Institutes of Health, National Cancer Institute

Biographical Sketch

NAME : Frank J. Rauscher, Jr., Ph.D.

POSITION : Director, National Cancer Program, National Cancer Institute

BIRTHPLACE AND DATE : Hellertown, Pennsylvania, May 24, 1931

EDUCATION : Moravian College, Bethlehem, Pennsylvania, 1953, B.S.,
 Premedical Curriculum; Ph.D., Rutgers, The State
 University, New Brunswick, N. J. June 1957.

EXPERIENCE :

Present : Director, National Cancer Program, National Cancer Institute

1970-1972 : Scientific Director for Etiology, NCI

1969-1970 : Acting Scientific Director for Etiology, NCI

1967-1970 : Associate Scientific Director for Viral Oncology, Etiology, NCI

1966-1967 : Chief, Viral Leukemia & Lymphoma Branch, Etiology, NCI

1965-1966 : Acting Chief, Viral Leukemia & Lymphoma Branch, Etiology, NCI

1964-1970 : Chairman, Special Virus (Leukemia) Cancer Program, Etiology, NCI

1964-1966 : Head, Viral Oncology Section, Laboratory of Viral Oncology, NCI

1962-1967 : Visiting Investigator of Viral Oncology, Rutgers University

1959-1964 : Microbiologist, National Cancer Institute, Laboratory of Viral
 Oncology

1959- : Visiting Instructor of Animal Virology, Trinity College,
 Washington, D. C.

1958-1959 : Assistant Professor of Virology, Rutgers University Graduate
 School, New Brunswick, New Jersey

1957-1958 : Research Associate in Virology, Rutgers University Graduate
 School, New Brunswick, New Jersey

1955-1957 : Research Assistant in Virology, Rutgers University Graduate
 School, New Brunswick, New Jersey

1953-1955 : Research Fellow in Virology, Rutgers University Graduate
 School, New Brunswick, New Jersey

ASSOCIATION MEMBERSHIPS : The Theobald Smith Society, New Jersey, Society of Sigma Xi,
 The American Association for Cancer Research, The American
 Association of Immunologists, The American Association for
 Advancement of Science, World Society for Leukemia &
 Related Diseases, American Society of Clinical Oncology,
 Honorary Member of American Academy of Microbiology.

SPECIAL AWARDS
CITATIONS, OR
PUBLICATIONS

- : Comenius Award--Presented annually by Moravian College, Bethlehem, Pa., to a person "for outstanding scientific achievement." April 1963.
- United States Junior Chamber of Commerce Award--Presented to the Nation's "Ten Outstanding Young Men." January 1965.
- Selman A. Waksman Honorary Lectureship Award--Presented annually by the Theobald Smith Society, the New Jersey Branch of the American Society for Microbiology for "Outstanding contributions to Microbiology." March 1967.
- Arthur S. Flemming Award--Presented annually to the "Ten Outstanding Young Men in the Federal Government." February 1968.
- Vice President, World Society for Comparative Leukemia Research, 1967-1972.
- Elected to Board of Directors, American Association for Cancer Research, 1970.
- Elected--Board of Trustees, April 1970, of Moravian College, Bethlehem, Pennsylvania, for the period 1971-1974.
- Appointment--International Agency for Research on Cancer; Member of Scientific Council, 1972-74; Chairman, U.S. Delegation, Governing Council, 1972--.
- Superior Service Award--Presented by the Department of Health, Education, and Welfare. July 1972.
- Lucy Wortham James Laboratory Research Award--Presented annually by the James Ewing Society, 1973.
- Honorary Degree of Doctor of Science, Rutgers University, May 31, 1973.
- And 59 publications on virology, cancer research, cancer planning and biomedical management.

VAGINAL CANCER AFTER MATERNAL TREATMENT WITH SYNTHETIC ESTROGENS

PETER GREENWALD, M.D.,
JOSEPH J. BARLOW, M.D.,
PHILIP C. NASCA, M.S., AND
WILLIAM S. BURNETT, M.D.

VAGINAL adenocarcinoma in young women was recently reported by Herbst, Ulfelder and Poskanzer¹ as being associated with stilbestrol therapy of the mother during pregnancy. In an accompanying editorial, Dr. Alexander D. Langmuir² emphasized the scientific and social implications of this observation, and stated the need for confirmatory data. Our findings confirm the association and provide additional information on dose and time relations.

The New York State Cancer Registry receives reports of all cancer diagnosed in New York State, exclusive of New York City. During the period 1950 through 1970, five adenocarcinomas of the vagina were reported in women under age 30. These patients were studied in detail for history of drug use by their mothers during pregnancy.

METHODS

A standardized form was developed for collection of demographic, clinical, growth and development, neonatal and maternal-pregnancy history. Clinical information was obtained from hospital records and physicians.

Data about prenatal history were obtained from hospital delivery and obstetrician records and by interview with the patients' mothers. Patients born in Upstate New York³ and the patient born in Pennsylvania were matched two to one with girl babies born at the same hospital at about the same time to mothers of the same five-year age group and with the same number of previous children. Matching was done with the aid of birth certificates on file in the Health Department. Records of controls were searched for history of stilbestrol use.

RESULTS

The five patients with vaginal adenocarcinoma were born in the years 1951, 1952 and 1953, and were 15 through 19 years old at the time of diagnosis. Place of birth varied widely, with three patients being born in Upstate New York, one in New York City and one in Pennsylvania. All diagnoses were made in Upstate New York, which had a 1970 census of 10,322,950.

Synthetic estrogen therapy was given to mothers

of all five patients (Table 1). Obstetricians used the therapy to prevent threatened abortion. Mothers of Cases 1, 2, 3 and 5 received stilbestrol, and the mother of Case 4 received dienestrol.

The technic of administration to mothers of Cases 1 and 3 roughly followed that proposed by the Smiths,³ starting with 5 mg per day and gradually increasing to 100 mg or more per day. Case 3's mother had been taking 0.1 mg of stilbestrol per day in an effort to become pregnant after 2½ years of apparent infertility. The dosage was increased stepwise after diagnosis of pregnancy.

The mother of Case 2 stated that she had taken "estrogen" tablets during pregnancy because of spotting. This could not be confirmed by the hospital delivery record or by the obstetrician, who had recorded only five intramuscular injections of vitamin B6 and no other medications. However, pharmacy records showed that a prescription for the mother for 100 5-mg stilbestrol tablets had been filled at 2½ weeks of gestation, and another prescription for 50 25-mg stilbestrol tablets had been filled at 11 weeks of gestation.

Dienestrol, 5 mg per day, was given to Case 4's mother from 84 to 182 days after the onset of her last menstrual period before pregnancy. This mother also received two injections of estrone during her third month, and 25 mg of progesterone (intramuscularly) every three days, from the third through the seventh month, decreased to 15 mg per day until delivery, and 120 mg of thyroid orally per day from the third month until delivery.

The mother of Case 5 recalled taking 13 small, red-coated tablets — which she thought were estrogens — per day from 2½ months to the fifth month. The delivery record confirmed that this mother had received stilbestrol from 2½ months to the fifth month. The 1950 Physicians' Desk Reference⁴ describes a 5-mg tablet of this type; however, there was also a 0.1-mg red stilbestrol tablet available. The obstetrician has since died, and his office records have been destroyed; thus, it is not possible to be certain of the exact dose. (Because of the number of tablets per day, we thought the larger dose tablet more likely.) This mother also stated that she received 28 "estrogen" shots from 2½ months to 4½ months, and had retained a physician's bill verifying the number of shots. (Stilbestrol was not available as an injectable.)

All patients were single and had no children. Their ages at onset of menses were all 12 or 13 years old with catamenia at one year before the first symptoms described as regular with a cycle of 28 to 30 days. None had hormone or contraceptive therapy before onset of the first symptoms.

Histologically, all tumors resembled those described by Herbst and Scully,⁵ containing the characteristic clear cells and "hobnail" cells.

Diagnosis was made within two months of known onset of symptoms in three patients. All three died

From the New York State Department of Health, Cancer Control Bureau and Roswell Park Memorial Institute (address reprint requests to Dr. Greenwald at the New York State Department of Health, Albany, N.Y. 12208).

Table 1. Adenocarcinoma of the Vagina and Maternal Use of Synthetic Estrogen in Patients Reported to the New York State Cancer Registry, 1950-1970.

CASE NO.	DATE OF BIRTH	AGE (YR) AT DIAGNOSIS	MATERNAL SYNTHETIC ESTROGEN THERAPY DURING PREGNANCY		
			TIME STARTED*	TIME ENDED*	DRUG & DOSE
1	2/9/51	15 (1966)	5 wk	Delivery	Stilbestrol (oral), 5 mg/day initially, increased 5 mg/wk to 125 mg/day
2	4/5/52	19 (1971)	2½ wk	3½-4 mo	Stilbestrol (oral), 5-mg tablets initially & 25-mg tablets later (exact dose unknown)
3	9/28/52	15 (1968)	Conception	Delivery	Stilbestrol (oral), 0.1 mg/day until 3d week, then 5 mg/day increased by 5 mg/wk to 100 mg/day
4	10/2/52	17 (1970)	3 mo	6 mo	Dienestrol (oral), 5 mg/day; also estrone (intramuscularly) for 2 doses at 3d mo; progesterone & thyroid 3d mo to delivery
5	4/20/53	17 (1970)	2½ mo	5 mo	Stilbestrol (oral), possibly 65 mg/day; also, 28 "estrogen" shots from 2½ mo to 4½ mo.

*Time of gestation.

of advanced disease. Case 2 had symptoms for 18 months before diagnosis and is now in the hospital recovering from an anterior exenteration, total vaginectomy and pelvic lymph-node dissection, with creation of an ileal vagina.

Case 5 had symptoms for 10 months before diagnosis. She was treated with radical hysterectomy, total vaginectomy with ovaries left intact and development of an artificial vagina. Her physician believes that she is probably cured.

None of the mothers of the eight control patients received stilbestrol therapy during pregnancy. No controls were obtained for Case 1, born in New York City.

DISCUSSION

The observation that mothers of the five patients with adenocarcinoma of the vagina had synthetic estrogens during pregnancy confirms the previously reported association. Although we do not know how frequently these compounds were used, obstetricians in several Upstate New York cities believe that stilbestrol for threatened abortion was used fairly widely and in large doses during the early 1950's and that use has since declined. Dienestrol and stilbestrol are nonsteroidal estrogens, similar in structure and dose.⁶

Large doses of stilbestrol for threatened abortion were recommended by two major pharmaceutical companies in the 1950 Physicians' Desk Reference.¹ Dosages were similar to those recommended by the Smiths,³ starting in the seventh week with 5 mg per day and increasing stepwise to 135 mg per day at the 35th week, when stilbestrol was discontinued. In other conditions such as senile vaginitis the rec-

ommended dose range was 0.1 to 1 mg daily, and for suppression of lactation, the recommended dose was 15 mg daily, for two to four days.

The uniformity of histologic pattern supports the possibility of common etiology. The clustering of patients by date of birth within a three-year period when synthetic estrogen therapy for threatened abortion was common suggests that the cancer was related to maternal therapy rather than to threatened abortion in the absence of therapy. Control mothers had noncomplicated pregnancies and no synthetic estrogen therapy.

The true risk of miscarriage in these pregnancies could not be definitely established. Records for mothers of Cases 1 and 3 mentioned only first-trimester spotting or staining, and there was no history of previous abortion. Case 2's mother had had a previous miscarriage and stated that she had spotting during the pregnancy in question (not mentioned in the obstetric record). Case 4's mother had had three previous abortions and spotting and cramps during this pregnancy, and Case 5's mother had had no previous miscarriages, but stated that therapy was begun because of a gush of bright-red blood, which continued intermittently for one week. Since the risk of miscarriage in one or more patients may have been low, it appears that synthetic estrogens in the absence of threatened abortion may lead to vaginal cancer.

The New York State Cancer Registry reviewed records from 1950 through 1970. All vaginal adenocarcinomas were diagnosed during the period 1966 through 1971, with three of the five being diagnosed last year or this year. This raises concern about the future. It is not known how many more

vaginal carcinomas will be developing, whether other types of cancer will also develop in men or women, or whether a longer induction period may be present for those who received a smaller dose.

There can no longer be doubt that synthetic estrogens are absolutely contraindicated in pregnancy. Young women with persistent irregular bleeding should have careful intravaginal inspection to rule out possible neoplastic disease.

We are indebted to Drs. Sidney B. Doolittle and Robert E. L. Nesbitt, Jr., Syracuse, and Dr. James N. Nicklas, Glen Cove, Mrs. Katherine Richard, public-health nurse, St. Lawrence County, and Mr. Joseph M. Cuneo, biostatistician, Nassau County Health Department, New York, for reporting of patients and assistance with this study.

REFERENCES

1. Herbst AL, Ulfelder H, Poskanzer DC: Adenocarcinoma of the vagina: association of maternal stilbestrol therapy with tumor appearance in young women. *N Engl J Med* 284:878-881, 1971
2. Langmuir AD: New environmental factor in congenital disease. *N Engl J Med* 284:912-913, 1971
3. Smith OW: Diethylstilbestrol in the prevention and treatment of complications of pregnancy. *Am J Obstet Gynecol* 56:821-834, 1948
4. Physicians' Desk Reference to Pharmaceutical Specialties and Biologicals (PDR). Rutherford, New Jersey, Medical Economics, Inc. 1950, pp 468, 500
5. Herbst AL, Scully RE: Adenocarcinoma of the vagina in adolescence: a report of 7 cases including 6 clear-cell carcinomas (so-called mesonephromas). *Cancer* 25:745-757, 1970
6. Goth A: Medical Pharmacology: Principles and concepts. Second edition. St Louis, CV Mosby Company, 1964, pp 426-427

NOTES OF A BIOLOGY-WATCHER

A Fear of Pheromones

LEWIS THOMAS, M.D.

WHAT are we going to do if it turns out that we have pheromones? What on earth would we be doing with such things? With the richness of speech, and all our new devices for communication, why would we want to release odors into the air to convey information about anything? We can send notes, telephone, whisper cryptic invitations, announce the giving of parties, even bounce words off the moon and make them carom around the planets. Why a gas, or droplets of moisture made to be deposited on fenceposts?

Comfort¹ has recently reviewed the reasons for believing that we are, in fact, in possession of anatomic structures for which there is no rational explanation except as sources of pheromones — tufts of hair, strategically located apocrine glands, unaccountable areas of moisture. We even have folds of skin here and there designed for the controlled nurture of bacteria, and it is known that certain microbes eke out a living, like 18th-century musicians,

producing chemical signals by ornamenting the products of their hosts.²

Most of the known pheromones are small, simple molecules, active in extremely small concentrations. Eight or 10 carbon atoms in a chain are all that are needed to generate precise, unequivocal directions about all kinds of matters — when and where to cluster in crowds, when to disperse, how to behave to the opposite sex, how to ascertain what is the opposite sex, how to organize members of a society in the proper ranking orders of dominance, how to mark out exact boundaries of real estate, and how to establish that one is, beyond argument, one's self. Trails can be laid and followed, antagonists frightened and confused, friends attracted and enchanted.

The messages are urgent, but they may arrive, for all we know, in a fragrance of ambiguity. "At home, 4 p.m. today," says the female moth, and releases a brief explosion of bombykol, a single molecule of which will tremble the hairs of any male within miles and send him driving upwind in a confusion of ardor. But it is doubtful if he has an awareness of being caught in an aerosol of chemical attractant. On the contrary, he probably finds suddenly that it has become an excellent day, the weather remarkably bracing, the time appropriate for a bit of exercise of the old wings, a brisk turn upwind. En route, traveling the gradient of bombykol, he notes the presence of other males, heading in the same direction, all in a good mood, inclined to race for the sheer sport of it. Then, when he reaches his destination, it may seem to him the most extraordinary of coincidences, the greatest piece of luck: "Bless my soul, what have we here!"

It has been soberly calculated that if a single female moth were to release all the bombykol in her sac in a single spray, all at once, she could theoretically attract a trillion males in the instant.³ This is, of course, not done.

Fish make use of chemical signals for the identification of individual members of a species, and also for the announcement of changes in the status of certain individuals. A catfish that has had a career as a local leader smells one way, but as soon as he is displaced in an administrative reorganization, he smells differently, and everyone recognizes the loss of standing. A bullhead can immediately identify the water in which a recent adversary has been swimming, and can distinguish between this fish and all others in the school.⁴

There is some preliminary, still fragmentary evidence for important pheromones in primates. Short-chain aliphatic compounds are elaborated by female monkeys in response to estradiol, and these are of consuming interest to the males.⁵ Whether there are other sorts of social communication by pheromones among primates is not known.

The possibility that human beings are involved in this sort of thing has not attracted much attention until recently. It is still too early to say how it will

Address reprint requests to Dr. Thomas at the Department of Pathology, Yale University School of Medicine, 310 Cedar St., New Haven, Conn. 06510.



NOVEMBER 1971

DRUG BULLETIN

DIETHYLSTILBESTROL
CONTRAINDICATED
IN PREGNANCY

DRUG'S USE LINKED TO ADENOCARCINOMA IN THE OFFSPRING

We wish to bring to the attention of all physicians, hospitals, and medical personnel an important possible toxic effect of diethylstilbestrol reported for the first time in April 1971 by Herbst, et al¹. From their studies the authors concluded that maternal ingestion of diethylstilbestrol during pregnancy appears to increase the risk of vaginal adenocarcinoma developing years later in the offspring exposed. The authors studied eight cases of adenocarcinoma of the vagina in patients born between 1946 and 1951. The malignancies were identified and treated between 1966 and 1969. In seven of the eight cases, there was a history of maternal use of diethylstilbestrol. Because this type of malignancy in young girls had rarely been reported previously, the authors conducted a retrospective investigation in an attempt to find factors that may be associated with such malignancy in this age group. Four matched controls were established for each patient and the data obtained were subjected to statistical analysis. A statistically significant relationship was observed for three variables: diethylstilbestrol given during pregnancy ($p=.00001$), bleeding in that pregnancy ($p=\text{less than } .05$) and prior pregnancy loss ($p=\text{less than } .01$). It is obvious that the most significant of the variables is the administration of diethylstilbestrol during pregnancy.

Since publication of this study, five additional cases of this malignancy associated with the maternal use of diethylstilbestrol have been reported by Greenwald, et al². Dr. Herbst, in a recent communication to FDA, has reported an additional 15 cases associated with use of this drug, bringing the total number of known cases to 27. It must be emphasized that this type of epidemiologic study defines only an association and not necessarily a cause-and-effect relationship. Further studies are underway to clarify the significance of these findings.

In the meantime, the FDA is initiating the

following precautionary actions:

1. All manufacturers of DES or closely related congeners (dienestrol, hexestrol, benestrol, promethestrol) are being notified that appropriate changes will be required in the labeling for such drugs. This change will consist in the listing of pregnancy as a contraindication to the use of diethylstilbestrol and the other above-mentioned compounds.
2. All other estrogens will be required to have the following WARNING in their labeling: "A statistically significant association has been reported between maternal ingestion during pregnancy of diethylstilbestrol and the occurrence of vaginal carcinoma developing years later in the offspring. Whether such an association is applicable to all estrogens is not known at this time. In any event, estrogens are not indicated for use during pregnancy."
3. Epidemiological studies are being initiated to determine the true incidence of this disease in young women, the number at risk, the characteristics of patient populations with this malignancy, and the probability of a cause-and-effect relationship.

Both FDA and the medical profession face a responsibility to help determine whether this reported association constitutes a cause-and-effect relationship. We ask that all physicians consider appropriate steps to assist FDA case-finding and to protect any patients who might be at risk.

It may be possible to trace the offspring of those mothers who received DES during pregnancy. All physicians should be especially alert for young women whose mothers may have received hormonal therapy during pregnancy, particularly those young women who may be experiencing irregular vaginal bleeding. The association should be a routine consideration for physicians whose practice includes young women.

This is a previously unsuspected health problem. Further information is essential to the FDA and to the medical profession. We ask your help in reporting any cases you encounter for entry in a case registry.

1. Herbst, et al — Adenocarcinoma of the Vagina — New England Journal of Medicine — Volume 284, Number 16 (April 22, 1971).

2. Greenwald, et al — Vaginal Cancer After Maternal Treatment with Synthetic Estrogens — New England Journal of Medicine, Volume 285, Number 7, (August 12, 1971).

FDA will take every possible step to insure that you are kept abreast of new information as soon as it can be gathered and analyzed.

For your convenience, an adverse reaction

reporting form is printed in this bulletin. FDA will forward a supply of forms to each practicing physician as soon as they are printed. Facsimile forms are acceptable.

DRUG EXPERIENCE REPORT (IN CONFIDENCE)		Form Approved OMB No. XXXXXXX	
PATIENT INITIALS (Optional)		DATE OF REACTION ONSET	
SUSPECTED REACTION(S)			
SUSPECTED DRUG(S); TRADE/GENERIC NAME (Manufacturer's name, if possible)			
DISORDER OR REASON FOR USE OF DRUG(S) (Optional)	ROUTE	TOTAL DAILY DOSE	DATES OF ADMINISTRATION
OTHER DRUGS TAKEN CONCOMITANTLY			
COMMENTS (Optional)			
PHYSICIAN'S NAME, ADDRESS, AND ZIP CODE			

FD PROPOSED FORM

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
FOOD AND DRUG ADMINISTRATION
5600 Fishers Lane
Rockville, Maryland 20852
OFFICIAL BUSINESS

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF H.E.W.



FIRST CLASS

IMPORTANT PRESCRIBING INFORMATION
FROM CHARLES C. EDWARDS, M.D.,
COMMISSIONER OF FOOD AND DRUGS

FDA DRUG BULLETIN

News and Reports of Interest to
Practicing Physicians and Allied
Health Professionals, Issued by
the Food and Drug Administra-
tion, Department of Health,
Education, and Welfare. Com-
ments are invited. All corre-
spondence should be addressed
to the Assistant to the Director
for Medical Communications,
Bureau of Drugs, BD-40, Food
and Drug Administration,
5600 Fishers Lane, Rockville,
Maryland 20852

ADENOCARCINOMA OF THE VAGINA*

Association of Maternal Stilbestrol Therapy with Tumor Appearance in Young Women

ARTHUR L. HERBST, M.D., HOWARD ULFELDER, M.D., AND DAVID C. POSKANZER, M.D.

Abstract Adenocarcinoma of the vagina in young women had been recorded rarely before the report of several cases treated at the Vincent Memorial Hospital between 1966 and 1969. The unusual occurrence of this tumor in eight patients born in New England hospitals between 1946 and 1951 led us to conduct a retrospective investigation in search of factors that might be associated with tumor appearance. Four matched controls were established for each patient; data were obtained by personal interview. Results show maternal

bleeding during the current pregnancy and previous pregnancy loss were more common in the study group. Most significantly, seven of the eight mothers of patients with carcinoma had been treated with diethylstilbestrol started during the first trimester. None in the control group were so treated (p less than 0.00001). Maternal ingestion of stilbestrol during early pregnancy appears to have enhanced the risk of vaginal adenocarcinoma developing years later in the offspring exposed.

CANCER of the vagina is rare, occurring usually as epidermoid carcinoma in women over the age of 50 years.¹ Between 1966 and 1969, however, seven girls 15 to 22 years of age with adenocarcinoma of the vagina (clear-cell or endometrial type) were seen at the Vincent Memorial Hospital.² Although isolated case reports of histologically similar adenocarcinomas of the vagina had previously been published,^{3,4} these carcinomas, too, were usually in older patients. No such case in the younger age group had been seen at this institution before 1966.

The tumor typically caused prolonged vaginal bleeding that, occurring in young women, was mistaken for anovulatory bleeding and delayed the correct diagnosis. Routine vaginal cytology was often negative, and the tumor was not palpated on rectal examination. The correct diagnosis was arrived at only after vaginal examination had been performed.

Histologically, one of the tumors resembled endometrial carcinoma, but the remainder were characterized by tubules and glands lined by clear cells containing glycogen or "hobnail" cells. The clear cells also appeared in solid nests. There was a high prevalence of benign adenosis of the vagina in this group of patients. Although these tumors with clear cells and hobnail cells have been termed "mesonephroma," there is evidence that they are of Müllerian origin.⁵

Because of the apparent clustering of these cases, which appeared within four years, attention was focused on possible other similarities among them. However, they did not uniformly use any intra-vaginal irritant, douches or tampon. Only one patient had had sexual exposure. Before the onset of the present illness, none had been given birth-control pills. We then decided to conduct a case-control, retrospective study that would compare in detail

these patients and their families with an appropriate control group to uncover factors that might be associated with the sudden appearance of these tumors.

METHODS

Four matched controls for each patient with vaginal carcinoma were selected by examination of the birth records of the hospital in which each patient was born. Females born within five days and on the same type of service (ward or private) as the eight patients were identified. Women who gave birth to daughters closest in time to each patient with carcinoma were first considered. Interviewing of all mothers was done from a standard questionnaire by personal interview carried out by a trained interviewer.

In addition to the seven cases cited above, an eighth identical case of clear-cell adenocarcinoma of the vagina occurred in 1969 in a 20-year-old patient, who was treated at another Boston hospital.† Because she and her family with their matched controls were as available as our own cases, this patient has been included with the original group, and these eight cases form the basis of this study.

Comparison of the data obtained from patients and controls was carried out with the use of the paired t -test for parametric data and the matched control method suggested by Pike and Morrow⁶ for nonparametric data. Unpaired t -tests and chi-square tests with Yates correction were also carried out but were not significantly different from the results obtained with the paired methodologies.

RESULTS

Table 1 summarizes chronologic details of each patient with her therapy and results. The table demonstrates the clustering of patients for time of birth and occurrence of tumor. In Table 2 the data for seven pertinent areas of inquiry for each patient

*From the Vincent Memorial Hospital (Gynecological Service of the Massachusetts General Hospital) (address reprint requests to Dr. Herbst at the Vincent Memorial Hospital, Fruit St., Boston, Mass. 02114).

Supported by a grant (1373-C-1) from the American Cancer Society (Massachusetts Division), Inc.

†We are indebted to Dr. Donald P. Goldstein, of Boston, for permission to include his case in this study.

Table 1. Summary of Cases with Carcinoma.

CASE NO.	AGE AT 1ST SYMPTOMS (Yr)	Yr OF BIRTH	Yr OF TREATMENT	THERAPY	STATUS 1971
1	20	1949	1969	Posterior exenteration & vaginectomy	Living & well
2	15	1951	1967	Radical hysterectomy & vaginectomy, with vaginal replacement	Living & well
3	14	1950	1968	Exploratory laparotomy	Died (1968)
4	15	1950	1966	Wide local excision	Living & well
5	19	1949	1969	Radical hysterectomy & vaginectomy, with vaginal replacement	Living & well
6	16	1951	1967	Radical hysterectomy & vaginectomy, with vaginal replacement	Living & well
7	18	1949	1968	Anterior exenteration, with bowel substitution of vagina	Living & well
8	22	1946	1968	Anterior exenteration, with bowel substitution of vagina	Living & well

and her matched controls are displayed, including maternal age at the birth of the child, maternal smoking (at least 10 cigarettes per day before the birth of the child), bleeding during study pregnancy, any prior pregnancy loss, maternal estrogen therapy during study pregnancy, breast feeding of infant and intrauterine x-ray exposure.

There is a highly significant association between the treatment of the mothers with estrogen diethylstilbestrol during pregnancy and the subsequent development of adenocarcinoma of the vagina in their daughters (p less than 0.00001). Other factors found to be different between probandae and controls but at lower levels of significance are maternal bleeding in the study pregnancy (p less than 0.05) and any prior pregnancy loss (p less than 0.01). No significant differences between the populations were found for maternal age at time of birth of patient, smoking in parents, intrauterine x-ray exposure and breast feeding. Other topics covered in the questionnaire that also were not statistically significant are listed in Table 3.

All the mothers who took stilbestrol began therapy in the first trimester of pregnancy. They received either a constant dose administered throughout the pregnancy, or a continually increasing dose given almost to term. Six of the seven mothers volunteered the information that stilbestrol had been prescribed for them. The seventh was uncertain, but her obstetrician identified the drug as diethylstilbestrol. Bleeding during this pregnancy or previous pregnancy loss (or both) led to the administration of stilbestrol in all seven cases. The programs of management for these pregnancies occasionally included vitamins, iron or calcium.

DISCUSSION

By the choice of a control group consisting of females born within five days of the birth of the probandae in the same hospital and on the same type of service, socioeconomic differences are reduced. Of the candidates for the control group found on hospital birth lists 25 per cent could not be located. A selection bias is therefore possible because only the families

Table 2. Summary of Data Comparing Patients with Matched Controls.

CASE NO.	MATERNAL AGE (Yr)		MATERNAL SMOKING		BLEEDING IN THIS PREGNANCY		ANY PRIOR PREGNANCY LOSS		ESTROGEN GIVEN IN THIS PREGNANCY		BREAST FEEDING		INTRA-UTERINE X-RAY EXPOSURE	
	CASE	MEAN OF 4 CONTROLS	CASE	CONTROL	CASE	CONTROL	CASE	CONTROL	CASE	CONTROL	CASE	CONTROL	CASE	CONTROL
1	25	32	Yes	2/4	No	0/4	Yes	1/4	Yes	0/4	No	0/4	No	1/4
2	30	30	Yes	3/4	No	0/4	Yes	1/4	Yes	0/4	No	1/4	No	0/4
3	22	31	Yes	1/4	Yes	0/4	No	1/4	Yes	0/4	Yes	0/4	No	0/4
4	33	30	Yes	3/4	Yes	0/4	Yes	0/4	Yes	0/4	Yes	2/4	No	0/4
5	22	27	Yes	11/34	No	1/4	No	1/4	No	0/4	No	0/4	No	0/4
6	21	29	Yes	3/4	Yes	0/4	Yes	0/4	Yes	0/4	No	0/4	No	1/4
7	30	27	No	3/4	No	0/4	Yes	1/4	Yes	0/4	Yes	0/4	No	1/4
8	26	28	Yes	13/4	No	0/4	Yes	0/4	Yes	0/4	No	0/4	Yes	1/4
Total			7/8	21/32	3/8	1/32	6/8	5/32	7/8	0/32	3/8	3/32	1/8	4/32
Mean	26.1	29.3												
Chi square (1 df)*			0.53		4.52		7.15		23.22		2.35		0	
p value			0.50		<0.05		<0.01		<0.0001		0.20			
		(N.S.)		(N.S.)							(N.S.)			(N.S.)

* Matched control chi-square test used as described by Pike & Morrow.²

† Standard error of difference 1.7 yr (paired t-test); N.S. = not statistically significant.

Table 3. Additional Factors Compared in Patients and Controls Not Found to Be Significantly Different.*

Birth weight
Age at onset of menses
Complications & outcome of study pregnancy
Ingestion of other medications during pregnancy
Childhood diseases of mothers & patients
History of tonsillectomy
Childhood ingestions
Household pets
Noteworthy illnesses of patients & parents
Cosmetic use in patients & mothers
Cigarette smoking in patients
Alcohol consumption in parents
Occupation & yr of education of parents

*Events compared before date of onset of present illness for each study patient & her matched controls.

remaining in the same area could be reached for comparison. However, all eight of the families of our patients are still living in or near the community where the patients were born. Control subjects still living in the community may be a more suitably matched study population. One potential control family was excluded because the birth record indicated that the offspring had Down's syndrome. It was necessary to locate only 34 women to obtain 32 control families who would collaborate with this study.

It should be emphasized that among the eight study mothers there was a total of 10 prior pregnancy losses and only six among the 32 controls. As can be seen from Table 2, bleeding during pregnancy was also more frequent in the study group. The fact that these were truly high-risk pregnancies was the indication for stilbestrol administration. The associations observed with bleeding in the study pregnancy and with previous pregnancy loss may reflect the characteristics of the population that was selected for estrogen treatment. In one of the eight mothers whose daughter had clear-cell adenocarcinoma, there was no evidence that estrogens were administered during pregnancy, nor had she experienced prior pregnancy loss or bleeding during the study pregnancy. Furthermore, these tumors were known to occur, though rarely, in women born before the availability of oral estrogens. Thus, factors other than maternal stilbestrol ingestion appear to be operative in their development. Moreover, the stilbestrol pills prescribed for these mothers were those available between 1946 and 1951. The ingredients of these tablets, the estrogenic potency of stilbestrol and its other chemical properties must all be recognized as possible elements in the association observed. Finally, among four of the eight families there are five female siblings, ranging in age from 18 to 22 years, who are also products of pregnancies during which their mothers took diethylstilbestrol. Up to the present, a vaginal tumor has not developed in any of these girls.

To try to estimate the frequency of stilbestrol administration and the risk of development of these

tumors in female offspring whose mothers took stilbestrol during pregnancy, we have examined the files of one of the hospitals in this study for the years 1946 through 1951. During this interval there was a special high-risk pregnancy clinic at the Boston Lying-in Hospital in which stilbestrol was prescribed to 675 ward patients. There were approximately 14,500 ward deliveries, indicating that at that time roughly one in 21 ward patients at the Boston Lying-in Hospital were treated during pregnancy with stilbestrol. Thus, it appears to be well within the range of statistical expectation to have a control group in which the frequency of stilbestrol use was 0 in 32. In the interval 1946 to 1951 the private service at the Boston Lying-in Hospital had more deliveries than the ward service. We have knowledge of only one case of clear-cell adenocarcinoma developing in a patient born at the Boston Lying-in Hospital, and she was delivered on the private service. Whatever the risk of tumor development in the exposed offspring, it appears to be small.

The high concurrence of benign vaginal adenosis with these adenocarcinomas suggests that an anomaly of vaginal epithelial development may be a predisposing condition. Previous reports have described an association between adenosis and this tumor in older women,^{2,3} and their concurrence in younger patients was initially noted in the present cases.² It may be that an increase in adenosis occurs at menarche in these patients and results in greater quantities of benign tissue at risk for malignant change. It is also possible that stilbestrol alters fetal vaginal cells in utero, with changes that do not become manifest in a malignant form until years later. Animal experiments as well as further follow-up data on patients who were exposed to estrogens in utero may provide some answers. Regardless of the ultimate explanation, histologic observations of associated adenosis combined with the known estrogenic effect of stilbestrol further support a Müllerian and not a mesonephric origin for these adenocarcinomas.

The time of birth of these patients (1946 to 1951) coincides with the beginning of the widespread use of estrogens in support of high-risk pregnancy.¹⁰ It is likely that more patients with this tumor will appear as girls who were exposed in utero come to maturity. Furthermore, although our oldest patient was discovered at the age of 22 years, it is possible that these tumors will appear in even older women as the "at-risk" population matures. Although the chance of development of these tumors appears to be very small, the results of this study suggest that it is unwise to administer stilbestrol to women early in pregnancy. Furthermore, abnormal bleeding in adolescent girls can no longer be assumed to be due to involution, and the possibility of vaginal tumor should be excluded by a physician's examination.



MAY 1973

DRUG BULLETIN

POSTCOITAL DIETHYLSTILBESTROL

NITROFURAZONE LABELING REVISED
TO ELIMINATE ALL-PURPOSE USE

TARDIVE DYSKINESIA ASSOCIATED
WITH ANTIPSYCHOTIC DRUGS

REQUIREMENTS FOR PROTECTION AGAINST X RAYS

U-100 INSULIN

POSTCOITAL DIETHYLSTILBESTROL

In agreement with its extragovernmental physician-advisers, FDA has approved, under restricted conditions, postcoital (contraceptive) use of diethylstilbestrol (DES), a synthetic estrogen. Adequate evidence to support the use of any other estrogen for this purpose is not presently available.

The Agency considers the use of DES for this purpose to be safe only as an emergency measure (in situations such as rape, incest, or where, in the physician's judgment, the patient's physical or mental well-being is in jeopardy) and explicitly warns against its routine or frequent use as a contraceptive.

Physicians are urged, prior to prescribing DES for this purpose, to inform patients (or guardians) fully of the possible side effects of the drug, and of alternative measures available and their hazards, so that the patient may participate in an informed way in the decision to use the drug. Pregnancy should be ruled out by appropriate tests prior to instituting therapy, so that no unnecessary exposure of a fetus to DES occurs.

The efficacy of DES in preventing pregnancy depends upon the time-lapse after coitus and dosage of the drug. The currently recommended dosage is 25 mg twice a day for 5 continuous days beginning, preferably, within 24 hours and not later than 72 hours after exposure. When this dosage is given within the specified time interval after sexual intercourse, DES is highly effective in preventing conception. But the patient must be warned to take the full course of the drug in spite of the nausea which commonly occurs, if it is to be effective.

There is at present no positive evidence that the restricted postcoital use of DES carries a significant carcinogenic risk either to the mother or fetus. However, because existing data support the possibility of delayed appearance of carcinoma in females whose mothers have been given DES later in pregnancy, and because teratogenic and other adverse effects on the fetus with the very early administration recommended are ill understood, failure of postcoital treatment with DES deserves serious consideration of voluntary termination of pregnancy.

Before prescribing, the physician should be familiar with the complete FDA-approved labeling on products intended for this use.

NITROFURAZONE LABELING REVISED TO ELIMINATE ALL-PURPOSE USE

The indications for nitrofurazone, a topically applied antibacterial sold most widely under the trade name Furacin, are being changed to eliminate all purpose use of the drug.

New indications will say that nitrofurazone is indicated in two circumstances:

- (1) For adjunctive therapy of patients with second and third-degree burns when bacterial resistance to other drugs is a real or potential problem, and
- (2) In skin grafting where bacterial contamination may cause graft rejection and/or donor site infection, particularly in hospitals with historical resistant bacteria epidemics.

Some members of the class of chemicals to which nitrofurazone belongs are known to induce tumors of various types in rodents. Nitrofurazone itself has been shown to promote the development of mammary tumors when fed in high doses to female rats.

The relevance of these findings in man is unknown, but nitrofurazone is known to be absorbed through the skin. Topically applied nitrofurazone also carries the risk of cutaneous sensitization. There are no well-controlled studies to support the prophylactic use of topical antimicrobial agents in minor and usually self-limited cutaneous traumas.

TARDIVE DYSKINESIA ASSOCIATED WITH ANTIPSYCHOTIC DRUGS

Tardive dyskinesia, a syndrome characterized by rhythmical involuntary movements, may be associated with the use of phenothiazines and certain other antipsychotic medications. The condition appears in some patients on long-term therapy, sometimes even after it has been discontinued. FDA recommends that the antipsychotic medications be withdrawn immediately if the syndrome appears, and has added the following statement to the ADVERSE REACTIONS section of the package inserts of antipsychotic drugs:

Tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy with phenothiazines and related agents has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Involuntary movements of the extremities sometimes occur. There is no known treatment for tardive dyskinesia; antiparkinsonism agents usually do not alleviate the symptoms. It is advised that all antipsychotic agents be discontinued if the above symptoms appear. If treatment is re-instituted, or dosage of the particular drug increased, or another drug substituted, the syndrome may be masked. It has been suggested that fine vermicular movements of the tongue may be an early sign of the syndrome, and that the full-blown syndrome may not develop if medication is stopped when lingual vermiculation appears.

At times a choice between two evils must be made, as when on the one hand a patient's psychosis worsens without a given antipsychotic drug whereas on the other hand administration of the drug causes severe side effects. Use of the lowest possible dose of the drug adequate to control symptoms appears to be one possible answer. Alternatively, the patient may be given another drug chemically least like that causing the dyskinesia.

The incidence of tardive dyskinesia is not well established. It is rarely seen in acute psychiatric units, even in patients with recurring schizophrenia. But incidence rates of about 20 percent have been reported in older, institutionalized, chronically ill patients. Perhaps 3 percent to 6 percent of patients in a mixed psychiatric population receiving neuroleptics exhibit some aspects of the syndrome at one time or another.

The physician may be able to reduce the risk of producing tardive dyskinesia by:

1. Minimizing the unnecessary use of neuroleptic medication (especially in high doses) in chronically ill patients. Many of the latter can be satisfactorily maintained for long periods without antipsychotic drugs. Drug holidays are advised in patients receiving long-term medication.
2. Discontinuing neuroleptics, if possible, at the first sign of abnormal oral or lingual movements or other possible manifestations of tardive dyskinesia.
3. Observing these precautions carefully in the elderly (females especially) and probably in all patients over age 50.

REQUIREMENTS FOR PROTECTION AGAINST X RAYS

From 1300 to 6000 cancer deaths annually are caused by exposure of the American public to present levels of diagnostic x rays. In addition, ill health results from genetic damage caused by the exposure. These conclusions were reached by the National Academy of Sciences/National Research Council through its study on *The Effects on Populations of Exposure to Low Levels of Ionizing Radiation*. A report on the study was recently released.

Improved X-ray Technique Needed - The NAS-NRC study further shows that present exposure of the population to x rays, and the associated toll in lives, can be significantly reduced through simple improvements in x-ray techniques. For example, present genetic damage from x rays can be reduced by up to 50 percent through improved techniques such as using gonad shielding, particularly on male patients and restricting the size of the x-ray beam to the area of clinical interest. This is especially important

during those x-ray procedures in which the reproductive organs are in the direct x-ray beam, as during examinations of the lower back, lower abdomen, and hip. In view of the known leukemogenic effect of x rays, avoiding needless exposure of the bone marrow is also of special significance. Because of the increased radiosensitivity of embryonic tissue, special prudence should be exercised in prescribing x-ray examinations for pregnant or potentially pregnant women.

Existing X-ray Equipment Need Not Be Upgraded - FDA has asked State radiation control agencies to advise diagnostic x-ray equipment dealers and users that the new Federal radiation protection standard for x-ray machines and components does not require modification of equipment now being used. The action was taken after FDA learned that some dealers were suggesting that all existing x-ray equipment will have to be upgraded to meet the Federal standard when it becomes effective next August 15. FDA noted that, although equipment now in use will not have to be modified before the standard becomes effective, manufacturer-certified components installed in x-ray systems after August 15 must be of the type called for by the standard. All changes made in equipment and all sales must be in compliance with the regulations.

U-100 INSULIN

U-100 insulin, which is now being made available, offers distinct advantages over U-40 and U-80 preparations. It is offered as regular and in a variety of long-acting forms.

Each milliliter of U-100 insulin contains 100 units of insulin. The drug is dispensed in 10 ml (1000 unit) vials.

It is important that patients for whom this new insulin is prescribed be instructed in the use of the new 1 ml U-100 syringe. Each calibration of this syringe represents 2 units or 0.02 ml. Every 0.1 ml or 10 unit calibration is marked with corresponding numerals.

When small doses are given or accuracy down to 1 unit is necessary, a 0.35 ml (35 unit) syringe is available in which each calibration represents 0.01 ml or 1 unit.

U-40 and U-80 insulins will continue to be marketed until the use of U-100 is generally accepted.

RESPONSE TO DRUG EXPERIENCE REPORT

The FDA deeply appreciates the response to the Drug Experience Report (short form) enclosed with the last issue of the *Drug Bulletin*. More than 2000 adverse drug reaction reports have been received, the best short term accumulation on record. Replacement forms have been sent to all physicians who responded and a summary of the evaluated data will be sent to them as soon as it is available.

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
FOOD AND DRUG ADMINISTRATION
5600 Fishers Lane
Rockville, Maryland 20852
OFFICIAL BUSINESS

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF H.E.W.
HEW 393



FIRST CLASS

IMPORTANT PRESCRIBING INFORMATION



MAY 1973

DRUG BULLETIN

FDA DRUG BULLETIN

News and Reports of Interest to Practicing Physicians and Other Health Professionals, Issued by the Food and Drug Administration, Department of Health, Education, and Welfare. Comments are invited. All correspondence should be addressed to the Assistant to the Director for Medical Communications, Bureau of Drugs, BD-40, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20852.

PRENATAL EXPOSURE TO STILBESTROL

A Prospective Comparison of Exposed Female Offspring with Unexposed Controls

ARTHUR L. HERBST, M.D., DAVID C. POSKANZER, M.D., STANLEY J. ROBBOY, M.D.,
LAWRENCE FRIEDLANDER, M.D., AND ROBERT E. SCULLY, M.D.

Abstract The effects of prenatal exposure to diethylstilbestrol were studied by a prospective cohort investigation of 110 exposed and 82 unexposed females. The general health characteristics of mothers and daughters in both groups were similar. Among the exposed, there were striking benign alterations of the genital tract, which included transverse ridges (22 per cent), abnormal vaginal mucosa (56 per cent), and biopsy-proved adenosis (35 per cent). Among the unexposed there were no ridges and one case of vaginal mucosal

abnormality including adenosis ($p < 0.0001$). Abnormal cervical epithelium occurred in almost all exposed subjects but in only half the unexposed ($p < 0.0001$). The incidence of vaginal adenosis was highest when diethylstilbestrol was begun in early pregnancy. It was not detected when treatment was initiated in the 18th week or later. Oral contraceptive use and prior pregnancy were associated with less adenosis and erosion, respectively ($p < 0.05$). No cases of cancer were observed. (N Engl J Med 292:334-339, 1975)

IN 1971 a case-control epidemiologic investigation associated the recent occurrence of clear-cell adenocarcinoma of the vagina in young women with intrauterine exposure to diethylstilbestrol administered to their mothers for the therapy of high-risk pregnancies.¹ The results of this investigation were soon confirmed,² and since then, over 170 cases of vaginal and cervical clear-cell adenocarcinomas have been collected, with a definite history of maternal exposure to non-steroidal estrogens in 65 per cent of the investigated cases.³ Although these carcinomas have been encountered only rarely in females exposed to diethylstilbestrol, a variety of other abnormalities of the lower genital tract have been reported to occur with great frequency. These include vaginal adenosis (the presence of glandular epithelium in the vagina), cervical erosion, or ectropion (glandular epithelium on the portio of the cervix), and transverse fibrous ridges in the vagina and on the cervix ("cervical pseudopolyp," "cockscorn cervix," or "cervical hood").⁴⁻⁸ Although most of these abnormalities were known to occur rarely in the prestilbestrol era, their prevalence in unexposed women examined as carefully as those who have been exposed has not been established. The present study was undertaken to compare the results of epidemiologic, clinical, and pathological investigations of exposed women with those of unexposed controls, as well as to ascertain the current status of the exposed post-menarchal women whose mothers had been treated in the Boston Lying-in Hospital Diethylstilbestrol Clinic between 1947 and 1958.

MATERIALS AND METHODS

Identification of Exposed and Control Subjects

Through the generous cooperation of Drs. Olive and George van S. Smith, accurate research records of the 841 mothers treated in the Diethylstilbestrol Clinic of the Boston Lying-in Hospital between 1947 and 1958 were made available to us. These records contain both the dates of all the pregnancies and the details of

therapy. The drug was administered according to a standard schedule, with the dosage depending on the week in pregnancy in which the therapy was started. During or before the sixth week, 2.5 mg daily was given, increasing to 5 mg in the seventh week. An additional 5 mg was administered every two weeks until the 15th week, when 25 mg per day was prescribed. The daily dosage was then increased by 25 mg each month, reaching a maximum of 150 mg. All the mothers began therapy before the 23d week, and the drug was discontinued at the end of the 35th week.^{9,10} We assigned a random number to each diethylstilbestrol pregnancy, and, starting with the lowest assigned number, located the hospital birth records and then traced the parents of each female offspring. Telephone books and city directories were consulted, and the generous assistance of the Massachusetts Registry of Motor Vehicles was obtained. The correct identity of the mother was then verified by telephone or letter, and an examination of her female offspring was offered without charge if she lived within approximately 1000 km of Boston.

We selected the control group simultaneously by examining the hospital birth records and identifying an unexposed female who was born on the clinic service closest in time to (and always within five days of) each exposed female. It was further required that the mother's initial visit to the prenatal clinic occur before the 23d week of gestation. The controlled portion of the study was limited to white women 18 years of age or older, for several reasons. First of all, it appeared unreasonable to request healthy, unexposed girls under the age of 18 years to be examined. Secondly, since all but five exposed subjects were white, it was decided to limit the controlled portion of the study to whites. Finally, it was not possible within the hospital data base to match maternal gravidity and parity and still find an adequate number of unexposed subjects. Therefore, these factors were not controlled. The same techniques used to find exposed subjects were used to locate controls. The results of the examination and tests with appropriate recommendations for follow-up observation were sent by letter to the subject and her physician. In addition to those included in the controlled study, all exposed post-menarchal subjects who could be located were offered appointments, to be certain that they would be examined by a physician. This precaution also permitted analysis of a larger number of cases in the second, uncontrolled portion of this investigation.

Investigation of the Subjects

Special clinics at each of which six to eight subjects were examined were conducted over an 18-month period. The two research analysts who identified and communicated with the mothers and their daughters knew which of the latter had a history of exposure to diethylstilbestrol, but this information was not available to those who performed the physical, pathological, or cytologic examinations. The maternal health histories were obtained by personal or telephone interview by the two research analysts. Each subject's medical history was obtained by the examining physician, and a thorough general physical examination was performed, followed by a pelvic examination that included

From the Vincent Memorial Hospital (Gynecological Service of the Massachusetts General Hospital) and the James Homer Wright Pathology Laboratories, Massachusetts General Hospital (address reprint requests to Dr. Herbst at the Adenocarcinoma Registry, Warren 275, 275 Charles St., Boston, MA 02114).

Supported in part by a grant (ROI CA13139-03) from the National Cancer Institute and a grant (ET-52) from the American Cancer Society (Dr. Robboy is a junior faculty fellow of the American Cancer Society).

both a scrape of the vaginal mucosa and a pool aspiration for cytologic testing and careful inspection, palpation, and iodine staining of the vagina and cervix. Areas that appeared red or otherwise abnormal or that failed to stain with iodine solution were recorded and biopsied. Rectangular pieces of tissue up to 3 mm in diameter were obtained for microscopical examination with the use of either the Young or the Kervorkian punch.

Pathological Evaluation of Tissue

Biopsies from the fornices of the vagina or areas distal to it were classified as vaginal. Those from the cervix or from fibrous ridges on or in apposition to the cervix (cervical rim or hood) were classified as cervical. At least five slides were prepared from each specimen; two were stained with hematoxylin and eosin, and one each with mucicarmine and periodic-acid-Schiff with and without diastase.

Analysis of Data

In the controlled portion of the study, the findings in the exposed and unexposed subjects were compared statistically by chi-square analysis. In the second portion of the study, the variation in the incidence of vaginal adenosis as a function of the time of initiation of diethylstilbestrol therapy during pregnancy was examined by testing for a linear trend in proportions.¹¹ The findings among the exposed subjects were analyzed further by the use of a multiple logistic model¹² to provide estimates of the effect of several independent variables (log of diethylstilbestrol dosage, week during pregnancy of initiation of therapy, age, history of intercourse, use of oral contraceptives, and pregnancy history of the subject) on three dependent variables (vaginal adenosis, failure of iodine staining of the vagina, and cervical erosion). This method enabled the testing of the effect of one or more independent variables after adjustment for effects of a different independent variable—e.g., the effect of use of oral contraceptives on the presence of vaginal adenosis, with adjustment for the week in pregnancy during which diethylstilbestrol therapy was begun.

RESULTS

Investigation of 110 Exposed and 82 Control Subjects 18 to 25 Years of Age

Epidemiology (subjects and parents). The 841 pregnancies of mothers treated in the Clinic yielded 731 viable births (407 male and 324 female). Among the 324 female subjects, there were 267 white women 18 years of age or older who were compared to 267 unexposed women for the control portion of the study. As shown in Table 1, although 192 of the exposed and 203 of the unexposed were located, only 110 exposed and 82 unexposed women agreed to be examined. Among these, 66 per cent were 24 to 25 years and the remainder were 18 to 23 years of age. Because only those who were willing to participate in the study could be examined, it is possible that bias was introduced by the greater reluctance of the unexposed women to accept an examination. However, a comparison of the characteristics of the exposed and the unexposed subjects and those of their parents revealed a surprisingly close correspondence (Table 2). Sociologic factors such as maternal education and family social class were similar.

Table 1. Results of Search for White Subjects 18 Years of Age or Older.

GROUP	NO. OF MOTHERS WITH FEMALE CHILDREN	NO. FOUND	NO. OF DAUGHTERS EXAMINED
Exposed	267	192	110
Controls	267	203	82

There was no difference in the maternal histories of serious illnesses, including cancer. Likewise, no differences were noted in the health histories of the exposed and the control daughters, none of whom had cancer; both groups were also similar in age at onset and frequency of menstruation. The reproductive histories of both groups of daughters were also similar.

Physical examination. Between the two groups of subjects several differences that did not achieve statistical significance were noted on general physical examination. Abnormalities detected included scoliosis (three exposed), Charcot-Marie-Tooth disease (one exposed), and cardiac murmurs that were interpreted as organic (nine exposed and seven control). There was a difference in the height (160.5 cm exposed vs. 158.2 cm control, $p < 0.05$) but not in the weight (60.0 kg vs. 56.9 kg respectively) or in the ponderal index, which integrates weight as a factor of height (12.6 vs. 12.7 respectively). Otherwise, the general physical characteristics of the exposed and control subjects were similar.

Pelvic examination. No differences were detected in the appearance of the external genitalia, or in the estimated sizes of the uterus or the ovaries. Vaginal examination, however, revealed numerous differences between the two groups that were highly significant statistically (Table 3). Transverse fibrous ridges of the vagina and cervix were seen in 22 per cent of the exposed females, but in none of the controls. These ridges usually appeared as transverse bands in the upper vagina or near the cervix. They occasionally obliterated the vaginal fornices and often obscured the boundary between the vagina and cervix. Failure of portions of the vaginal mucosa to stain with iodine solution was observed in over half (56 per cent) the exposed subjects but in only 1 per cent of the controls. Some of these abnormal areas appeared red in the exposed subjects before iodine staining, but red areas in the vagina were not observed in the controls. Also, failure of portions of the cervix to stain with iodine was noted almost twice as often in the exposed (95 per cent) as in the control subjects.

Table 2. Characteristics of Exposed and Control Populations That Were Not Significantly Different.*

CHARACTERISTIC	
Parents:	
Education of mother (11.8 vs 11.9 yr)	
Maternal smoking	
Paternal smoking	
Social class	
Maternal history of surgery	
Maternal history of cancer or serious illness	
Daughters:	
Intrauterine exposure to x-rays	
Length of gestation	
Birth weight (3120 vs 3200 g)	
Breast feeding	
Smoking	
Onset of menses (12.7 vs 12.5 yr)	
Frequency of menses	
Use of oral contraceptives (37 vs 38%)	
No. who had been pregnant (46 vs 52%)	
No. who produced viable births (23 vs 28%)	
History of surgery	
History of cancer or serious illness	

*At 0.05 level or less.

Table 3. Results of Pelvic Examinations.

GROUP	NUMBER EXAMINED	FAILURE OF PART OF VAGINA TO STAIN WITH IODINE (%)	VAGINAL ADENOSIS IDENTIFIED IN BIOPSY SPECIMEN (%) ^a	FAILURE OF PART OF CERVIX TO STAIN WITH IODINE (%)	CERVICAL EROSION IDENTIFIED IN BIOPSY SPECIMEN (%) ^a	VAGINAL OR CERVICAL FIBROUS RIDGES (%)
Exposed	110	56	35	95	85	22
Control	82	1	1	49	38	0
chi-square		64.8	33.4	52.5	47	20.4
p value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

^aBiopsies taken from areas that appeared red or failed to stain with iodine solution.

(49 per cent). Red areas on the cervix were seen before iodine staining in both groups.

Pathology. Vaginal adenosis was detected by biopsy in 35 per cent of the exposed but only 1 per cent of the control subjects. In the former the adenosis was usually multifocal. On microscopical examination it was characterized by the presence of a single layer of mucinous columnar cells of endocervical type or a single or pseudostratified layer of cells that resembled endometrial and tubal epithelial cells. The latter cells were often ciliated; most of them had dark, deeply eosinophilic cytoplasm, but some had clear cytoplasm. In occasional cases, minor degrees of atypicality or loss of polarity of the nuclei were observed. The columnar epithelium lined the surface of the vagina or formed glands in the lamina propria (Fig. 1). Often, the glands were largely or totally replaced by solid masses of squamous epithelium (squamous pegs), which were continuous with the surface squamous epithelium (Fig. 1); the epithelium both in the pegs and on the surface was almost always composed of glycogen-poor or glycogen-free basal and prickly cells. This characteristic of the squamous cells or in some cases the replacement of the surface squamous epithelium by a layer of glandular epithelium accounted for the lack of staining with iodine. Two histologic variants of adenosis that were observed in the squamous pegs or in the surface squamous epithelium were droplets of mucin within individual squamous cells



Figure 1. Vaginal Adenosis (Hematoxylin and Eosin Stain). Glands with ciliated dark cells that resemble the endometrial or tubal lining lie in the lamina propria and merge in areas with squamous pegs (arrow). Both the squamous epithelium that lines the surface of the vagina and the squamous pegs continuous with it are composed of glycogen-free basal and prickly cells.

(Fig. 2) and small pools of mucin surrounded by tall to inconspicuously flat cells with mucinous cytoplasm (Fig. 3). The mucin droplets and pools, which sometimes became apparent only after mucin staining, were present in 74 per cent of the subjects with adenosis and were the only evidence of it in 29 per cent of these cases (8 per cent of all the exposed subjects). Squamous pegs were observed in 76 per cent of the exposed subjects with biopsy-proved adenosis. Although pegs were observed in the vaginal biopsies of 16 per cent of the exposed subjects without adenosis, they were not observed in the unexposed.

Adenosis was detected in only one control, and it differed from the typical form of the disorder in the exposed subjects. In that case a single cystic gland lined by mucinous epithelium lay in the lamina propria; the overlying squamous epithelium was normally glycogenated, and no squamous pegs were seen.

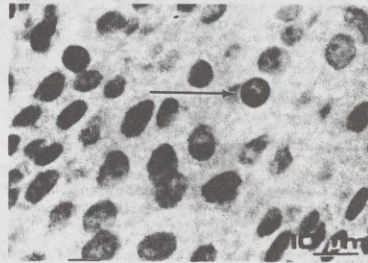


Figure 2. Vaginal Adenosis (Mucicarmine Stain). In the tissue slide the mucin droplet (arrow) is bright red, whereas the nuclei of the cells are brown-black, and the cytoplasm pale yellow.

In contrast to vaginal adenosis, the cervical erosions were morphologically similar in the exposed and the control subjects, being characterized by an epithelium that was almost always mucinous; cells of tubal or endometrial type were only occasionally seen. The glandular epithelium lay on the surface, sometimes covering micropapillae, or lined glands in the lamina propria. There were, however, quantitative differences in the erosions of the two groups of subjects. Squamous pegs were more frequent in the cervical biopsies of the exposed (43 per cent) than in the control series (6 per cent). Also, mucinous droplets and pools were more commonly encountered in the former.

Cytology. Quantitative differences also existed in the cytologic specimens of the two groups. In the vaginal scraping, columnar cells, metaplastic squamous cells, squamous cells containing mucous droplets, or dysplastic cells were found in 9 per cent of the exposed subjects (11 per cent in those with adenosis and 7 per cent in those without), in contrast to 1 per cent of the controls. In the aspirates of the vaginal pool, these abnormalities were also observed more frequently in the exposed (19 per cent) than in the control subjects (9 per cent), being present

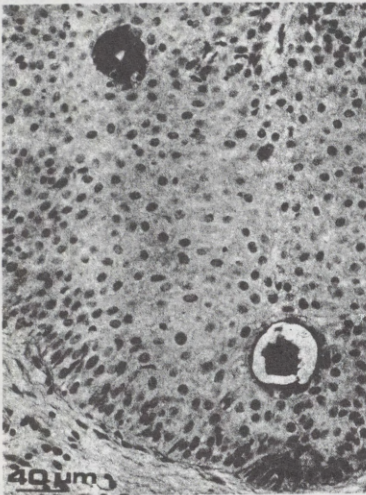


Figure 3. Vaginal Adenosis (Mucicarmine Stain).

One pool of mucin is surrounded by flat cells with mucinous cytoplasm that were obvious only with mucin stains (upper left), whereas a second pool is surrounded by cells with foamy cytoplasm obvious both with hematoxylin and eosin and with mucicarmine stains (lower right).

in 27 per cent of the exposed girls with biopsy-proved adenosis. Although mild squamous-cell dysplasia was observed in the vaginal scrapings from three exposed subjects and in the vaginal aspirate from a fourth, this change was not confirmed in any by multiple punch biopsies.

Other factors. The increased occurrence of adenosis, erosion, non-iodine-staining areas, and ridges in the exposed in comparison to the unexposed subjects was investigated further to determine whether other features (e.g., intrauterine x-ray exposure, smoking by parents and daughters, or maternal medications other than diethylstilbestrol) could have also had a role. No association with any factor other than intrauterine diethylstilbestrol could be identified.

Investigation of the Total Exposed Population of 133 Subjects (13 to 25 Years of Age)

Eighteen exposed white female subjects 13 to 17 and five non-white subjects 19 to 24 years of age were also examined, and the findings were combined with those of the 110 exposed subjects from the controlled study to provide the results of the investigation of all the post-menarchal females from the Diethylstilbestrol Clinic who agreed to be examined. Non-iodine-staining areas of the vagina were detected in 80 (60 per cent), and biopsy-proved adenosis in 49 (37 per cent). Non-iodine-staining epithelium was found on the cervix in 126 (95 per cent),

and biopsy-proved erosion or ectropion in 112 (84 per cent). Fibrous ridges of the vagina and cervix were found in 28 (21 per cent) of the subjects. No cases of cancer were detected. Only seven (5 per cent) of the subjects had pelvic examinations that were normal on inspection and after staining with iodine solution.

Table 4 examines the relation between the week of initiation of diethylstilbestrol therapy and the proportion of subjects having abnormalities of the vagina or cervix.

Vaginal adenosis was more frequent in those daughters whose mothers began diethylstilbestrol in early pregnancy. It was observed in 73 per cent of subjects initially exposed during the first two months of pregnancy, but in only 7 per cent of the 30 initially exposed in the 17th week or later (Table 4). None of 19 subjects whose mothers began therapy in the 18th week or later were found to have adenosis. The linear regression of the proportion of those found to have adenosis with respect to the month of initiation of therapy was highly significant ($p < 0.001$).¹¹ Similarly, cervical erosion was more frequent when therapy was begun in early pregnancy, but the regression ($p < 0.01$) was not as striking as for vaginal adenosis (Table 4). This result can be explained in part by the fact that cervical erosion often occurs in the absence of diethylstilbestrol exposure (Table 3). No association was demonstrated between the time of initiation of therapy and the presence of vaginal or cervical fibrous ridges, and one ridge was detected in a subject whose mother began treatment as late as the 21st week. The location and appearance of the ridges, however, varied to some extent with the time therapy was initiated. Nine of the 10 daughters with ridges who were exposed before the 12th week had a concentric ridge surrounding the external os of the cervix, with the formation of a pseudopolyp; the 10th had a transverse narrowing in the upper vagina. Both pseudopolyps and cervical ridges that were only partly circumferential were observed in subjects exposed between the 13th and 16th weeks of gestation. None of the four with ridges whose mothers started treatment in the 17th week of pregnancy or later had a cervical pseudopolyp, but all had partial ridges on the cervix or in the vagina. Because the mothers who were treated in the Diethylstilbestrol Clinic maintained a strict and identical dosage schedule, the total dosage of maternal medication was directly related to the time in pregnancy diethylstilbestrol was begun, so that it was impossible in this study to separate the effect of dosage from that of the onset of medication.

The analysis by the use of a multiple logistic model¹² revealed no correlation of vaginal or cervical abnormalities with the age of the subjects at the time of examination or with their sexual histories. As individual factors, the

Table 4. Frequency of Abnormalities in 133 Exposed Subjects in Relation to Week of Initiation of Diethylstilbestrol Therapy During Pregnancy.

Wk	TOTAL NUMBER	VAGINAL ADENOSIS (%)	CERVICAL EROSION (%)	— RIDGE (%)
≤8	22	73	100	23
9-12	39	49	92	28
13-16	42	29	81	19
>17	30	7	70	13

age of the subjects at the time of examination, as well as the week in pregnancy in which diethylstilbestrol was begun, did affect the incidence of adenosis. However, the mothers of the younger subjects began diethylstilbestrol earlier in pregnancy, resulting in a high correlation between subject age and the week of initiation of maternal medication. After adjustment of the incidence of adenosis for the week in which diethylstilbestrol was started, there was no residual effect owing to the age of the subjects. Vaginal adenosis, when adjusted for the week in which the estrogen was started, was detected less frequently in patients who had used oral contraceptives (chi-square = 5.05, $p < 0.05$), but the use of oral contraceptives had no effect on the frequency of non-iodine-staining areas in the vagina. Cervical erosion, adjusted for the week in which diethylstilbestrol was started, was less frequent among those who had been pregnant (chi-square = 5.44, $p < 0.05$). Pregnancy did not affect the incidence of vaginal adenosis or of non-iodine-staining areas in the vagina.

DISCUSSION

The results of this investigation of diethylstilbestrol-exposed and unexposed female subjects are consistent with previous uncontrolled observations that vaginal adenosis as well as transverse vaginal and cervical ridges are very rare in young females in the absence of intrauterine exposure to diethylstilbestrol.^{4,6} Although cervical abnormalities (failure of the portio mucosa to stain with iodine and erosion) were encountered in almost all the exposed subjects in this study, these findings were less specific, being present in about half the controls. There were no significant differences between the exposed and control groups in postnatal medical histories, including the onset and frequency of menstrual bleeding. These limited data suggest that ovarian function is not altered, at least in the first three decades of life, as a result of prenatal exposure to diethylstilbestrol. Similarly, the fact that there was no significant difference in health histories of the mothers in each group up to the present time, including the development of cancer after the ingestion of diethylstilbestrol, suggests that the medication did not affect their health. This interpretation, however, is based only on interview histories and not on physical or laboratory examinations.

The gynecologic and pathological findings of the present study were based on inspection, iodine staining, cytologic sampling and biopsies of the vagina and cervix. In view of the fact that scraping the vagina yielded cells compatible with vaginal adenosis (columnar cells or mucin droplets within squamous cells) in only 11 per cent of the cases of adenosis, and aspiration of the vaginal pool in only 27 per cent, cytology must be considered unreliable as a screening test for this disorder. Nevertheless, the identification of these cell types in a routine vaginal-pool aspiration, as well as the failure of the vagina to stain with iodine during a pelvic examination, should raise a high index of suspicion of diethylstilbestrol exposure in a young woman, who may be unaware of her prenatal history. The additional performance of mucin staining of biopsy specimens of the vagina facilitates the detection of mucin

droplets and pools in squamous epithelium, permitting the pathologist to recognize adenosis more easily than with the use of routine hematoxylin and eosin stains alone.

The failure to detect vaginal adenosis in any subject whose mother began therapy during the 18th week of pregnancy or later suggests that this disorder is congenital, reflecting a derangement of vaginal development related to the action of diethylstilbestrol before that time.¹³ This observation correlates well with data from the Registry of Clear-Cell Adenocarcinoma of the Genital Tract in Young Females, in which no cancers have yet been uncovered in female subjects exposed to diethylstilbestrol or similar drugs later than the 17th week of gestation.⁷ Although it was not possible from the current study to separate the effects of the total dosage of diethylstilbestrol from the time of its initiation during pregnancy, previous uncontrolled studies^{4,5} as well as data from the Registry³ have provided evidence that neither adenosis nor carcinoma is dose related, within the wide range of the amounts of diethylstilbestrol that are known to have been prescribed.

The incidence of vaginal adenosis that has been reported in diethylstilbestrol-exposed female subjects has varied. For example, Stafil and his associates⁶ found it in 57 of 63 exposed subjects on colposcopic and biopsy examination. Their results are in contrast with those of Townsend, who also used the colposcope but demonstrated adenosis in only 30 per cent of 286 exposed females; he identified a metaplastic squamous transformation zone corresponding to non-iodine-staining areas of the mucosa in an additional 30 per cent (personal communication). These results are similar to those of the present study, in which the method of examination was palpation and iodine staining followed by biopsy of abnormal areas. Some of the reported variations in incidence of adenosis may be related to differing estimates by the examiners of the boundary between the vagina and the cervix, which may be difficult to define in the presence of ridges, as well as differences in histologic terminology, the time of initiation of diethylstilbestrol therapy, and the population examined (e.g., unselected, asymptomatic, exposed subjects vs. symptomatic patients or those referred because of abnormalities noted by other physicians).

A proposed mechanism by which intrauterine exposure to diethylstilbestrol acts to result in vaginal adenosis is inhibition of the normal replacement of the embryonic müllerian epithelium of the vagina by the upgrowing squamous epithelium of the vaginal plate, which may be of either wolffian or urogenital-sinus origin.^{4,8} Normally, in the unexposed mature female, the transformation zone between the two types of epithelium is at or near the external os of the cervix. It has been suggested that cervical erosion and vaginal adenosis in exposed subjects represent simply an increasingly more distal positioning of the transformation zone onto the cervical portio and vagina, respectively.⁶ If this hypothesis were true, one might expect that cervical erosion and vaginal adenosis would be identical on histologic examination, but differences do exist. For example, in the biopsy specimens of cervical erosion in the present investigation, almost all the glan-

dular epithelial cells had the appearance of mucinous cells of the endocervix, whereas in vaginal adenosis, many of them resembled those of the endometrium or fallopian tube. These findings suggest that the pathogenesis of cervical erosion and vaginal adenosis may not be identical, and that the two processes may differ in biologic behavior on long-term investigation.

The data from the current study indicate a decreased frequency of vaginal adenosis in exposed subjects who have used oral contraceptives. This apparent healing might be related to the progestational component of these agents, in view of the suggestive evidence provided by a recent pilot study that healing of vaginal adenosis is promoted by the use of progesterone-theobroma oil suppositories.⁷ However, in spite of these preliminary findings, we have not advised the routine use of these agents because of the uncertainty regarding their long-term effects. The decreased frequency of cervical erosions observed in the exposed subjects in this study who had been pregnant might have been due to cervical cauterization after delivery, rather than to the effects of the pregnancy itself, but the inaccurate histories of that procedure did not allow testing of this hypothesis.

It has been suggested that replacement of glands by squamous epithelium may be a mechanism by which vaginal adenosis and cervical erosion heal,^{6,7,14,15} and because metaplastic squamous epithelium was observed frequently, it was anticipated that these disorders might be less frequent in older subjects as a consequence of spontaneous healing. Although the data afforded no evidence in support of this expectation, all the subjects in this study were younger than 26 years of age at the time of examination, and follow-up observation as they age further may reveal spontaneous healing.

Because the presence of vaginal adenosis has been demonstrated in almost all the cases of clear-cell adenocarcinoma of the vagina in young women when adequate tissue has been available for examination, and because cervical erosion is a consistent finding in association with clear-cell adenocarcinoma of the cervix,³ it is logical to assume that the glandular tissue characterizing adenosis and erosion may provide the base from which these adenocarcinomas develop. Although glandular atypicity has been reported in the vicinity of one clear-cell adenocarcinoma of the vagina,¹⁶ to our knowledge no case has yet been recorded in which a direct temporal or spatial transition from adenosis to adenocarcinoma has been documented in a diethylstilbestrol-exposed woman. In the present study, only minor degrees of glandular atypicity were observed in the biopsy specimens of the cervix and vagina. The results of many studies continue to show that non-neoplastic cervical and vaginal abnormalities are common in the exposed population, whereas clear-cell adenocarcinomas and glandular abnormalities that can be recognized morphologically as precancerous are very rare.

An additional hazard to diethylstilbestrol-exposed female subjects has been suggested by some authors¹⁷ who have proposed that squamous-cell carcinomas also may occur with increasing frequency as these patients age, in

view of the recent rare findings of squamous dysplasia and carcinoma-in-situ of the cervix and vagina in them (Staff and Mattingly,¹⁷ Lanier et al.,¹⁸ Robboy, S.J., Scully, R.E., and Herbst, A.L.: unpublished data) and the knowledge that the peak incidence of such alterations in the general population is at an older age than that of exposed women at present. In this study, only four of the 110 exposed subjects (4 per cent) had squamous dysplasia on cytologic examination, and it was slight in all four. With only sporadic reports of these precancerous or possibly precancerous squamous changes, it is impossible to be certain how often they will either progress to invasive cancer or prove to be only a transitory phenomenon related to active squamous metaplasia.

Obviously, many years may be required to determine the risk of development of genital cancer in diethylstilbestrol-exposed female subjects. During this time, thorough periodic examination is clearly indicated.

We are indebted to Dr. Theodore Colton and Dr. Klim McPherson, of the Department of Preventive and Social Medicine, Harvard Medical School, for assistance with statistical analysis, and to Nancy Dreyer Arkin and Jean Sheridan for their efforts in the completion of this study.

REFERENCES

- Herbst AL, Ulfelder H, Poskanzer DC: Adenocarcinoma of the vagina: association of maternal stilbestrol therapy with tumor appearance in young women. *N Engl J Med* 284:878-881, 1971
- Greenwald P, Barlow JJ, Nasca PC, et al: Vaginal cancer after maternal treatment with synthetic estrogens. *N Engl J Med* 285:390-392, 1971
- Herbst AL, Robboy SJ, Scully RE, et al: Clear-cell adenocarcinoma of the vagina and cervix in girls: an analysis of 170 Registry cases. *Am J Obstet Gynecol* 149:713-724, 1974
- Herbst AL, Kfirman RJ, Scully RE: Vaginal and cervical abnormalities after exposure to stilbestrol *in utero*. *Obstet Gynecol* 40:287-298, 1972
- Pomerance W: Post-stilbestrol secondary syndrome. *Obstet Gynecol* 42:12-18, 1973
- Staff A, Mattingly RF, Foley DV, et al: Clinical diagnosis of vaginal adenosis. *Obstet Gynecol* 43:118-128, 1974
- Herbst AL, Robboy SJ, MacDonald GJ, et al: The effects of local progesterone on stilbestrol-associated vaginal adenosis. *Am J Obstet Gynecol* 118:607-615, 1974
- Scully RE, Robboy SJ, Herbst AL: Vaginal and cervical abnormalities including clear-cell adenocarcinoma, related to prenatal exposure to stilbestrol. *Ann Clin Lab Sci* 4:222-233, 1974
- Smith OW, Smith G van S, Hurwitz D: Increased excretion of pregnadiol in pregnancy from diethylstilbestrol with special reference to the prevention of late pregnancy accidents. *Am J Obstet Gynecol* 51:411-415, 1946
- Smith OW: Diethylstilbestrol in the prevention and treatment of complications of pregnancy. *Am J Obstet Gynecol* 56:821-834, 1948
- Snedecor GW, Cochran WG: Statistical Methods. Sixth edition. Ames, Iowa State University Press, 1967, pp 246-247
- Walker SH, Duncan DB: Estimation of the probability of an event as a function of several independent variables. *Biometrika* 54:167-179, 1967
- Kurman RJ, Scully RE: The incidence and histogenesis of vaginal adenosis: an autopsy study. *Hum Pathol* 5:265-276, 1974
- Burghardt E: Early Histological Diagnosis of Cervical Cancer. Philadelphia, WB Saunders Company, 1973, pp 8, 61-65
- Coppleson M, Pixley E, Reid B: Colposcopy: A scientific and practical approach to the cervix in health and disease. Springfield, Illinois, Charles C Thomas, 1971
- Barber HRK, Sommers SC: Vaginal adenosis, dysplasia, and clear-cell adenocarcinoma after diethylstilbestrol treatment in pregnancy. *Obstet Gynecol* 43:645-652, 1974
- Staff A, Mattingly RF: Vaginal adenosis — a precancerous lesion? *Am J Obstet Gynecol* 120:666-677, 1974
- Lanier AP, Noller KL, Decker DG, et al: Cancer and stilbestrol: a follow-up of 1719 persons exposed to estrogen *in utero* and born in 1943-59. *Mayo Clin Proc* 48:793-799, 1973

Postcoital Contraception With Diethylstilbestrol

Lucile Kirtland Kuchera, MD

One thousand women of child bearing age were given, within 72 hours of sexual exposure, 25 mg of diethylstilbestrol twice daily for five days. No pregnancies resulted and there were no serious adverse reactions. It was emphasized to the patient that this was an emergency type of treatment and, should she have a continuing need for contraception, other means should be sought.

This communication presents the follow-up findings in 1,000 women of child bearing age who were given, within 72 hours of sexual exposure, 25 mg of diethylstilbestrol twice daily for five days. Tables are presented giving the time of exposure in relation to the menstrual cycle (Table 1), prophylaxis, if any (Table 2), side reactions to the medication (Table 3), patients using this therapy more than once (Table 4), and the character of the following menses (Table 5). It was explained to the patient that, though this was not a new drug, it was a new use and a follow-up was expected. Possible undesirable effects were discussed before it was prescribed. It was given only to consenting women. It was emphasized to the patient that this was an emergency type of treatment, and, should she have a continuing need for contraception, she should use other means.

To evaluate its effectiveness, one needs to know the incidence of pregnancy from one act of unprotected sexual intercourse in the women of child bearing age. From analyzing available statistics, C. Tietze, MD, ar-

rived at the probability of conception from a single unprotected coitus to be between 1 in 50 and 1 in 25.¹

The problem of requests for postcoital help by the female patient when she has been exposed to unprotected sexual intercourse for whatever reasons—rape, neglect to use prophylaxis, or failure of prophylaxis, such as condom breakage is familiar and challenging to most practicing physicians. Formerly in this clinic we had only told the patient to wait for her next menses—not very consoling advice to a woman who does not want to be pregnant.

Great credit is due Morris and the New Haven group for their work on effective postcoital antifertility agents.² The antizygotic action of es-

trogens on various animal species has been known for many years.^{3,4}

My study of patients using diethylstilbestrol for postcoital contraception at our Health Service began in the fall of 1967. In each of the 1,000 cases, an interview or letter was obtained following the ingestion of diethylstilbestrol, so that it was definitely known that her next menses came and that she was not pregnant.

The therapy was under the plan and direction of our consulting gynecologist from the University of Michigan Medical Center. The therapy and follow-up was continued by our staff and the data were collected and analyzed by the author.

In the tables when the data are

Table 1.—Time of Exposure in Relation to the Menstrual Cycle

	No. Patients	%
Midcycle*	715	71.5
Not midcycle	180	18.0
Irregular	54	5.4
Recent discontinuance of oral contraceptive	9	0.9
Postabortion and before first following menses	2	0.2
Unknown	40	4.0

*Midcycle only includes exposures to sexual intercourse 3 days before or 3 days after expected time of ovulation.

Table 2.—Use of Prophylaxis

	No. Patients	%
None*	890	89
Coitus interruptus	56	5.6
Condom alone	16	1.6
Contraceptive foam alone	16	1.6
Ejaculation on external genitalia	7	0.7
Tampon	3	0.3
Forgot birth control pills	2	0.2
Douche after intercourse	2	0.2
Condom and foam	2	0.2
Spermicidal jelly alone	1	0.1
Received birth control pills 2 days before	1	0.1
Received birth control pills 3 days before	1	0.1
Unknown	13	1.3

*None includes cases when condom came off intravaginally, or condom broke intravaginally.

From the University of Michigan Health Service, Ann Arbor, Mich 48104 (Dr. Kuchera).

Reprint requests to 207 Fletcher Ave, Ann Arbor, Mich 48104 (Dr. Kuchera).

Diethylstilbestrol—Kuchera

Table 3.—Side Reactions to Diethylstilbestrol

	No. Patients	%
None*	315	31.5
Nausea, slight, hardly noticeable, on day 1 only, and no other reaction	137	13.7
Nausea, intermittent, 1 day	120	12.0
Nausea, intermittent, 2 days	53	5.3
Nausea, intermittent, 3 days	26	2.6
Nausea, intermittent, 4 days	5	0.5
Nausea, intermittent, 5 days	43	4.3
Nausea and vomiting, intermittent, 1 day	134	13.4
Nausea and vomiting, intermittent, 2 days	21	2.1
Nausea and vomiting, intermittent, 3 days	2	0.2
Nausea and vomiting, intermittent, 4 days		0.0
Nausea and vomiting, intermittent, 5 days	3	0.3
Headache	14	1.4
Vaginal spotting while taking medication or soon after finishing course	12	1.2
Dizziness	12	1.2
Diarrhea	10	1.0
Bloated or swollen condition	10	1.0
Mild lower abdominal cramps	9	0.9
Tenderness of breasts	8	0.8
Weight gain	7	0.7
Increased vaginal secretion	5	0.5
Irritability	3	0.3
Darkening of breast areola	3	0.3
Vesicular rash, slightly pruritic	1	0.1
Gas	1	0.1
Increased		
Anorexia	1	0.1
Leg cramps	1	0.1
Depression	1	

Table 4.—Patients Using the Course of Diethylstilbestrol for This Indication More Than Once

Total Use	No. Patients	%
2 times	117	11.7
3 times	65	6.5
4 times	9	0.9
5 times	6	0.6
6 times	1	0.1

Table 5.—Character of Menses Following the Course of Diethylstilbestrol

	No. Patients	%
Normal time and flow	400	40.0
Normal time and lighter flow	76	7.6
Normal time and heavier flow	27	2.7
Early onset (usually few days only)	52	5.2
Late onset (1-7 days)	62	6.2
Late onset (7-14 days)	59	5.9
Irregular	30	3.0
Unknown	294	29.4

listed under "unknown," it is because the patient failed to note the information in her correspondence or the clinician did not note the information on the inquiry form.

Side Reactions

Table 3 shows the incidence of side effects following administration of diethylstilbestrol. Usually, no reaction was noted before a lapse of at least six hours after ingestion of the first pill. Enteric coated diethylstilbestrol only delayed the onset of reaction but did not prevent it. No serious side effect was known in any of the 1,000 cases while taking diethylstilbestrol or afterward. It will be noted that 45.2% had virtually no side reactions. In some cases, patients observed more than one side effect.

Patients having headaches were carefully questioned. The headaches varied in location from frontal to generalized and most were dull. Only one girl had a vascular headache by history, and she was known to have a past history of migraine. The character of the following menses varied

from the usual, as noted in Table 5.

The mechanism of action appears to be on the endometrial implantation site, though other actions such as increase in speed of ovum transport through the genital tract, have been noted in animal observations. There are many animal studies in the literature concerning this subject, and a few additional references are listed.

References

1. Tietze C: Problems of pregnancy resulting from a single unprotected coitus. *Fertil Steril* 11:483-485, 1960.
2. Morris JM, Van Wazenen G: Compounds. *Amer J Obstet Gynec* 96:204, 1966.
3. Heckel GP, Allen WM: Maintenance of corpus luteum and inhibition of parturition in rabbits by injection of estrogenic hormone. *Endocrinology* 24:137, 1939.
4. Courrier R, Reynaud R: Etude quantitative de l'avortement folliculaire provoqué chez la lapine par l'hormone cristalline: Réalisation d'un avortement partiel. *Compt Rend Soc Biol* 116:1073, 1934.
5. Nutting EF, Saunders FJ: Postcoital effect of two antifertility agents on ova transport and implantation. *Sex Etp Biol* 1:131-132-133, 1969.
6. Jacob D, Morris J: Estrogenic activity of postcoital antifertility compounds. *Fertil Steril* 20:211-222, 1969.
7. Emmens CW: Postcoital contraception. *Brit Med Bull* 26:45-51, 1970.

(53)

UNIV. OF MICHIGAN

Diethylstilbestrol as a "Morning After" Pill

The morning after pill is a means of preventing pregnancy after unprotected intercourse. Effectiveness of this treatment decreases rapidly after 72 hours (3 days) have elapsed since intercourse.

Treatment usually consists of taking 25 mg of diethylstilbestrol (DES) twice daily for five days. An overdose of oral contraceptives will not have the same effect because DES contains large doses of estrogen (a thousand times higher than the estrogen dosage of oral contraceptives). A five day course of DES is equivalent to taking birth control pills for several decades.

The most common side effects of the treatment are nausea and vomiting. It is important to take the full course of therapy in spite of the nausea, if it is to be effective. The long-term effects of DES are not known. However, this treatment does carry the same immediate risks of blood clotting which are associated with the use of oral contraceptives. The physical effects of repeated treatment are also unknown. For these reasons, this method of preventing pregnancy should be used only in extreme emergencies.

If by chance you are already pregnant, DES will not cause an abortion.

Also, if there is any possibility a pregnancy has developed from a previous sexual exposure, DES should not be taken. DES carries a potential risk of being harmful to the fetus in its life (if it's female). Because of this, if a pregnancy ensues after taking DES, voluntary termination of the pregnancy should receive serious consideration.

This treatment is not a contraceptive. It does not protect against pregnancy during treatment or for the rest of the menstrual cycle. If you are having intercourse, a regular, effective method of contraception should be used.

26824

NOTICES

Flag of registry	1963	1964	1965	1966	1967	1968	1969	1970	1971	1972	1973	Total
British	133	180	136	101	73	62	45	33	18	10	4	810
Cyprus	1	17	27	42	68	115	109	173	86		86	784
Lebanon	64	91	68	25	16	18	4	1				276
Greece	99	27	23	27	29	7		1	1			214
Italian	16	20	24	11	11	10	18	13	9			129
Yugoslav	12	11	15	10	14	9	6	7	9	5		103
French	8	9	9	10	10	4	2	2	2			61
Finnish	1	4	6	11	12	8	2	1				44
Spanish	9	17										26
Norwegian	14	10										24
Moroccan	9	13	1						1			24
Maltese	2	6	1	4	8	1	2					28
Somali								6	6	12		48
Netherlands	4	2							8	7		26
Sweden	3	8										11
Kuwait	2	1										3
Israeli	1	2										3
Japanese												1
Danish	1											1
German (West)	1											1
Italian			1									1
Morocco				1								1
Singapore												1
Subtotal	371	394	220	224	218	204	197	285	210	119	84	2,038
Polish	18	16	12	10	11			2	4			63
Grand total	389	410	302	234	229	211	199	288	213	119	84	2,101

NOTE.—Trip totals in section 4 exceed ship totals in sections 1 and 2 because some of the ships made more than one trip to Cuba. Monthly totals subject to revision as additional data becomes available.

By order of the Assistant Secretary of Commerce for Maritime Affairs.

Dated September 10, 1973.

JAMES S. DAWSON, Jr.,
Secretary.

[FR Doc.73-20435 Filed 9-25-73; 8:45 am]

National Bureau of Standards

EXPANDED VINYL FABRICS FOR APPAREL USE

Withdrawal of Commercial Standard

In accordance with § 10.12 of the Department's "Procedures for the Development of Voluntary Product Standards" (15 CFR Part 10, as revised; 35 FR 8349 dated May 28, 1970), notice is hereby given of the withdrawal of Commercial Standard CS 258-63, "Expanded Vinyl Fabrics for Apparel Use."

This action is taken in furtherance of the Department's announced intentions as set forth in the public notice appearing in the FEDERAL REGISTER of July 2, 1973 (35 FR 17520), to withdraw this standard.

The effective date for the withdrawal of this standard will be November 26, 1973. This withdrawal action terminates the authority to refer to this standard as a voluntary standard developed under the Department of Commerce Procedures.

Dated September 19, 1973.

RICHARD W. ROBERTS,
Director.

[FR Doc.73-20475 Filed 9-25-73; 8:45 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

(DESI 740; Docket No. FDC-8-664; NDA 4-038, etc.)

CERTAIN ESTROGENS FOR ORAL OR PARENTERAL USE

Drugs for Human Use; Drug Efficacy Study Implementation; Follow-Up Notice

In a notice published in the FEDERAL

REGISTER of November 10, 1971 (35 FR 21537), the Commissioner of Foods and Drugs announced his conclusions pursuant to evaluation of reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group on the following drugs:

a. *Preparations containing diethylstilbestrol*:

1. *Retrol tablets*; The Central Pharmacy Co., 116-128 East Third Street, Seymour, IN 47274 (NDA 6-428). (Two reports.)

2. *Synestrol tablets*; White Laboratories, Inc., Kenilworth, N.J. 07033 (NDA 5-991).

3. *Preparations containing diethylstilbestrol*: a. *Diethylstilbestrol Enseals and Tablets*; Eli Lilly and Co., Post Office Box 318, Indianapolis, IN 46204 (NDA 4-039 and 4-041 (previously stated to be 4-040)). (Three reports.)

b. *Diethylstilbestrol tablets*; Vale Chemical Co., Inc., 1201 Liberty Street, Allentown, PA 18102 (NDA 4-638).

c. *Diethylstilbestrol (Stilbestrol) Tablets*; Rexall Drug Co., 3901 North Kingshighway Boulevard, St. Louis, MO 63115 (NDA 6-603).

d. *Diethylstilbestrol tablets*; S. F. Durst and Co., Inc., 5317 North Third Street, Philadelphia, PA 19120 (NDA 4-297).

e. *Stilbestrol tablets*; High Chemical Co., 1760 North Howard Street, Philadelphia, PA 19122 (NDA 5-233).

f. *Stilbestin tablets and enteric coated tablets*; E. R. Squibb and Sons, Inc., Georges Road, New Brunswick, N.J. 08903 (NDA 4-056).

g. *Diethylstilbestrol Perles*; The Upjohn Co., 7171 Portage Road, Kalamazoo, MI 49002 (NDA 4-073).

h. *Diethylstilbestrol in oil injections*; Eli Lilly and Co. (NDA 4-038 (previously stated to be 1-221)).

i. *Diethylstilbestrol in ethyl oleate injection*; Eli Lilly and Co. (NDA 1-844).

3. *Preparations containing other diethylstilbestrol derivatives*: a. *D.S.B. tablets and enteric coated tablets*, containing diethylstilbestrol dipropionate; The Blue Line Chemical Co., 302 South Broadway, St. Louis, MO 63102 (NDA 5-159).

b. *Stilphostrol ampoules and tablets*, containing diethylstilbestrol diphosphate; Dome Laboratories, Division of Miles Laboratories, Inc., 400 McLean Lane, West Haven, CT 06516 (NDA 10-010).

4. *Preparation containing promethestrol dipropionate*: a. *Mefrane Dipropionate tablets*; Reed and Carnrick Pharmaceuticals, 30 Boright Avenue, Kenilworth, N.J. 07033 (NDA 6-012).

The notice stated that these drugs were regarded as effective, probably effective, possibly effective, and lacking substantial evidence of effectiveness for their various indications.

No data were submitted in support of any of the less than effective indications and the drugs are now regarded to either lack substantial evidence of effectiveness or are not shown to be safe for those indications.

Accordingly, with respect to these products, the revised effectiveness classification and marketing status are as follows:

A. *Effectiveness classification*. The Food and Drug Administration has considered the Academy's reports, as well as other available evidence, and concludes that, except for oral dosage forms containing 25 milligrams or more of diethylstilbestrol per tablet and parenteral dosage forms containing 25 milligrams or more of diethylstilbestrol per milliliter, the drugs are effective for those indications described as effective in the notice of November 10, 1971. Dosage forms containing 25 milligrams or more of diethylstilbestrol per tablet or milliliter are either regarded as contraindicated or inappropriate dosages for the indications claimed in the labeling and raise a question of safety. Appearing elsewhere in this issue of the FEDERAL REGISTER is a notice of opportunity for hearing on the proposal to withdraw approval of those parts of new drug applications providing for such dosage form strengths.

The drugs lack substantial evidence of effectiveness for all of their other labeled indications.

B. *Conditions for approval and marketing*. The Food and Drug Administration is prepared to approve abbreviated new drug applications and abbreviated supplements to previously approved new drug applications under the conditions described herein.

1. *Form of drug*. These preparations are in tablet, enteric coated tablet, or capsule form suitable for oral administration; or are sterile preparations in a form suitable for parenteral administration.

2. *Labeling conditions*. The labeling conditions are the same as those described in the notice of November 10, 1971, except that the probably effective and possibly effective indications are no longer allowable. Complete labeling guidelines are available upon request.

3. *Marketing status*. Marketing of such drugs may be continued under the conditions described in the notice entitled "Conditions for Marketing New Drugs Evaluated in Drug Efficacy Study," published in the FEDERAL REGISTER July 14, 1970 (35 FR 11273), as follows:

NOTICES

26825

a. For holders of "deemed approved" new drug applications (i.e., an application which became effective on the basis of safety prior to October 10, 1962), the submission of a supplement for revised labeling and an abbreviated supplement for updating information as described in paragraphs (a) (1) (i) and (iii) of the notice of July 14, 1970.

b. For any person who does not hold an approved or effective new drug application, the submission of an abbreviated new drug application as described in paragraph (a) (3) (i) of that notice.

c. For any distributor of the drug, the use of labeling in accord with this announcement for any such drug shipped within the jurisdiction of the Act as described in paragraph (b) of that notice.

C. *Notice of opportunity for a hearing.* Notice is given to the holder(s) of the new drug application(s) and to any other interested person that the Commissioner proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of the listed new drug application(s) and all amendments and supplements thereto providing for indications lacking substantial evidence of effectiveness referred to in paragraph A of this notice on the grounds that new information before him with respect to the drug(s), evaluated together with the evidence available to him at the time of approval of the application(s), shows there is a lack of substantial evidence that the drug(s) will have all the effects purported or represented to have under the conditions of use prescribed, recommended, or suggested in the labeling. An order withdrawing approval will not issue with respect to any application(s) supplemented in accord with this notice, to delete the claim(s) lacking substantial evidence of effectiveness.

Any manufacturer or distributor of such an identical, related, or similar product is an interested person who may in response to this notice submit data and information, request that the new drug application(s) not be withdrawn, request a hearing, and participate as a party in any hearing.

In accordance with the provisions of section 505 of the Act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Part 130), the Commissioner hereby gives the applicant(s) and any other interested person an opportunity for a hearing to show why approval of the new drug application(s) providing for the claim(s) involved should not be withdrawn.

On or before October 26, 1973, the applicant(s) and any other interested person may file with the Hearing Clerk, Food and Drug Administration, Room 6-86, 5600 Fishers Lane, Rockville, Maryland 20852, a written appearance electing whether or not to avail himself of the opportunity for a hearing. Failure of an applicant or any other interested person to file a written appearance of election within the specified time will constitute an election by him not to avail himself of the opportunity for a hearing. No extension of time may be granted.

If no person elects to avail himself of the opportunity for a hearing, the Commissioner without further notice will enter a final order withdrawing approval of the application(s) which have not been supplemented to delete the indication(s) lacking substantial evidence of effectiveness.

If an applicant or any other interested person elects to avail himself of the opportunity for a hearing, he must file, on or before October 26, 1973, a written appearance requesting the hearing, giving the reasons why approval of the new drug application(s) should not be withdrawn, together with a well-organized and full-factual analysis of the clinical and other investigational data he is prepared to prove in support of his opposition. A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that a genuine and substantial issue of fact requires a hearing (21 CFR 130.14(b)).

If review of the data submitted by an applicant or any other interested person warrants the conclusion that there exists substantial evidence demonstrating the effectiveness of the product(s) for the labeling claim(s) involved, the Commissioner will rescind this notice of opportunity for hearing.

If review of the data in the application(s) and data submitted by the applicant(s) or any other interested person in a request for a hearing, together with the reasoning and factual analysis in a request for a hearing, warrants the conclusion that no genuine and substantial issue of fact precludes the withdrawal of approval of the application(s), the Commissioner will enter an order making findings and conclusions on such data and withdrawing approval of application(s) not supplemented to delete the claim(s) involved.

If, upon the request of the new drug applicant(s) or any other interested person, a hearing is justified, the issues will be defined, a hearing examiner will be named, and he shall issue, as soon as practicable after October 26, 1973, a written notice of the time and place at which the hearing will commence. All persons interested in identical, related, or similar products covered by the new drug application(s) will be afforded an opportunity to appear at the hearing, file briefs, present evidence, cross-examine witnesses, submit suggested findings of fact, and otherwise participate as a party. The hearing contemplated by this notice will be open to the public except that any portion of the hearing that concerns a method or process the Commissioner finds entitled to protection as a trade secret will not be open to the public, unless the respondent specifies otherwise in his appearance.

Communications forwarded in response to this notice should be identified with the reference number DESI 740, directed to the attention of the appropriate office listed below, and addressed to the Food and Drug Administration, 600 Fishers Lane, Rockville, MD 20852.

Supplements (Identify with NDA number):
Office of Scientific Evaluation (BD-100),
Bureau of Drugs.

Original abbreviated new drug applications (Identify as such): Generic Drug Staff (BD-59), Office of Scientific Evaluation,
Bureau of Drugs.

Request for Hearing (Identify with Docket number): Hearing Clerk (CC-20), Room 6-86, Parklawn Building.

Requests for Academy's report: Drug Efficacy Study Information Control (BD-66), Bureau of Drugs.

All other communications regarding this announcement: Drug Efficacy Study Implementation Project Manager (BD-101), Bureau of Drugs.

Received requests for a hearing may be seen in the Office of the Hearing Clerk (address given above) during regular business hours, Monday through Friday.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended; 21 U.S.C. 352, 355), and the Administrative Procedure Act (5 U.S.C. 554), and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated September 12, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc. 73-20442 Filed 9-21-73; 8:45 am]

[DESI 740; Docket No. FDG-D-680, NDA 4-039, etc.]

CERTAIN ESTROGENS FOR ORAL OR PARENTERAL USE

Opportunity for Hearing on Proposal To Withdraw Approval of New Drug Applications

In a notice (DESI 740) published in the FEDERAL REGISTER of November 10, 1971 (36 FR 21537), the Commissioner of Food and Drugs announced his conclusions pursuant to evaluation of reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group concerning certain orally and parenterally administered estrogens. Appearing elsewhere in this issue of the FEDERAL REGISTER is a followup notice describing the conditions under which certain of those products are regarded to be effective:

The following new drug applications referenced in the notice provide for oral dosage forms containing 25 mg. or more of diethylstilbestrol and a parenteral dosage form (1 ml. ampule) containing 25 mg. of diethylstilbestrol. Such large single dosages of diethylstilbestrol are regarded as either contraindicated (e.g., for accidents of pregnancy), and/or are in excess of the amounts recognized as appropriate for the indications claimed in the labeling reviewed by the Academy, thus raising a question of safety for use for the indications claimed.

NDA's 4-039 and 4-041: Those parts of the NDA's providing for Diethylstilbestrol Tablets and Enseals containing 25 mg. diethylstilbestrol; Eli Lilly and Co., Post Office Box 618, Indianapolis, IN 46206.

NDA 6-603: Those parts of the NDA providing for a tablet containing 25 mg.

26826

NOTICES

diethylstilbestrol; Rexall Drug Company, 3901 North Kingshighway, St. Louis, MO 63115.

NDA 7-054: Those parts of the NDA providing for tablets containing 25 and 100 mg. diethylstilbestrol; E. R. Squibb and Sons, Lawrenceville-Princeton Road, Post Office Box 4000, Princeton, N.J. 08540.

NDA 7-844: Diethylstilbestrol Ampoules (1 ml.), containing 25 mg. diethylstilbestrol in ethyl oleate; Eli Lilly and Co. This dosage form had been labeled only for use in certain types of accidents of pregnancy. Lilly discontinued this product in 1966 and approval of the NDA was withdrawn February 8, 1972 (37 FR 2851), on grounds that the applicant had failed to make reports under section 505(f) of the Act (21 U.S.C. 355(j)) and § 130.13 or § 130.35(e) and (f) of the new drug regulations (21 CFR 130.13 and 130.35). In view of that, this product is included in this notice only for the purpose of informing interested persons of the conclusions reached in the Drug Efficacy Study concerning it.

Therefore, notice is given to the holder(s) of the new drug application(s) and to any other interested person that the Commissioner proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355 (e)) withdrawing approval of pertinent parts of the listed new drug application(s) and all amendments and supplements thereto on the grounds that new information before him with respect to the drug(s), evaluated together with the evidence available to him at the time of approval of the application(s) shows that the drugs are not shown to be safe for use under the conditions of use prescribed, recommended, or suggested in the labeling.

All identical, related, or similar products, not the subject of an approved new drug application, are covered by the new drug application(s) reviewed. See 21 CFR 130.40 (37 F.R. 23185, October 31, 1972). Any manufacturer or distributor of such an identical, related, or similar product is an interested person who may in response to this notice submit data and information, request that the new drug application(s) not be withdrawn, request a hearing, and participate as a party in any hearing. Any person who wishes to determine whether a specific product is covered by this notice should write to the Food and Drug Administration, Bureau of Drugs, Office of Compliance (BD-300), 5600 Fishers Lane, Rockville, Maryland 20852.

In accordance with the provisions of section 505 of the Act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Part 130), the Commissioner hereby gives the applicant(s) and any other interested person an opportunity for a hearing to show why approval of the new drug application(s) should not be withdrawn.

On or before October 26, 1973, the applicant(s) and any other interested person is required to file with the Hearing

Clerk, Food and Drug Administration, Room 6-86, 5600 Fishers Lane, Rockville, Maryland 20852, a written appearance electing whether or not to avail himself of the opportunity for a hearing. Failure of an applicant or any other interested person to file a written appearance of election within the specified time will constitute an election by him not to avail himself of the opportunity for a hearing. No extension of time may be granted.

If no person elects to avail himself of the opportunity for a hearing, the Commissioner without further notice will enter a final order withdrawing approval of pertinent parts of the application(s).

If an applicant or any other interested person elects to avail himself of the opportunity for a hearing, he must file, on or before October 26, 1973, a written appearance requesting the hearing, giving the reasons why approval of the new drug application(s) should not be withdrawn, together with a well-organized and full-factual analysis of the clinical and other investigational data he is prepared to prove in support of his opposition. A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that a genuine and substantial issue of fact requires a hearing (21 CFR 130.14 (b)).

If review of the data submitted by an applicant or any other interested person warrants the conclusion that the drugs are safe for use for the labeling claims involved, the Commissioner will rescind this notice of opportunity for hearing.

If review of the data in the application(s) and data submitted by the applicant(s) or any other interested person in a request for a hearing, together with the reasoning and factual analysis in a request for a hearing, warrants the conclusion that no genuine and substantial issue of fact precludes the withdrawal of approval of the application(s), the Commissioner will enter an order of withdrawal making findings and conclusions on such data.

If, upon the request of the new drug applicant(s) or any other interested person, a hearing is justified, the issues will be defined, a hearing examiner will be named, and he shall issue, as soon as practicable after October 26, 1973, a written notice of the time and place at which the hearing will commence. All persons interested in identical, related, or similar products covered by the new drug application(s) will be afforded an opportunity to appear at the hearing, file briefs, present evidence, cross-examine witnesses, submit suggested findings of fact, and otherwise participate as a party. The hearing contemplated by this notice will be open to the public except that any portion of the hearing that concerns a method or process the Commissioner finds entitled to protection as a trade secret will not be open to the public, unless the respondent specifies otherwise in his appearance.

Requests for a hearing and/or elections not to request a hearing may be seen in the Office of the Hearing Clerk

(address given above) during regular business hours, Monday through Friday.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505, 52 Stat. 1052-53, as amended; 21 U.S.C. 355) and the Administrative Procedure Act (5 U.S.C. 554), and under authority delegated to the Commissioner (21 CFR 2.120).

Dated September 12, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc. 73-20443 Filed 9-21-73; 8:45 am]

Office of Education NATIONAL ADVISORY COUNCIL ON INDIAN EDUCATION

Notice of Meeting

Notice is hereby given, pursuant to section 10(a) (2) of the Federal Advisory Committee Act (P.L. 92-463), that the next meeting of the National Advisory Council on Indian Education will be held on October 23-24, 1973, from 9:00 a.m. to 5:00 p.m., at the Northern Hotel, Billings, Montana.

The National Advisory Council on Indian Education is established under section 401 of the Indian Education Act (P.L. 92-318, Title IV). The Council is directed to:

Advise the Commissioner in the preparation of general regulations and with respect to policy matters arising in the administration of this title, including policies and procedures governing the approval of State plans under section 318 and policies to eliminate duplication, and to effectuate the coordination of programs under this title and other programs offering Indian Education activities and services.

The Council shall review the administration and effectiveness of programs under this title, make recommendations with respect thereto, and make annual reports to the President of its findings and recommendations (including recommendations for changes in this title and other general laws relating to Indian Education activities and services). The President shall transmit each such report to the Congress together with its comments and recommendations.

The meeting of the Council, under the authority of Section 10(b) of the Federal Advisory Committee Act (P.L. 92-463) and section 552(b) of Title 5 of the United States Code, will be partially closed to the public during the selection of nominees for the position of Deputy Commissioner of Indian Education. The proposed agenda includes:

Executive Director's Report.
Committee Reports.
Selection of nominees for Deputy Commissioner of Indian Education.
Review of Title IV Indian Education.
Indian Education Inter-Change.

Records shall be kept of all Council proceedings (and shall be available for public inspection at the Office of the National Advisory Council on Indian Education located at 425 13th Street, NW, Pennsylvania Bldg., Washington, D.C. 20004).

HEW**NEWS**

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

73-39

(Food and Drug Administration)

FOR RELEASE: A.M.

NIDA--(301) 443-3285

Friday, September 21, 1973

(Home)--XXXXXXXXXXXXXXXXXX

The Food and Drug Administration today said it will require label and packaging changes for diethylstilbestrol (DES), a synthetic hormone, to insure its safety and effectiveness when used as an emergency "morning after" contraceptive.

The Agency will require manufacturers who sell the drug for this use to provide an FDA-approved brochure for patients explaining the risks and benefits of the drug. The brochure will explain possible side effects and how the patient can recognize them.

DES has long been marketed for labeled conditions such as breast engorgement in the new mother, prostate cancer, and breast cancer. It has also been used by physicians increasingly in recent years for post-coital contraception, although it had not been officially approved by FDA for this use.

In moving to add approval for contraceptive use to the official labeling, FDA and its Obstetrics and Gynecology Advisory Committee reviewed all available studies conducted with this drug. The Agency emphasizes that it does not consider the drug safe for routine or repeated contraceptive use because of the relatively large amounts of estrogen taken over a short period of time. The amounts of estrogen used in conventional oral contraceptives are

73-39

-2-

smaller and given over a longer time and are judged less likely than frequent use of post-coital DES to cause side effects such as abnormal blood clotting. The revised labeling for DES will reflect this view.

The decision to require patient labeling for DES follows a pattern set by FDA three years ago for all conventional forms of oral contraception ("The Pill").

In announcing today's action, Alexander M. Schmidt, M.D., Commissioner of Food and Drugs, said: "FDA and the medical community generally must develop better procedures for informing patients about their drug therapy. Our reasons for requiring patient package inserts on chemicals for contraception are simple: The drugs are normally given to young, healthy women. There is a finite risk of delayed side effects that the patient must be able to recognize. Furthermore, there are non-chemical alternatives for preventing pregnancy. For these reasons, the patient should know the options available and participate on an informed basis with her physician in the decision making."

The effectiveness of DES in preventing pregnancy depends on the time lapse between intercourse and taking DES -- within 24 hours and not later than 72 hours after sexual exposure. Its use, however, will not terminate an existing pregnancy. FDA, therefore, is recommending that a pregnancy test be given before the drug is prescribed.

73-39

-3-

FDA also is recommending that the patient consult with her physician on the question of continuing any pregnancy that does occur in spite of DES, because daughters born to some mothers given DES during pregnancy have developed cancer of the vagina or cervix. There is no evidence that the limited use of DES in non-pregnant women to achieve contraception carries a risk of cancer for the woman.

Interested persons may comment within 60 days after publication of the new FDA position in today's FEDERAL REGISTER. Comments should be sent to the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-88, Parklawn Building, 5600 Fishers Lane, Rockville, Maryland 20852.

#

RULES AND REGULATIONS

5351

to the offspring when exposed in utero to DES. It was also requested that the patient leaflet indicate that there is some risk of cancer to the patient herself from taking DES.

In considering the use of DES as a postcoital oral contraceptive, the Commissioner has carefully reviewed all available data and also consulted with the Obstetrics and Gynecology Advisory Committee for the Food and Drug Administration on the issues of both safety and effectiveness.

a. Fetal risks: It has been reported by Herbst et al. in *The New England Journal of Medicine* of April 22, 1971 (284: 878-881) that DES, if taken, usually for a prolonged period, by a woman who is pregnant, increases the risk of carcinoma of the vagina or cervix in the female offspring. It has been estimated that less than one percent of the offspring of women who have received DES treatment during pregnancy have developed cancer. The directions for use proposed for DES state that pregnancy should be ruled out prior to use of the drug. Obviously, if there is no pre-existing or ensuing pregnancy, issues involving a fetus are moot. Where it is later discovered that there is a pre-existing or ensuing pregnancy, however, the patient package insert advises that the patient consult with her physician regarding the continuation of the pregnancy. The physician's labeling also fully discusses this issue.

In order to emphasize this risk, the former fourth sentence in the third paragraph of the patient package insert, set forth in the proposal published in the *Federal Register* of September 26, 1973, has been revised to delete the word "some" preceding "evidence" and to change the word "may" to "will" in the phrase "the child may have an increased risk of developing cancer of the vagina or cervix later in life." This discussion has also been highlighted by setting it out separately as a new fourth paragraph.

Although it was stated in paragraph (b)(2) of the proposed regulation that teratogenic and other adverse effects on the fetus with the very early administration recommended are not well understood, this was not mentioned in the proposed patient package insert. The Commissioner concludes that it should be mentioned. The patient package insert accordingly contains the following statement as the third sentence of the new fourth paragraph: "Also, it is not definitely known whether this drug may cause other abnormalities in the fetus." The statement is also included in the labeling for the physician.

b. Adult risks: In *The New England Journal of Medicine* of September 28, 1972 (287: 628-631) Cutler et al. reported the occurrence of endometrial carcinoma after stilbestrol therapy in patients with gonadal dysgenesis who were treated with the drug for long periods of time, i.e., 5 years or more. For many years there has been concern that estrogens, both exogenous and endogenous, may have an etiologic role in the

development of cancer of the genital tract or breast. The observation felt to support this is that certain functioning ovarian tumors, such as granulosa cell and theca cell types which secrete large amounts of estrogen, are associated with an increased frequency of carcinoma of the endometrium. The paper by Cutler et al. may also be considered to support this possibility for certain unusual circumstances. Cutler's cases all had chromosomal abnormalities (only one X chromosome instead of the normal two) and the authors themselves observe that a genetic predisposition of such patients to this type of cancer, enhancing the effect of prolonged estrogen therapy, cannot be excluded. They further point out that abnormal chromosomal constitutions are known to be associated with an increased incidence of specific types of malignant tumors. The Commissioner concludes that the study of Cutler et al. is not applicable to a 5-day course of DES in normal women because the Cutler study involved the cyclic administration of DES for many years to women with chromosomal abnormalities. Therefore, in spite of the Cutler study, there continues to be no relevant evidence at the present time that a short course of DES in normal women, as would be used in postcoital contraception, would expose a woman to an increased risk of cancer. At the same time, it cannot be said that such a risk definitely does not exist.

The Commissioner recognizes that the patient package insert, as originally proposed, did not deal with the carcinogenicity of DES in animals and the possible relevance of these data to human use. In the regulation previously promulgated concerning oral contraceptives, § 310.501 (a)(6)(xi) requires that patient information include a statement regarding production of cancer in certain animals, and provides that such statement may be coupled with a statement that there is no proof of such effect in human beings.

The Commissioner concludes that such a requirement is equally applicable for the patient information to be supplied with DES as a postcoital oral contraceptive. Accordingly, the last sentence in the third paragraph of the proposed patient package insert has been deleted and is replaced by a new fifth paragraph, which cites the tests conducted in animals resulting in increased frequency of cancer, and warns that high dosages of estrogen are recommended for emergencies only, and not for repeated use.

c. Effectiveness: The Commissioner concludes that data from clinical investigations provide substantial evidence that DES is effective in preventing conception; however, its effectiveness depends upon close adherence to the dosage regimen of 25 milligrams twice a day for 5 consecutive days, with initiation of administration preferably within 24 hours and not later than 72 hours after coitus. On reconsideration, the Commissioner believes the words "highly effective," which appeared in the proposed patient package insert, may be misconstrued by some readers to imply a greater degree of effectiveness than other forms

SUBCHAPTER D—DRUGS FOR HUMAN USE

PART 310—NEW DRUGS

Diethylstilbestrol as Postcoital Oral Contraceptive; Patient Labeling

In the *Federal Register* of September 26, 1973 (38 FR 26309) the Commissioner of Food and Drugs proposed to amend § 310.45 (subsequently recodified as § 310.501 and published in the *Federal Register* of March 29, 1974 (39 FR 11630)) by redesignating the existing text of the entire section as paragraph (a) and by adding a new paragraph (b) establishing requirements for marketing diethylstilbestrol (DES) for use as a postcoital oral contraceptive, setting forth the text of patient labeling for that use, and providing for and inviting abbreviated new drug applications. Sixty days were provided for comment on the proposal.

An amendment to the proposed restructured paragraph (a) was published in the *Federal Register* of April 19, 1974 (39 FR 13972), upon which, since it is still under consideration, action will be taken at a later date.

In response to the September 1973 proposal, comments were received from 21 persons including several from consumer organizations, one from a religious organization, one from a municipality, one from a private physician, one from an individual employed by a pharmaceutical concern, and several from private individuals.

One abbreviated new drug application has been received.

Three respondents endorsed the proposal. Several endorsed the concept of requiring patient labeling, but were critical of its proposed content. The remainder were generally opposed to approval of DES for oral contraception. The comments, organized into categories, and the Commissioner's response with respect to each, are as follows:

1. Some comments asserted that DES is a dangerous drug due to its carcinogenic potential both to the fetus and to the mother, and should not be allowed on the market. One comment urged that the leaflet state more honestly the risk

RULES AND REGULATIONS

of contraception or to imply that this treatment is always successful. To minimize the possibility of such misconception, the words "highly effective" in the first sentence of the third paragraph of the proposed patient package insert and in the last sentence of § 310.501(b) (1) have been changed to "usually effective."

The following studies are regarded as providing substantial evidence of effectiveness:

(1) Morris, J. M. and G. van Wageningen, "Postcoital Oral Contraception," Proc. 8th Int. Conf. International Planned Parenthood Federation, Santiago, 1967, p. 256.

(2) Kuchera, L. K., "Postcoital Contraception with Diethylstilbestrol," *Journal of the American Medical Association* 4:562, 1971.

The following studies and review paper provide supportive evidence of effectiveness:

(1) Morris, J. M. and G. van Wageningen, "Compounds Interfering with Ovum Implantation and Development," *American Journal of Obstetrics and Gynecology* 96:804, 1966.

(2) Haspel, A. A., "The Effect of Large Doses of Estrogens Postcoitally in 2000 Women," Unpublished paper (available from the Food and Drug Administration).

(3) Morris, J. M. and G. van Wageningen, "Interception: The Use of Postovulatory Estrogens to Prevent Implantation," *American Journal of Obstetrics and Gynecology* 115: 101, 1973.

(4) Biye, R. P., "The Use of Estrogens as Postcoital Contraceptive Agents," *American Journal of Obstetrics and Gynecology* 115: 1044, 1973. Presented at the 26th meeting of the Obstetrics and Gynecology Advisory Committee to the Bureau of Drugs, Food and Drug Administration, January 26, 1973. This paper reviewed the studies currently available in support of the efficacy of DES as well as other estrogens (ethinyl estradiol, conjugated equine estrogens, dienestrol, estradiol cyclopentylpropionate). This paper supports the finding that estrogens are biologically effective as contraceptive agents and that there is need to determine the appropriate safe and effective dose with respect to each estrogen.

2. Several comments contended that DES is an abortifacient and not a contraceptive.

The exact mechanism of action through which DES prevents pregnancy when used postcoitally is presently unknown. There have been several theories advanced as to the mechanism, including interference with nidation through effects on the endometrium (the most likely), accelerated tubal transport of ovum, closure of the uterotubal junction, and luteolytic activity. The definition of an abortifacient is a matter of controversy. On the one hand, it may be defined as a drug or device which is capable of destroying an implanted ovum. Under this definition, DES cannot be an abortifacient because it cannot do this. Alternatively, an abortifacient could be defined as a drug or device which can prevent implantation of a fertilized ovum. Intrauterine devices and certain oral contraceptives are considered by experts to act, at least in part, by preventing implantation. These devices and drugs are generally classified as contraceptives rather than abortifacients. There is no scientific basis for

distinguishing DES from such oral drugs or intrauterine devices on the basis of mechanism of action.

Since classification of DES as an abortifacient would be arbitrary unless many other devices and drugs were similarly classified, the Commissioner concludes it is proper to call DES a contraceptive.

3. A number of persons expressed considerable concern regarding what they construed as a "recommendation" that abortion be performed in the event that the method fails.

The patient package insert advises the patient to consult with her physician regarding continuation of the pregnancy if there is pre-existing pregnancy or if pregnancy ensues. The final decision as to the course of action to be taken rests with the patient and her physician. Thus, there is no "recommendation" that an abortion be performed.

4. One comment requested that the patient leaflet make it clear that the drug is for emergency use only, and define exactly what emergency use is.

The Commissioner agrees that the patient package insert should make it quite clear that this use is an emergency measure and that it is not to be used as a routine or frequent method of contraception. Therefore, in order to emphasize this, the first sentence in the first paragraph of the patient package insert has been changed by revising the phrase "emergency measure to prevent pregnancy" to read "measure to prevent pregnancy in an emergency, for example, after a rape." In addition, the second paragraph of the patient package insert has been revised to state: "You should use this drug only under the direction of your physician. This treatment is for emergencies only and should not be used repeatedly. If you find it necessary to use this treatment more than once, you should consult with your physician to obtain an adequate method of routine contraception." Finally, the point is again emphasized in the new fifth paragraph of the patient package insert.

The Commissioner believes that these additions to the patient package insert provide sufficient emphasis that DES is intended for emergency use only, but that a definition of what constitutes an emergency is unnecessary and should properly be left to the patient and her physician.

5. A comment stated that women should be fully informed concerning possible side effects. Another suggested that all possible contraindications to the drug be included in the patient package insert.

The Commissioner agrees with these comments. All contraindications to the use of the drug are listed in the patient package insert. The patient package insert does list the most common as well as the most serious adverse effects which may be encountered with the use of an estrogenic preparation such as DES. Additionally, the patient package insert does list special health problems that

should be brought to the attention of the physician. Each and every side effect associated with the use of DES is not listed in the patient package insert because, although they apply to estrogens as a class, they have not been associated with the use of DES as a postcoital contraceptive to an appreciable extent. All side effects are listed in the package insert intended for the physician and such information should be readily available to the patient from her physician if she requests it. Furthermore, the physician's package insert states in the "Important Notes" section that "patients should be informed of . . . all other existing information relative to known and potential side effects prior to use of DES for this indication."

In order to discourage use for postcoital contraception of dosage strengths of DES other than the 25 mg. tablets which are accompanied by the patient package insert, the physician's package insert for such dosage strengths will be required to include the following in block letters before the description:

THIS DRUG PRODUCT SHOULD NOT BE USED AS A POSTCOITAL CONTRACEPTIVE

A FEDERAL REGISTER notice will be published in the near future setting forth this requirement.

6. It was requested that users of DES be strongly cautioned to contact a physician if they are pregnant, because of the association between DES and carcinoma of the vagina in female offspring.

The Commissioner agrees and notes that the patient package insert does recommend that the patient consult her physician regarding continuation of pregnancy in the event the drug is not successful.

7. One comment requested that a medical history of the patient be taken, including any history of cancer in the family.

Good medical practice dictates that an appropriate medical history be taken prior to initiation of therapy with any drug. Thus, the Commissioner concludes that such a statement is unnecessary and inappropriate for inclusion in any drug labeling.

8. A comment urged that patient followup be made to assure that the patient did not become pregnant, to discover possible adverse side effects, and to determine pregnancy rates associated with this use of DES.

In order to assure patient followup in the event that pregnancy occurs, the Commissioner has concluded that the sixth sentence in the original third paragraph of the proposed patient package insert should be deleted and replaced by a new sentence inserted at the end of the new fourth paragraph, to read as follows: "If you have not had a normal menstrual period within 4 weeks after taking the last tablet, you should contact your physician to determine if you are pregnant, and if you are, consult with him regarding continuation of the pregnancy."

RULES AND REGULATIONS

5353

With respect to adverse effects, the proposed labeling informs the patient that if any of the serious adverse effects mentioned in the labeling are noted, these should be reported to her physician.

With respect to collecting data on adverse effects and pregnancy rates associated with this treatment, it is highly unlikely that meaningful and valid results could be obtained unless such follow-up visits were done as part of a controlled study.

9. Two comments contended that provisions for informed patient consent are inadequate and that written consent should be required in some cases.

The Commissioner concludes that the patient who has consulted her physician, discussed her problem with him, and read her patient package insert, will ordinarily be adequately informed. The physician may consult with a parent or guardian if he finds it appropriate or necessary. If experience should prove that the present requirements do not ensure that patients are adequately informed, the Commissioner will consider other measures.

10. One comment recommended that every possible attempt be made to ensure that a patient is never prescribed DES for this particular indication more than once.

Both the patient package insert and the physician's package insert indicate that DES is not to be used routinely or frequently as a method of contraception, and draw attention to the lack of evidence of safety in repeated use. This point is now emphasized in both the second and fifth paragraphs of the revised patient package insert. The Commissioner believes that this labeling adequately discloses current knowledge to both physician and patient and that further measures to limit usage are not warranted at this time.

11. One comment objected to the proposal and requested that the reasons for his objections be explored in public hearings.

The regulation proposed is not the type of regulation on which the Food and Drug Administration is required to hold a public hearing, although the Commissioner may exercise his discretion in that regard. The topic of DES as a postcoital contraceptive was considered during a public hearing at the open session of the Obstetrics and Gynecology Advisory Committee on January 26, 1973. Anyone wishing to present his views on this subject was invited to do so and several people availed themselves of this opportunity either through personal appearance or through correspondence. Their views were carefully considered by the members of the Advisory Committee and by the Food and Drug Administration in reaching their final decision relative to DES as a postcoital contraceptive. The Commissioner has carefully considered the data and information available, finds that the proposed approval of DES as a postcoital contraceptive is justified by the facts, and concludes that a further

public hearing at this time on this matter would serve no useful purpose.

The Commissioner, having considered the comments received, finds no basis for altering his finding that DES is safe and effective as a postcoital contraceptive for emergency use when used under the conditions proposed, and concludes that, except for the revisions in the patient package insert and the regulation noted above, the regulation shall be promulgated as proposed.

Shipment in interstate commerce of diethylstilbestrol for use as a postcoital contraceptive is unlawful unless such use is provided for in an approved new drug application as described in the regulation below.

The references cited in this preamble, and other related background material have been assembled and are on display in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishbein Lane, Rockville, MD 20852. The following is a list of the material on display:

- (1) Proposed DES regulation, *FEDERAL REGISTER*, September 26, 1973.
- (2) Notice that DES is contraindicated in pregnancy *FEDERAL REGISTER*, November 10, 1971.
- (3) "Postcoital Diethylstilbestrol," *FDA Drug Bulletin*, May 1973.
- (4) "Diethylstilbestrol Contraindicated in Pregnancy," *FDA Drug Bulletin*, November 1971.
- (5) Obstetrics and Gynecology Advisory Committee: Minutes of December 1971 meeting. Material not relevant to DES has been deleted.
- (6) Obstetrics and Gynecology Advisory Committee: Minutes of March 1972 meeting. Material not relevant to DES has been deleted.
- (7) Obstetrics and Gynecology Advisory Committee: Minutes of January 1973 meeting (both open and closed sessions).
- (8) Results of NIH/FDA Workshop on Pregnancy Prevention by Estrogens, held February 14, 1972.
- (9) Ruchera, L. E., M.D., "Postcoital Contraception with Diethylstilbestrol," *Journal of the American Medical Association* 4: 662-663, 1971.
- (10) Haspels, A. A., M.D., "The Effect of Large Doses of Estrogens Post-Coitus in 2000 Women," Unpublished paper.
- (11) Connell, E. B., M.D., "New York State Survey on 'Morning After' Estrogen Contraceptive Therapy," report presented at NIH Workshop on Aversion of Pregnancy by Estrogens, held February 14, 1972.
- (12) Herbst, A. L., et al., "Adenocarcinoma of the Vagina," *New England Journal of Medicine* 284:878-881, 1971.
- (13) Cutler, B. E., et al., "Endometrial Carcinoma after Stilbestrol Therapy in Gonadal Dysgenesis," *New England Journal of Medicine* 287:628-631, 1972.
- (14) Morris, J. M., et al., "Compounds Interfering with Ovarian Implantation and Development," *American Journal of Obstetrics and Gynecology* 96:804, 1968.
- (15) Morris, J. M., et al., "Post-Coital Oral Contraception," *Proc. 8th Int. Conf. International Planned Parenthood Federation*, Santiago, 1967, p. 256.
- (16) Blye, R. P., "The Use of Estrogens as Postcoital Contraceptive Agents," *American Journal of Obstetrics and Gynecology* 7:1044, 1920.
- (17) Morris, J. M. and G. van Wageningen, "Interception: The Use of Postovulatory

Estrogens to Prevent Implantation," *American Journal of Obstetrics and Gynecology* 115:101, 1973.

(18) Morris, J. M., "Mechanisms Involved in Progesterone Contraception and Estrogen Interception," *American Journal of Obstetrics and Gynecology* September 15, 1973.

Accordingly, the Commissioner concludes that § 310.501 should be amended by revising the section heading; redesignating paragraph (a) as paragraph (a) (1) and adding a new heading for paragraph (a) (2); redesignating paragraph (b) as paragraph (a) (2); redesignating the remainder of the existing paragraphs as subparagraphs of paragraph (a) with no change in the existing text; and by adding a new paragraph (b).

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502(a) and (f), 505, 701(a), 52 Stat. 1050-1053, 1935, as amended; 21 U.S.C. 352(a) and (f), 355, 371(a)) and under authority delegated to him (21 CFR 2.120), Part 310 is amended by revising § 310.501 to read as follows:

§ 310.501 Preparations for contraception; labeling directed to the patient.

(a) *Oral contraceptives.* (1) The Food and Drug Administration is charged with assuring both physicians and patients that drugs are safe and effective for their intended uses. The full disclosure of information to physicians concerning such things as the effectiveness, contraindications, warnings, precautions and adverse reactions is an important element in the discharge of this responsibility. In view of this, the Administration has reviewed the oral contraceptive products, taking into account the following factors: The products contain potent steroid hormones which affect many organ systems; they are used for long periods of time by large numbers of women who, for the most part, are healthy and take them as a matter of choice for prophylaxis against pregnancy, in full knowledge of other means of contraception; and there is no present assurance that persons for whom the drugs are prescribed or dispensed are uniformly being provided the necessary information for safe and effective use of the drugs.

(2) In view of the foregoing, it is deemed in the public interest to present to users of the oral contraceptives a brief notice of the nature of the drugs, the fact that continued medical supervision is needed for safe and effective use, that the drugs may cause side effects and are contraindicated in some cases, that the most important complication is abnormal blood clotting which can have a fatal outcome, that the physician recognizes an obligation to discuss the potential hazards of taking the drugs with the patient, that he has available for the patient written material discussing the effectiveness and the hazards of the drugs, and that users of the oral contraceptives should notify their physicians if they notice any unusual physical disturbance or discomfort.

(3) The Commissioner agrees that the physician is the proper person for providing use information to his patients,

RULES AND REGULATIONS

and these regulations will provide him a balanced discussion of the effectiveness and the risks attendant upon the use of oral contraceptives for his use in discussing the drugs with his patients.

(4) The oral contraceptives are restricted to prescription sale, and their labeling is required to bear information under which practitioners licensed to administer the drugs can use them safely and for the purpose for which they are intended. In addition, in the case of oral contraceptive drugs, the Commissioner concludes that it is necessary in the best interests of users that the following printed information for patients be included in or with the package dispensed to the patient:

(Patient Package Information)

ORAL CONTRACEPTIVES

(Birth Control Pills)

Do Not Take This Drug Without Your Doctor's Continued Supervision

The oral contraceptives are powerful and effective drugs which can cause side effects in some users and should not be used at all by some women. The most serious known side effect is abnormal blood clotting which can be fatal.

Care use of this drug requires a careful discussion with your doctor. To assist him in providing you with the necessary information, _____ has prepared a booklet (or other form) written in a style understandable to you as the drug user. This provides information on the effectiveness and known hazards of the drug including warnings, side effects and who should not use it. Your doctor will give you this booklet (or other form) if you ask for it and he can answer any questions you may have about the use of this drug.

Notify your doctor if you notice any unusual physical disturbance or discomfort.

(5) Providing the patient package information to users may be accomplished by including it in each package of the type intended for the user as follows:

(i) If such package includes additional printed materials for the patient (e.g., dosage schedules), the text of the information in paragraph (a) (4) of this section shall be an integral part of the printed material and be in boldface type set out in a box, preceding all other printed text.

(ii) If such package does not include other printed material for the patient, the text of the information in paragraph (a) (1) of this section shall be provided as a printed leaflet in boldface type.

(iii) Include in each bulk package intended for multiple dispensing a sufficient number of the patient package information leaflets, with instructions to the pharmacist to include one with each prescription dispensed.

(6) Written, printed, or graphic materials on the use of a drug that are disseminated by or on behalf of the manufacturer, packager, or distributor and are intended to be made available to the patient, are regarded as labeling. The commissioner also concludes that it is necessary that information in lay language, concerning effectiveness, contraindications, warnings, precautions; and

adverse reactions be incorporated prominently in the beginning of any such materials, and that such labeling must be made available to physicians for all patients who may request it. Such labeling shall be substantially as follows, based on the approved package insert for prescribers of the oral contraceptives, and shall include the following points:

(i) A statement that the drug should be taken only under continued supervision of a physician.

(ii) A statement regarding the effectiveness of the product.

(iii) A warning regarding the serious side effects with special attention to thromboembolic disorders and stating the estimated morbidity and mortality in users vs. nonusers. Other serious side effects to be mentioned include mental depression, edema, rash, and jaundice. The possibility of infertility following discontinuation of the drug should be mentioned.

(iv) A statement of contraindications. (v) A statement of the need for special supervision of some patients including those with heart or kidney disease, asthma, high blood pressure, diabetes, epilepsy, fibroids of the uterus, migraine, mental depression or history thereof.

(vi) A statement of the most frequently encountered side effects such as spotting, breast changes, weight changes, skin changes, and nausea and vomiting. (vii) A statement of the side effects frequently reported in association with the use of oral contraceptives, but not proved to be directly related, such as nervousness, dizziness, changes in appetite, loss of scalp hair, increase in body hair, and increased or decreased libido.

(viii) A statement regarding metabolic effects such as on blood sugar and cholesterol setting forth our current lack of knowledge regarding the long term significance of these effects.

(ix) Instructions in the event of missed menstrual periods.

(x) A statement cautioning the patient to consult her physician before resuming the use of the drug after childbirth, especially if she intends to breast-feed the baby, pointing out that the hormones in the drug are known to appear in the milk and may decrease the flow.

(xi) A statement regarding production of cancer in certain animals. This may be coupled with a statement that there is no proof of such effect in human beings.

(xii) A reminder to the patient to report promptly to her physician any unusual change in her general physical condition and to have regular examinations.

Optionally, the booklet may also contain factual information on family planning, the usefulness and hazards of other available methods of contraception, and the hazards of pregnancy. This material shall be neither false nor misleading in any particular and shall follow the material presented above.

(7) The marketing of oral contraceptives may be continued if all the following conditions are met on or before

May 6, 1975, the date of publication of this section in the Federal Register.

(i) The labeling of such preparations shipped within the jurisdiction of the Act is in accord with paragraph (a) (4), (5), and (6) of this section.

(ii) The holder of an approved new-drug application for such preparation submits a supplement to his new drug application under the provisions of § 314.8(d) of this chapter to provide for labeling as described in paragraph (a) (4), (5) and (6) of this section. Such labeling may be put into use without advance approval of the Food and Drug Administration.

(iii) Existing stocks may be shipped without the package insert for a period of 90 days, provided the labeling booklet is prepared and disseminated as promptly as possible.

(b) *Oral postcoital contraceptives.* (1) Diethylstilbestrol orally for postcoital contraception. Studies conducted with this drug have shown its effectiveness in contraception when administered under restricted conditions. The Commissioner, having considered comments by members of the Food and Drug Administration's Obstetrics and Gynecology Advisory Committee, concludes that the drug is safe and effective as an emergency treatment only, and not as a routine method of birth control. Repeated courses of therapy are to be avoided. The effectiveness of diethylstilbestrol in preventing pregnancy depends upon the time lapse after coitus and administration of the drug. The recommended dosage is one 25 milligram tablet twice a day, for 5 consecutive days beginning, preferably within 24 hours and not later than 72 hours after exposure. When this dosage is given within the specified time interval, the drug is usually effective in preventing conception. Its use, however, will not terminate pregnancy.

(2) There is at present no positive evidence that the restricted use of diethylstilbestrol for postcoital contraception carries a significant carcinogenic risk either to the mother or the fetus. However, because existing data support the possibility of delayed appearance of carcinoma in females whose mothers have been given diethylstilbestrol later in pregnancy, and because teratogenic and other adverse effects on the fetus with the very early administration recommended are not well understood, failure of postcoital treatment with the drug deserves serious consideration of voluntary termination of pregnancy. For these reasons, as well as possible adverse effects in the patient, the drug should not be used as a routine method of birth control. A pregnancy test should be performed prior to use of the drug as a postcoital contraceptive. If the test is positive, the drug should not be used.

(3) Because of the nature of the conditions surrounding this use of diethylstilbestrol, the Commissioner concludes that it is in the best interests of the patient that, in addition to receiving specific instructions from her physician, she also receive with her package of the drug

RULES AND REGULATIONS

a printed leaflet describing how to use the drug, limitations on its use, its potential for serious effects on the fetus in the event she is pregnant, and possible adverse effects, contraindications and precautions.

(4) Diethylstilbestrol for use as a post-coital contraceptive shall be packaged in containers of 10 tablets, each tablet to contain 25 milligrams diethylstilbestrol. Each drug package of 10 tablets shall contain, in addition to information under which the practitioner licensed to administer the drug can use it safely and for the purpose for which it is intended, a brief leaflet for the user to read as follows:

(Patient package information)

Your doctor has prescribed these tablets which contain estrogen (female hormone) as a measure to prevent pregnancy in an emergency, for example, after a rape. To be effective the treatment must be started within 3 days of sexual intercourse and preferably within 1 day. Also, you must take the full course of tablets (1 twice a day for 5 days) even if some nausea and vomiting occurs. These symptoms are common in patients receiving this medicine.

You should use this drug only under the direction of your physician. This treatment is for emergencies only and should not be used repeatedly. If you find it necessary to use this treatment more than once, you should consult with your physician to obtain an adequate method of routine contraception.

This treatment is usually effective in preventing pregnancy if used as described above. However, this drug will not cause an abortion if you are already pregnant. Before prescribing this drug, your physician will determine whether or not you may be pregnant.

An important reason for not taking the drug if you are already pregnant is that such usage exposes the fetus to an unnecessary hazard. There is evidence that, if the growing fetus is a female and the mother is given this drug during pregnancy, the child will have an increased risk of developing cancer of the vagina or cervix later in life. Also, it is not definitely known whether this drug may cause other abnormalities in the fetus. If you have not had a normal menstrual period within 4 weeks after taking the last tablet, you should contact your physician to determine if you are pregnant; and if you are, consult with him regarding continuation of the pregnancy.

In tests conducted in animals, estrogens given for long periods have increased the frequency of cancer in certain species. While there is no evidence from currently available studies in women to indicate that you will have an increased risk of developing cancer later in life if you use this treatment, there is no way to be certain that such evidence will not appear in the future. Therefore, it is sensible and prudent to avoid the high dose of estrogen used in this treatment unless absolutely necessary. That is why this method of contraception is recommended for emergency use only and should not be used repeatedly.

These tablets which contain estrogen may cause certain side effects, most of which are not serious. The most common side effects are nausea, vomiting, breast tenderness and swelling. The most serious side effect of estrogens, which is rare but can at times be fatal, is abnormal blood clotting, the symptoms of which may be severe leg or chest pain, coughing up of blood, difficulty in breathing, sudden severe headaches, dizziness or fainting, disturbances in vision or speech or weak-

ness or numbness of an arm or leg. If any of these occur, you should stop taking the tablets and notify your doctor as soon as possible.

Women who have or have had blood clotting disorders, serious liver conditions, cancer of the breast or womb, or undiagnosed vaginal bleeding in the past should not take these tablets. Furthermore, you should inform your physician if you have or have had a special health problem, such as migraine, mental depression, fibroids of the uterus, heart or kidney disease, asthma, high blood pressure, diabetes or epilepsy. He may wish to make sure that it is suitable for you to take these tablets.

(5) Diethylstilbestrol for use as a post-coital contraceptive may be marketed only on the basis of an approved new drug application containing information required by § 314.1(f) of this chapter, except that full information described under items 7 and 8 (composition and methods, facilities, and controls) of the new drug application Form FD-356H (§ 134.1(c) of this chapter) is required. Guidelines for labeling directed to the physician are available from the Food and Drug Administration, Bureau of Drugs, Division of Metabolic and Endocrine Drug Products (HFD-130), 5600 Fishers Lane, Rockville, MD 20852.

Effective date: This order shall be effective on March 7, 1975.

(Secs. 502 (a) and (f), 505, 701(a), 52 Stat. 1050-1053, 1055, as amended; 21 U.S.C. 353 (a) and (f), 505, 701(a).)

Dated: January 30, 1975.

A. M. SCHMIDT,
Commissioner of Food and Drugs.
[FR Doc. 75-3201 Filed 2-4-75; 8:45 am]



talk
paper*

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
FOOD AND DRUG ADMINISTRATION
5600 Fishers Lane
Rockville, Maryland 20852

T75-10
February 5, 1975

Edward R. Nida
(301)--443-3285

MORNING AFTER PILL: DIETHYLSTILBESTEROL (DES)

On February 5, 1975, the Food and Drug Administration established requirements for consumer labeling for diethylstilbestrol (DES), a synthetic hormone, to insure its safety and effectiveness when used as an emergency "morning after" contraceptive. One abbreviated new drug application for this use is now being considered by the Agency.

Manufacturers who sell the drug for emergency contraceptive use must provide an FDA-approved brochure for patients emphasizing the risks of the drug. The brochure will explain possible side effects and how the patient can recognize them.

Some concerns have been expressed about the safety and efficacy of DES as a contraceptive. These have been thoroughly studied by the Commissioner and the Bureau of Drugs and the following responses may be helpful for responding to inquiries:

Q. Do the studies cited as providing substantial evidence of effectiveness meet the scientific standards specified by the law?

A. This matter has again been reviewed by the Bureau of Drugs and the Bureau finds the studies cited in the final order are substantial evidence under the law. Estrogens in general have the fundamental property of preventing pregnancy if administered in sufficiently high dosage at the time of conception.

MORE

*FDA Talk Papers are issued by the FDA Press Office to provide guidance to FDA personnel in responding to requests for information on subjects of current interest. They are subject to change as more information or data becomes available.

A major objective of the human studies with this drug has been to establish the effective dose and the time interval around the period of conception when this treatment is effective in humans. The patient leaflet in the final order states that this treatment is "usually effective." FDA believes this to be a correct appraisal based on the available evidence.

- Q. The patient brochure recommends only emergency use of DES. Should the conditions constituting an emergency be defined precisely?
- A. The Bureau of Drugs has reconsidered the wording in the patient leaflet and physician package insert and recommended (a) that the words "for example, after a rape" be added to the phraseology relating to emergency use and (b) that the entire second paragraph of the patient leaflet be revised to read:

"You should use this drug only under the direction of a physician. This treatment is for emergencies only and should not be used repeatedly. If you find it necessary to use this treatment more than once, you should consult with your physician to obtain an adequate method of routine contraception."

FDA believes that the Federal Government should not attempt to specify by regulation all of the circumstances under which an act of unprotected intercourse might be considered an emergency. Such decisions should properly remain a part of the patient-doctor relationship. We have therefore not limited the indication strictly to rape and incest.

MORE

- Q. Should not physician's and patient's labeling for use as a post-coital contraceptive accompany all package inserts for diethylstilbestrol rather than just the 25 mg. tablets packaged specifically for this purpose?
- A. Instead of labeling all tablets of diethylstilbestrol for post-coital contraception, it is FDA's intention to require a warning in the package inserts of all dosage forms other than the 25 mg. tablets that these other dosage forms are not to be used for post-coital contraception.
- Q. Is sufficient emphasis given in the patient leaflet to the animal data on the potential carcinogenic hazard to the patient exposed to the drug?
- A. This point has been given more emphasis in the final labeling order.

####

NOTE: Update of Talk Paper T73-10, 1/31/73 and Press Release #73-39, 9/21/73.

Dr. Robert H. Furman is Vice-President, Lilly Research Laboratories.

A graduate of the Yale School of Medicine, he has been a faculty member at four leading medical schools and Associate Director, Oklahoma Medical Research Foundation. He is a member of the American Board of Internal Medicine.

Dr. Furman joined Eli Lilly and Company in 1970.

STATEMENT OF ELI LILLY AND COMPANY
REGARDING DIETHYLSTILBESTROL
TO THE
SUBCOMMITTEE ON HEALTH
OF THE
SENATE COMMITTEE ON LABOR AND PUBLIC WELFARE
AND THE
SUBCOMMITTEE ON ADMINISTRATIVE PRACTICE AND PROCEDURE
OF THE
SENATE COMMITTEE ON THE JUDICIARY

Presented by:

Robert H. Furman, M.D.
Vice President
Lilly Research Laboratories
February 27, 1975

Mr. Chairman and Members of the Committee:

Eli Lilly and Company is pleased to respond to the invitation of the Chairman to appear today. As requested, our statement will include comments on Lilly's decision not to market a 25-mg. dosage form of diethylstilbestrol for postcoital contraception. It also will discuss Lilly's suggestions for the proper use of prescription pharmaceuticals.

Diethylstilbestrol

Diethylstilbestrol (DES) is a synthetic compound capable of producing feminizing effects similar to those of the naturally occurring feminizing hormones (estrogens). It was synthesized by Dodds in 1938. DES was added to the Lilly product line in 1941, "at a time when the natural products were scarce and expensive."⁽¹⁾ It was regarded as a milestone in the development of effective hormone therapy, and it is used today in the treatment of a number of conditions.

The four principal conditions in which DES is most often employed are the following:

- (a) as replacement therapy in states of estrogen deficiency, e.g., the menopause or the absence of ovaries;
- (b) for the prevention of postpartum breast engorgement;
- (c) cancer of the prostate; and
- (d) breast cancer in post-menopausal women.

Since 1951, studies in animals and humans have indicated that high doses of estrogen, administered after the ovum (egg) had been released from the ovary (determined by body temperature rise),

prevent pregnancy. In 1966, and subsequently, reports by Morris and van Wagenen⁽²⁾ and by Kuchera⁽³⁾ demonstrated that DES prevented pregnancy when administered in large doses (25 mg. twice daily for 5 days) beginning no later than 72 hours after sexual contact.

Precisely how DES acts to prevent pregnancy when administered after sexual contact is not known. It probably interferes with the attachment of the fertilized ovum to the lining of the uterus (implantation). The term "interceptives" has been suggested for agents which interfere with implantation.⁽⁴⁾ We are not aware of any evidence that DES will interrupt an already implanted ovum.⁽⁵⁾

25-mg. Dosage for Postcoital Contraception

Lilly had provided a 25-mg. dosage form of DES for use in patients with carcinoma. In February of 1973, a spokesman for the FDA indicated to the Senate Subcommittee on Health that DES had been approved as a postcoital contraceptive. In the May, 1973 FDA Drug Bulletin the provisions of the newly approved indication were delineated.

In the Federal Register for September 26, 1973, the FDA gave notice to the effect that it was proposing to withdraw its approval of 25-mg. dosage forms of DES for all indications except postcoital contraception. Industry was invited to submit abbreviated new drug applications for the use of the 25-mg. DES dosage for this indication.

In the Federal Register for February 5, 1975, the final labeling, patient package information and package size are set forth. The notice indicates that only one abbreviated new drug application has been received.

After the Federal Register notice of September 26, 1973, Eli Lilly and Company deleted the 25-mg. dosage forms from its product line. These items had been made available to physicians for other uses, such as carcinoma. We elected not to submit an abbreviated NDA for the use of DES as a postcoital contraceptive. This decision was arrived at after careful review and evaluation of the medical and scientific aspects of the situation. After prior review by FDA, a letter was mailed to over 230,000 physicians and approximately 55,000 pharmacists in March of 1974, discussing the use of DES, including its use as a postcoital contraceptive. The letter informed them as follows:

"... although postcoital contraception is recognized by some authorities as an indication for diethylstilbestrol, Eli Lilly and Company has neither conducted nor supported laboratory or clinical investigations to establish efficacy and safety of its product for this indication. Therefore, diethylstilbestrol supplied by Eli Lilly and Company is not recommended for postcoital contraception, and we are deleting from our product line the 25-mg. dosage forms (Enseals No. 90 and Tablets No. 1724). We continue to endorse diethylstilbestrol for the indications included in our current literature.

"Although diethylstilbestrol is supplied by many manufacturers, Eli Lilly and Company believes it important to acquaint the medical profession with this information."

As stated in the Lilly letter to physicians, the primary basis for Lilly's decision was lack of its own clinical or laboratory information regarding efficacy or toxicity. This decision is consistent with our policy to secure adequate clinical information on safety and toxicity prior to introducing a new drug.

Providing for the Proper Use of Prescription Drugs

Let me turn now to the problem of minimizing the misuse of prescription drugs. You have asked for our suggestions.

There is regrettably no certain way to assure proper drug usage. We believe the only realistic way to ensure against the misuse of drugs is through a continuing effort to develop and disseminate information on drug usage.

The development of information necessary for the proper use of a drug must begin prior to the filing of an IND. It must continue through clinical investigations and after marketing as increasing clinical experience is developed. To have maximal effect, the educational process should involve several components: the industry, the university, the government, the physician, the pharmacist, and the patient.

The foregoing process produces a vast amount of complex information which must be effectively made available to the physician in order for him to make sound therapeutic judgments. This process of communication is an essential part of our responsibility to assure proper drug usage.

For this reason, we at Eli Lilly and Company examine very closely the information sent to health professionals. Company literature is reviewed to ensure that only medically and scientifically valid statements are made and that the necessary warnings and contraindications are provided. Of equal importance in the dissemination of scientific information is a balanced, accurate discussion of the available data by a competent, well-educated, and well-trained responsible sales representative. Most of our salesmen have pharmacy degrees, and all are university graduates.

The ultimate responsibility for the care of the patient rests with the physician. His ability to evaluate and to utilize new drug information depends on his knowledge of fundamental clinical pharmacology, the basis for all drug therapy. There is agreement that greater emphasis needs to be placed on clinical pharmacology training in our medical schools as well as in programs of continuing education for practicing physicians.

The pharmacist can help the patient understand the physician's instructions regarding his medical problem and its management. The clinical pharmacist, in the hospital or clinic setting, is an important member of the health care team. He is an important source of drug information in particular clinical situations.

The patient plays a role in the proper use of drugs. Lack of understanding on his part can spell therapeutic failure.

As we seek to insure that all drugs are properly used, we must not forget that unfortunately there is no risk-free drug and inherent in every therapeutic situation is the matter of risk versus benefit. Adequate knowledge, however, can diminish the risk.

Let me conclude by offering the following specific recommendations which Eli Lilly and Company believes will help insure that drugs are properly used:

- (1) A company should assume responsibility for its own independent evaluation of the safety and efficacy of the products which it offers the medical profession. This is essential if the company is to meet today's professional responsibility.

-6-

(2) A more intensive training in clinical pharmacology is needed for medical students and physicians.

(3) Measures should be developed to enhance consumer protection such as product coding systems, expiration dating, and identification of the manufacturer of the dosage form on the product label.

(4) Ethical practices and high standards of training for sales representatives on the part of all manufacturers should be a priority for all manufacturers.

We believe that it is in the context of these areas of concern that recommendations for better safeguards can be developed. Eli Lilly and Company is committed to and stands ready to assist in the accomplishment of these suggestions.

#

REFERENCES

1. Goodman, L.S., and Gilman, A.: The Pharmacological Basis of Therapeutics, 4th Ed., Macmillan, New York, 1970, p. 1539.
2. Morris, J.M., and van Wagenen, G., Am. J. Obstet. Gynecol. 96:804, 1966.
3. Kuchera, L.K., J.A.M.A., 4:562, 1971 (see also more recent references).
4. Naqvi, R.H., and Warren, J.C.: Steroids, 18:731, 1971.
5. Morris, J.M., and van Wagenen, G., Proc. Eighth Int. Conf. IPPF, San Diego, 1967, p. 256.

ELI LILLY AND COMPANY

INDIANAPOLIS, INDIANA 46206 • TELEPHONE (317) 636-2211

Dear Doctor:

This letter is to inform you of two current matters relating to diethylstilbestrol. The FDA Bulletin of November, 1971, referred to a report of statistically significant association between diethylstilbestrol and adenocarcinoma of the vagina. Since then, additional published reports have suggested an association between diethylstilbestrol and carcinoma of the cervix and other genital tract neoplasms in young women whose mothers received the drug during pregnancy.

In their most recent article, Herbst and co-workers* made the following observations:

1. The period of greatest risk may be soon after abnormal vaginal or cervical epithelium has been stimulated by ovarian hormones with the onset of puberty.
2. Although vaginal bleeding or discharge led to discovery of most tumors, many patients were asymptomatic, and cytology alone was not reliable for diagnosis.
3. Screening examinations of the "at-risk" population (postmenarche females whose mothers took diethylstilbestrol or similar compounds during pregnancy) are indicated.

Since a cause-and-effect relationship cannot be ruled out with the current state of knowledge, Eli Lilly and Company cautions physicians to be especially alert for neoplasms in young women whose mothers may have received diethylstilbestrol therapy during pregnancy. Even if these women are asymptomatic, periodic examinations of the genital tract are urged. Irregular vaginal bleeding or other symptoms that may be due to genital tract neoplasms, particularly in the young female population, should be watched for closely; if any are found, the patient should be examined promptly.

*Herbst, A. L., Kurman, R. J., Scully, R. E., and Poskanzer, D. C.: Clear-Cell Adenocarcinoma of the Genital Tract in Young Females, N. Engl. J. Med., 287:1259, 1972.

Secondly, although postcoital contraception is recognized by some authorities as an indication for diethylstilbestrol, Eli Lilly and Company has neither conducted nor supported laboratory or clinical investigations to establish efficacy and safety of its product for this indication. Therefore, diethylstilbestrol supplied by Eli Lilly and Company is not recommended for postcoital contraception, and we are deleting from our product line the 25-mg. dosage forms (Enseals® No. 90 and Tablets Np. 1724). We continue to endorse diethylstilbestrol for the indications included in our current literature.

Although diethylstilbestrol is supplied by many manufacturers, Eli Lilly and Company believes it important to acquaint the medical profession with this information.

Very truly yours,

ELI LILLY AND COMPANY

Enseals® (enteric-release tablets, Lilly)

P.S. Please see the following page of this letter for package literature.

60-16 PA 3774 AMP

STELLIS-ROL

DESCRIPTION

Diethylstilbestrol is a crystalline synthetic estrogenic substance capable of producing all the pharmacologic and therapeutic responses attributed to natural estrogens.

INDICATIONS

Diethylstilbestrol is indicated as replacement therapy in states of estrogen deficiency associated with the menopausal syndrome or female castration. It is also indicated for the prevention of postpartum breast cancer or mastitis.

In addition, diethylstilbestrol has been found of value in the following conditions: acute vaginitis, mastitis, vulvitis with or without pruritus, inoperable progressing mammary cancer (for palliation only when castration is not feasible or when castration fails), or delayed response following a response to castration in breast cancer and breast cancer (for palliation only in women with progressing inoperable or recurrent disease who are more than five years postmenopausal), and in those inoperable male patients in whom bilateral orchiectomy cannot be performed because of an independent surgical contraindication.

CONTRAINDICATIONS

The contraindications to diethylstilbestrol administration are the same as to estrogen therapy in general. Estrogens should not be administered in the absence of a positive indication, and they should be avoided in premenopausal women with carcinoma of the breast and in all women with genital malignancy. A family history of a high incidence of breast or genital malignancy may be a contraindication.

In young patients in whom bone growth is not complete, estrogen therapy is contraindicated because of its effect on epiphyseal closure.

Significant or known hepatic disease should be regarded as a contraindication to prolonged estrogen therapy.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. The use of diethylstilbestrol or any of its closely related congeners is contraindicated in pregnancy.

WARNING

Diethylstilbestrol has been reported to be associated with thromboembolic phenomena, especially in the postpartum patient.

PRECAUTIONS

Diethylstilbestrol is a potent drug, and caution must be employed in its use. Indiscriminate or injudicious administration may be dangerous. Patients receiving the drug should be under continuous medical supervision. In women, the breasts and pelvic organs should be examined before treatment is begun and at intervals during therapy.

Diethylstilbestrol should be administered with caution to a patient with bone, renal, or other disease involving calcium or phosphorus metabolism, since estrogens are known to affect metabolism of these substances. Conditions such as epilepsy, migraine, asthma, and cardiac or renal dysfunction require careful observation because the drug may produce varying degrees of fluid retention. Liver, thyroid, or adrenal function tests should not be performed until estrogen therapy has been discontinued for two months.

ADVERSE REACTIONS

As with natural estrogens, important side effects have been noted following diethylstilbestrol therapy. Most common is the occurrence of nausea, which may be severe enough to lead to vomiting. The incidence of nausea seems to differ significantly among various types of patients. Pregnant and postpartum women seem to be most susceptible.

Nausea and vomiting are most easily produced in the group of menopausal women. When dosage is minimal, nausea is infrequent and transient. When larger doses are given (1 mg. or more daily), and particularly when they are administered initially, nausea and vomiting are common in the menopausal group. Men and premenopausal women form an intermediate group, nausea in them being relatively uncommon from 0.5 to 1 mg. daily.

Continuous therapy over long periods of time, even in low dosage, may produce endometrial hypertrophy and uterine bleeding. This can be prevented in most instances by minimum dosage or by cyclic interruption of therapy when treatment must be prolonged. Porphyria cutanea tarda is also possible with extended use of the drug.

Other side-effects occasionally noted include abdominal distress or pain, breast tenderness and engorgement, anorexia, diarrhea, lassitude, parosmia, vertigo, headache, anxiety, insomnia, thirst, stomatitis, cutaneous rashes, purpura, and allergic reactions of various types. Side-effects may be expected to disappear on reduction of dosage or withdrawal of medication.

DOSAGE AND ADMINISTRATION

Menopause or Female Castration—0.2 to 0.5 mg. daily. This may be increased as indicated. Cyclic therapy is recommended after stabilization (a three-week regimen with a one-week rest period).

Postpartum Breast Engorgement—5 mg. one to three times daily for a total of 10 mg.

Carcinoma of Prostate—1 to 3 mg. daily initially, increased in advanced cases; later, the dose may be reduced to an average of 1 mg. daily.

Breast Cancer—15 mg. daily.

Stim. Vagina—0.5 to 2 mg. per day orally as tolerated (may produce nausea). Up to 1 mg. diethylstilbestrol in suppository form may also be used daily for ten to fourteen days while oral administration of diethylstilbestrol is continued.

Kneads Vagina—Up to 5 mg. weekly in suppository form.

HOW SUPPLIED

Enteric-release tablets, Lilly) Diethylstilbestrol Tablets, U.S.P. (Enteric), are supplied as follows: 0.1 mg. (No. 43), 0.25 mg. (No. 47), 0.5 mg. (No. 49), 1 mg. (No. 49), and 5 mg. (No. 83), in bottles of 100 and 1,000.

Suppositories—Diethylstilbestrol Suppositories, U.S.P. (Vaginal), 0.1 mg. (No. 14) and 0.5 mg. (No. 15), are supplied in packages of 6 and 50. In addition to the diethylstilbestrol, these suppositories contain glycerin, gelatin, polyethylene oil, and cetylalcohol.

Tablets—Diethylstilbestrol Tablets, U.S.P., are available as follows: 0.1 mg. (No. 1039), in bottles of 10 and 1,000; 0.25 mg. (No. 1047), in bottles of 100; 0.5 mg. (No. 1049) and 1 mg. (No. 1049), in bottles of 100 and 1,000; and 5 mg. (No. 1057), in bottles of 100 and 1,000 and in 10 strips of 10 individually labeled blisters each containing one tablet (10100).

Literature revised March 5, 1974

ELLY AND COMPANY
Indianapolis, Ind. 46203, U.S.A.

PA 3774 AMP

PRINTED IN U.S.A.



Tablicaps, Inc.

For Quality Generic Pharmaceuticals

A JOINT HEARING OF THE SENATE SUBCOMMITTEE ON HEALTH AND THE
SENATE SUBCOMMITTEE ON ADMINISTRATIVE PRACTICE AND PROCEDURE
ON THURSDAY, FEBRUARY 27, 1975

SUBMITTED BY: ROBERT L. PILLARELLA, PRESIDENT

We are pleased to appear before this joint session of the Subcommittees on Health and Administrative Practices and Procedures. We are delighted because a small company such as Tablicaps rarely has the opportunity to show the role small companies can play in this great country of ours. Probably more important, the reassuring anticipation that this joint subcommittee recognizes the same concern as Tablicaps. That is, in providing government approved medical therapy for rape victims. For the first time, a rape victim may have the opportunity to receive approved medication. A medical therapy which would provide the proper warnings, as noted in the Food and Drug Administration policy published in the Federal Register dated February 5, 1975.

We are presenting a brief and concise statement addressed to the following specific requests: a short Tablicaps biography, how Tablicaps became involved with Diethylstilbestrol, where we feel this dosage form belongs in medical therapy,

- 2 -

what constitutes appropriate and inappropriate use, minimizing the potential for misuse.

Tablicaps was incorporated in the State of New Jersey in 1969, and is located in Franklinville, Gloucester County, New Jersey.

Tablicaps was incorporated with the intent to establish a line of quality generic pharmaceutical products. We felt that a steadily aging population and the demand for higher standards of health would increase the need for drug products throughout the world, further increasing the number of third party payment plans and anticipated government interest in drug programs for the elderly would create a greater demand for generic drugs. Therefore, Tablicaps began to form a product line which would be the basis to implement our corporate philosophy.

Among the products selected, was the widely used generic estrogen, Diethylstilbestrol.

Tablicaps began manufacturing various strengths of Diethylstilbestrol tablets in 1970. The Food and Drug Administration in November, 1971 issued a Drug Efficacy Implementation report affecting Diethylstilbestrol. In accordance with this report, Tablicaps submitted to the Food and Drug Administration a request for the approval of Diethylstilbestrol in the .5 mg., 1.0 mg., and 5.0 mg. tablet dosage forms.

At a later date, we submitted an application for the 25 mg.

- 3 -

dosage form of Diethylstilbestrol for routine estrogen indications. The Food and Drug Administration notified us that:

"This application would not be reviewed until the appropriate Federal Register for this therapeutic indication, requiring higher dosages than those normally recommended, is published."

*move
to 25 mg*

In September, 1973, the Food and Drug Administration published in the Federal Register the proposed patient labelling for the use of Diethylstilbestrol 25 mg. as a postcoital contraceptive. It was stated herein, that drug applications would be entertained under the conditions proposed.

In January, 1974, Tablicaps submitted an application for the postcoital use of Diethylstilbestrol 25 mg. which we call "DESMA".

The "DESMA" application was submitted by Tablicaps because we considered the restricted market for this emergency medical therapy to be the right size for us. Whereas, a market void might develop due to the limited and restricted potential. Another consideration was the rape victim who is entitled to the opportunity of receiving approved medication. Lastly, "DESMA" complements the Diethylstilbestrol family of products for the corporation.

Tablicaps believes that "DESMA" has a place in medical therapy because it is the first product approved by the Food and Drug Administration as a postcoital contraceptive. Its use is important in cases such as rape and in those emergency

- 4 -

situations determined by a patient and her physician, and is not to be used as a routine or premeditated contraceptive.

As to what constitutes appropriate or inappropriate use of this product, Tablicaps emphasizes that "DESMA" is not to be considered for a routine method of birth control, nor for family planning, nor for premeditated contraceptive use, but for emergency treatment only.

Tablicaps recognizes the potential for the misuse of "DESMA" and we believe it will best be minimized by providing the physician with adequate information, and properly educating the patient. This is accomplished by the Physician and Patient package insert which is phrased in frank and specific language.

To further minimize the potential for misuse, Tablicaps suggests two measures in addition to the Food and Drug requirements, the first of which we have already implemented:

1. Tablicaps states as an introduction to the Patient Package information, the following in bold print:

"DEAR PATIENT: IT IS IMPORTANT THAT YOU READ THE FOLLOWING INFORMATION SO THAT YOU WILL UNDERSTAND THE NATURE OF THIS PRODUCT."

2. In addition, since the potential misuse is dependent upon the availability of the product to the patient, Tablicaps also recommends adding to the labelling requirement, the following:

"THIS PRESCRIPTION IS NOT RENEWABLE."

- 5 -

We fully realize our responsibility in making "DESMA" available to the Medical Community, and we will exert our best effort to assure its restricted use.

Tablicaps, Inc.

Dear Mr. Buyer:

DESMA, a postcoital contraceptive, which is the only one of its kind, is now being made available by TABLICAPS, INC. Since the recommended dosage is to be started within 72 hours after unprotected sexual exposure, we ask that you consider this fact when planning your inventory needs.

DESMA is the first and only approved postcoital contraceptive to date. The need for such a product has been clearly established by studies, which have appeared in the J.A.M.A., and New England Journal of Medicine, studies which indicate that the market for a postcoital contraceptive will be sizeable.

DESMAtm will be heavily promoted and personal contacts by detailmen will be made to physicians, Planned Parenthood, and hospital clinics. It will be advertised in the ObGyn Journal, ObGyn News, and J.A.M.A.

"DESMA"tm

Desma Pac (10's)	3.10
Carton of 6 Desma Pac (10's)	18.60

We feel that our discount policy of 20% off list price plus 2% additional if paid within 30 days allows for a fair mark-up and margin of profit, without sacrificing the high level of service. We, at TABLICAPS, INC., feel that this is the beginning of a long and happy relationship.

Sincerely yours,

TABLICAPS, INC.

Sil D'Eramo
Sales Manager

SD/dcp.

FOR FURTHER INFORMATION, PLEASE SEE PACKAGE INSERT ATTACHED.

For Quality Generic Pharmaceuticals

DESMA

THE GENERAL MARKET

Desma is a postcoital contraceptive that may be used by every woman of childbearing age. As outlined by the Food and Drug Administration, Desma is for emergency use (in situations such as rape, incest, or where, in the physician's judgment, the patient's physical or mental well-being is in jeopardy) and should not be used as a routine method of contraception. Until now all that could be offered a female who did not want to be pregnant was an abortion - not very consoling for a woman in such a predicament.

The number of rapes is increasing. More are being reported due to more humane treatment in the hospital emergency room. In 1972, 150,000 rape cases were reported and the F.B.I. said that three (3) to ten (10) times that many were unreported.

The A.M.A. has established a protocol for treating rape in the hospital emergency room. One of the victim's prime concerns is being impregnated. They suggest the use of DES. Two (2) tablets, 25 mg. DES, taken for five (5) days within 72 hours after an unprotected sex exposure will prevent pregnancy.

The National Organization for Women has set up a National Rape Task Force. There are twenty-seven Rape Crisis Centers nationally. Their objective is to get a more dignified manner in which rape cases can be handled so that more cases will be reported.

Desma is Diethylstilbestrol 25 mg. and is in the top 500 drugs prescribed. There were 653,000 new prescriptions written in 1972. It was 18th of the top twenty(20) generic written. It would appear that these prescriptions were for therapeutic use. It was seventeenth in refill, which was 1.4% increase over the previous year. 1,370,000 new and refill prescriptions, a .3% gain at an average price of \$2.28/prescription were made. It is possible that Desma will be prescribed for this purpose since it will be the only 25 mg. in packages of ten available with F.D.A. approval.

ORAL CONTRACEPTIVES

There are 7,500,000 women using the "Pill". Fourteen percent (14%) of these users will switch to some other method in the next six months. One in five will change to the I.U.D.

Page 2

I.U.D.

2.25 million women are using the I.U.D. The use of the I.U.D. rose from 3% in 1969 to 8% in 1973. There is a 3% pregnancy rate the first year; 10% are expelled; and 12% are removed because of bleeding and cramps. 2.3% cause infection and 1% perforation on insertion. 35-50% of those using the I.U.D. discontinued after two years.

DESMAtm

PROJECTED SALES - 1st YEAR

1 month	139,716 Units
2 "	46,512 "
3 "	28,800 "
4 "	28,800 "
5 "	32,448 "
6 "	32,448 "
7 "	32,592 "
8 "	34,032 "
9 "	59,184 "
10 "	60,624 "
11 "	63,504 "
12 "	67,824 "
Total	<u>626,484 "</u>

stocking 450 wholesalers (service), 50,000 retail pharmacy and 8,000 chain pharmacies with approximately one sale/month/store.

20,000 Obygyns and 45,000 G.P.s will be the prime targets for our Desma promotion.

For Quality Generic Pharmaceuticals

Dear Doctor:

TABLICAPS INC. introduced "Desma," the postcoital tablet, which will provide security in spontaneity. Desma, when taken postcoitally within 72 hours after an unprotected coital exposure, (one tablet in the morning and one tablet in the afternoon for five consecutive days), will prevent pregnancy. Desma provides a most completely effective, safe contraception. This mode of fertility control has received considerable attention as the optimum contraceptive since it does not compromise the spontaneity of the sex act.

Postcoital contraception in humans and subhuman primates has been extensively studied in the laboratories of Morris and Van Wagenen. These researchers showed that diethylstilbestrol was highly effective in preventing pregnancy when given in high doses, for 5 days, within 72 hours after unprotected coitus. "... The medical profession must accept the fact that many people do not plan ahead and even if they do the method may fail. A study carried out in 1970 showed that 1/2 the patients in obstetric clinics were unmarried, and 1/3 were less than 20 years of age. ... Until the advent of postovulatory estrogens nothing could be offered the girl who came in after sexual exposure other than a douche or abortion." The previous quote appeared in the New England Medical Journal, February 3, 1972.

The J.A.M.A., October 1971 and May 1973, reported Dr. L.Kuchera's clinical evaluation. Dr. Kuchera's study was done at the University of Michigan Health Service and Veterans Administration Hospital. The dosage regimen was 1-25 mg. Diethylstilbestrol in the morning and another in the afternoon within 72 hours after an unprotected exposure for five consecutive days. Dr. Kuchera reported in two separate studies. In the first 1000 women there were no pregnancies. There were no serious side effects. Only

13.4% had nausea and vomiting on the first day, and 2.1% on the second day. 1.4% experienced headache. Of these, only one had a vascular headache and she was known to have a history of migraine. In the second group, 31 of the 1298 did not meet the criteria of the study. Six of the 81 were pregnant due to multiple exposure after the last menses, different number of days prescribed for treatment, or incompleteness of the course. All six chose to end their pregnancies by abortion after counseling. In 3/4 of the patients the time of exposure was in mid-cycle. No method of contraception was used by 89% and 11% used unreliable methods.

Desma does not interfere with Gonadotropin mechanism nor is it an abortifacient. Desma is available in a compact type package, Desma Pac, 10 tablets 25 mg. each of diethylstilbestrol. Desma Pac is clearly numbered one through five on a blister card making the dosage rather easy to follow. This is the only package of this type approved by the F.D.A.

Doctor, Desma is for your patient who needs a highly effective, safe, birth control method the morning after.

Sincerely yours,

TABLICAPS, INC.

Sil D'Eramo
Sales Manager

SD/sjc

BIBLIOGRAPHY

Lucile K. Kuchera, M.D. "Postcoital Contraceptive With Diethylstilbestrol," (J.A.M.A. October 25, 1971)

1. 1000 Patients
2. 2 - 25 Mg. Diethylstilbestrol
3. No pregnancies
4. 71% Mid Cycle
5. Side Effects
 - a. Nausea 1 day 13.7%
 - 3 days .2%

Lancet (refers to Haspel and Kuchera) August 12, 1972

1. 2000 Women
2. 14 Pregnancies .07% 3 low dosage 3 repeated exposure and 3 dosage started after 48 hours
3. Half bad nausea not serious enough to discontinue

John M. Morris

1. Pregnancy - none exists not deter by physician
2. Failure - sperm may have survived several days

Hatcher and Conrad

1. Adeno Carcinoma in offspring
2. Advocate Limited use.

209,213 AMA -- 6-22-27-74

American - Obstetric and Gyn 9-4-7 Hot Spring, Va.

893 American Ass. of PIPH Memphis 4-15-17

10,842 American College of Obgyn April 29, May 2 Las Vegas

21,000 Southern Med. Assn. Nov. 17-20 Atlanta

EDUCATION

...that of men, you only be pregnant.

[illegible][illegible]

Bureau who have to work and find limited resources.
 economic level conditions, or for a change in
 amount of educational requirements in the United
 States, but also the fact that the Bureau has
 had special budget problems in the past and
 mental depression, fatigue of the program, and
 the Bureau's financial situation, which is not
 disheartening or discouraging, but it is not
 difficult to be optimistic for the future.

STYLICA™

PHYSIOLOGICAL CONCENTRATION AS AN INDICATOR TREATMENT ONLY. THIS THERAPY IS NOT TO BE USED AS A ROUTINE METHOD FOR HEALTH CENTERS. SEPARATE COURSES OF THERAPY ARE TO BE

www.elsevier.com/locate/bsc

2. Patient with known or suspected estrogen dependence.
3. Patient with known or suspected estrogen dependence.
4. Undergoing surgical genital healing.

been reported from several locations during prevalence of *Staphylococcus* and the occurrence of various carriers in the offspring. The use of *Staphylococcus* or any of its closely related carriers is contraindicated in pregnancy.

THE UNIVERSITY OF CHICAGO

Your doctor has prescribed these tablets which are for emergency (first-aid) use only. Do not use them for anything other than emergency treatment. Do not use them to prevent pregnancy. To be effective the tablets must be started within three days of the start of your menstrual intercourse and preferably within one day. You must take the full course of tablets, one twice a day for five days, even if some nausea and vomiting occurs. These symptoms are common and indicate that the medicine is working.

(3) Foster, W.P. and Dell, J. Investigation of
Relationship between Use of Oral Contraceptives and
Neoplastic Disease. A Final Report. Brit.
Med. J. 2: 1613-15, 1966.

(4) Sartorius, P. K., and Smith, H. K., *Pharmacokinetics of Drugs and Oral Contraceptives: An Epidemiological Case-Control Study*, *Am. J. Hygiene*, 97:355-369, (1968).

(5) Draper, M.R., May, P., Posters, B.,
Bresland, A., Thrombotic disease and the steroidal
content of oral contraceptives. Brit. Med. J., 25th April,
1977.

(6) Harriot et al - *Observations* of the *Yagine* -
New England Journal of Medicine - Volume 284, Number 16
April 22, 1971).

Prior to use of Dextrochloral as a post-anesthetic, patients should be informed of this procedure as well as all other pertinent information. It is suggested that the physician should first choose to use this method, prevention of pre-anxiety should be considered in the event no method is available. A pre-anxiety test should be performed on all patients prior to use of Dextrochloral as a post-anesthetic. If the test is positive, Dextrochloral should not be used.

There are many factors which may affect the results of a study. The most important of these are the quality of the data, the methods used to collect the data, and the methods used to analyze the data. The quality of the data is affected by the reliability of the instruments used to collect the data, the validity of the instruments, and the accuracy of the data. The methods used to collect the data are affected by the design of the study, the selection of the sample, and the methods used to collect the data. The methods used to analyze the data are affected by the statistical methods used, the assumptions made, and the interpretation of the results.

cells are associated with a certain amount of liver disease. In addition, such as elevated blood pressure, liver dysfunction, and reduced tolerance to carbohydrates, they are not as yet ascertained.

long term administration of such natural and synthetic analogs in a variety of clinical studies in millions of subjects has shown that increases in the frequency for new animal experiments. These data suggest that the proposed directly to man. The possible carcinogenicity due to the animal studies has neither been confirmed nor refuted at this time. The clinical surveillance of all women taking the drug must be continued.

21) Royal College of General Practitioners; Oral
Contraception and Therapeutic Issues. Dr. Collins
Mrs. Pratt. 23.267-4000, 1997.

2) Trumbo, V.A.V. and Vessey, M.P. Investigation of Deaths from Primary Coronary and Cerebral Vascular and Embolism in Women in Child-Bearing Age. Brit. Med. J. 2:1071-100 1964.

FOUO
NOFORN

CONFIDENTIAL

SECRET

III. 10 (Zincphthalate) is a white crystalline powder, insoluble in water, with crystalline powder, granular or leafy lustrous mass. Zincphthalate is known as zincphthalate with a molecular weight of 263.15 and is very soluble in water. Zincphthalate is used as a photo-resistive in accordance with the method of preparation of zinc phthalate. Zincphthalate is a white crystalline powder, granular or leafy lustrous mass.

WILLIAMS & BROS.

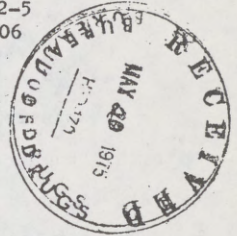
[illegible][illegible][illegible]

Tablicaps, Inc.
For Quality Generic Pharmaceuticals

Letter Ref: 5-75-T2-5
 CERTIFIED NO. 617506

May 14, 1975

Mr. W. Purvis
 Division of Drug Advertising
 H.F.D. - 170
 Food & Drug Administration
 6600 Fishers Lane
 Rockville, Maryland 20852



Dear Mr. Purvis:

This letter confirms our telephone call of Monday, May 12, 1975, wherein you instructed Tablicaps to initiate a "Dear Doctor" type letter to the few selected clients visited by Tablicaps representative during the week of January 27, 1975.

We submit to your request to keep this effort "low-keyed". However, we would also like to state some facts which should be part of any record which may be kept by your department.

1. Tablicaps submitted an application for approval to market a postcoital contraceptive in accordance with the Federal Register proposal request.
2. After many months of encouragement by many F.D.A. personnel and a concentrated effort by the F.D.A. to keep Tablicaps interested in the postcoital contraceptive we decided to investigate the real market potential to up-date our original projections.
3. A Tablicaps representative was sent to a few potential sales outlets during the week of January 27, 1975, with prepromotional type letters and very basic marketing data based upon the Federal Register proposal, Federal & Journal publications for this new postcoital emergency type field.
4. On February 5, 1975, after our representative made his visits, a Federal Register was published approving the postcoital contraceptive for emergency use. This register changed some of the original proposed guidelines.
5. We were invited to attend the Kennedy hearings on "DES" and at those hearings we put forth our corporate position that Tablicaps did not recommend Desma for pre-meditated contraceptive use or normal birth control application.

6. It was brought out prior to and in these hearings by other persons that low strength "DES" in combination form was being used for postcoital contraceptive, and, in fact, had been used for quite a long period of time, and, certainly before our January 27, 1975 calls, thus, in no way is Tablicaps responsible directly or indirectly for such a philosophy.

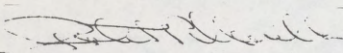
With this background we have initiated the following as requested:

1. A "Dear Doctor" type letter has been written as instructed.
2. A Tablicaps representative will revisit all parts covered during the week of January 27, 1975, to recover what data was left at such places, and, if such data is not available, to document our efforts to recover such material.
3. We shall hold such material recovered until instructions are received from the F.D.A.

We trust that this action on our part satisfies your instructions.

Very truly yours,

TABLICAPS, INC.



Robert L. Pillarella
President

RLP/kw

PAAUIJAZ RUEVFCZ0006 1351453-UUUU--RUEVEMR.
HWF

FM WILLIAM V. PURVIS HFD-170 DIVISION OF DRUG ADVERTISING
DHEW/FDA/ROCKVILLE, MARYLAND

GR: 380

TO RUEVEMR/1/NEWARK DISTRICT HFR--2350

ATTN: E. WILKENS, CHIEF INSPECTION BRANCH

BT

SUBJECT: SPECIAL INVESTIGATION - DESMA (DIETHYLSTILBESTROL)
25 MG. - REQUEST F/U YOUR 4/28/75 E/I

- 1) FOLLOWING YOUR 4/28/75 E/I TABLECAPS, THE FIRM WAS CONTACTED ON 5/13/75 BY THE DIVISION OF DRUG ADVERTISING CONCERNING THEIR DISTRIBUTION OF PROMOTIONAL LABELING FOR DESMA 25 MG.
- 2) MR. PILLARELLA WAS INFORMED THAT THE ADVERTISING MATERIAL DISTRIBUTED MISBRANDED THE THREE OTHER STRENGTHS OF DIETHYLSTILBESTROL (DES) THE FIRM MARKETED (5 MG., 1 MG., AND 0.1 MG.) AND EVEN IF THEIR ANDA WERE TO BE APPROVED THE ADVERTISING MATERIAL WOULD BE REGARDED AS MISBRANDING THE 25 MG. DESMA TABLETS (E.G., USE OF THE TERM "APPROVED"

PAGE TWO RUEVFCZ0006

-PROHIBITED BY SECTION 301(D); OMISSION OF OTHER VITAL AND CRITICAL LIMITING INFORMATION AS CONTAINED IN THE LABELING-USE ONLY IN EMERGENCIES, ETC.).

THEY WERE REQUESTED TO NOT DISTRIBUTE ANY REMAINING ADVERTISING AND DISPOSE OF ALL EXISTING MATERIAL CONTACT OR VISIT FIRMS (WHOLESALE DRUG DISTRIBUTORS, HOSPITALS, FAMILY PLANNING CLINICS, ETC.) THAT RECEIVED ANY OR ALL OF THE VIOLATIVE LETTERS AND REQUEST DISPOSAL OF THE MATERIAL. MR. PILLARELLA PROMISED COOPERATION.

3) IN THIS CONNECTION AND DUE TO THE SERIOUS POTENTIAL HAZARD INVOLVED PLEASE HAVE AN INSPECTOR VISIT THE FIRM DURING THE LATTER PART OF THE WEEK 5/9 - 23/75 AND DETERMINE IF THE FIRM HAS TAKEN THE REQUESTED ACTION (DESTRUCTION OF THEIR EXISTING STOCKS OF THE LETTERS AND CONTACTING CONSIGNERS THAT RECEIVED THE LETTERS). IF ACTION IS NOT BEING TAKEN BY THE FIRM ARRANGE FOR THE COLLECTION OF OFFICIAL SAMPLES (SEIZABLE SIZE LOT, IF POSSIBLE) OF ANY STRENGTH DES (5 MG., 1 MG., OR 0.1 MG.) DISTRIBUTED BY TABLICAPS INC. WITH COPIES OF THE PROMOTIONAL MATERIAL FOR REGULATORY CONSIDERATION, 3 X 100 TABLET BOTTLES WILL BE SUFFICIENT.

4) SUBMIT SAMPLE TO NEWARK- FLAG: EXHIBIT PURPOSES ONLY-NO ANALYSIS NECESSARY. REASON FOR COLLECTION: F/U, HFD-170 SPL

PAGE THREE RUEVFCZ0006

REQUEST CHECK ADVERTISING. FORWARD REPORT AND/OR COPIES OF COLLECTION REPORT(S) WITH ACCOMPANYING RECORDS TO DIVISION OF DRUG ADVERTISING, HFD-170 RM. 9B-31, 5600 FISHERS'S LANE, ROCKVILLE, MARYLAND 20852. ATTENTION: WILLIAM V. PURVIS. CHARGE TIME TO HIA-HFD-170-055. IF YOU HAVE ANY QUESTIONS OR ENCOUNTER ANY PROBLEMS CONTACT THIS OFFICE, A/C 301-443-3730.
BT

Tablicaps, Inc.
For Quality Generic Pharmaceuticals

Letter Ref: 5-75-T2-10
Certified No. 617507

May 16, 1975

Mr. Herbert M. Friedman:
Project Officer
Prescription Drug Compliance Branch
Division of Drugs
5600 Fishers Lane
Rockville, Maryland 20852

Dear Mr. Friedman:

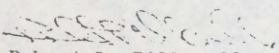
Pursuant to Mr. T.E. Byers letter dated May 14, 1975, (File No. HFD-313-187-5) regarding Diethylstilbestrol 25 Mg. or more per oral dosage unit/ and ml., we submit the following reply items for items requested:

1. We have made no shipments in the past 12 months. Our last shipment was made in September, 1973.
2. We have no inventory in our facilities except for that connected to our "DESMA" product pending approval of our NDA 83-915 and in a telephone check of two of the four customers shipped in 1973, there were about five (5) bottles of 1,000 tablets each remaining.
3. We discontinued marketing the above product in September, 1973.
4. We have no inventory to dispose of and the only inventory which we do have is packaged in accordance with the February 5, 1975 Federal Register which is held pending the approval of our NDA-83-915. The few bottles which remain in distribution under our control will be returned to our facilities for destruction.

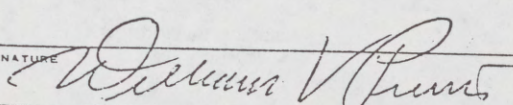
We trust this answers your inquiries, and, if you should have further need for additional information, please do not hesitate contacting us.

Very truly yours,

TABLICAPS, INC.


Robert L. Pillarella
President

RLP/lew

		PUT IT IN WRITING	5/23/75
FROM:	William V Purvis CSO HFD-170		OFFICE NDE
TO:	SEE BELOW		DIVISION Drug Advertising
SUBJECT:	DESMA (des) 25mg TABLICAPS, INC. RE: ADVERTISING PRACTICES		
SUMMARY			
Gene Schulz, Sup. CSO Newark Dist (Trenton Resident Post) telephoned me this AM to inform me of the results following a revisit to Tablicaps requested by Drug Advertising. The revisit was requested to insure that the form was, as promised by the president Mr Pillarella, actually carrying out their plans to remove the violative advertising piece distributed earlier this year for DESMA. According to the investigator, the firm as indicated in their May 14, 1975 letter to the Division was taking the action set forth in the letter : visiting each consignee that received the advertising and obtaining a signed statement that they were visited and the material was either picked up or destroyed. It appears that Tablicaps, Inc. is taking the necessary action to remove the questionable material from the market. Therefore, we are recommending that this action be considered resolved satisfactorily. Should other or additional information reach this division which is contrary to the conclusion of this case, we will obviously recommend/initiate regulatory action. ADDRESSEES: H. FRIEDMAN HFD-313 M. SEIFE HFD-69 F. KOHUN HFD-130			
SIGNATURE		DOCUMENT NUMBER	
			

ANDA 83-915
DES 25 mg.

MEMORANDUM OF TELECON

August 27, 1974

Between: Mr. R. Pillarella
Tablicaps

and

Marion J. Finkel, M.D.
Director, Office of
Scientific Evaluation/BD

Mr. Pillarella, President of Tablicaps, who had submitted an ANDA for DES for postcoital use phoned to ask me when the final F. R. publication would appear. In the preceding two months I had received a phone call from a Mr. DeFoney and one from a Mr. Jackson of Tablicaps asking me when the F. R. publication would be finalized. They had been referred to me by Dr. Seife, presumably. I had responded that we were working on it and it should be completed shortly.

My response to Mr. Pillarella was, again, that we expected publication soon because the material had been sent to the Commissioner's office for his approval. I suggested that he might inquire of Dr. Seife's office for a copy of the final patient labeling but that he should not print any labeling since it was possible that the Commissioner might want some revisions in the wording.

Mr. Pillarella thanked me for the information.

m.j.f.
Marion J. Finkel, M.D.

cc:
Orig. dup. ANDA 83-915
HFD-107
HFD-130
HFD-100
MJFinkel:eks 2/21/75

RECEIVED

FEB 24 1975

Assistant to the Director for
Regulatory Affairs
Bureau of Drugs

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 2/24/75
FROM: <i>N. Conrad</i>		OFFICE
TO: <i>Mr. Framer</i>		DIVISION
SUBJECT:		
SUMMARY Mr. Pellavella called repeatedly to the Office last September - October and I spoke to him once and asked him to put his excuse in a letter. No memo was made of that phone conversation since no regulatory matter was discussed. His letter of October 11, 1974, states the problem, and my letter of October 21, 1974, gives my reply. I had no other conversations with Mr. Pellavella I can recall, and my telephone log shows none none. He called here many times but always was referred to Mr. Seife or was given status reports of the FR statement by my secretary. <i>McCourt</i>		
SIGNATURE		DOCUMENT NUMBER

October 21, 1974

Mr. Robert L. Pillarella
President
Tablicaps, Inc.
P. O. Box 5555
Blackwood Road
Franklinville, New Jersey 98322

Dear Mr. Pillarella:

This is in response to your letter of October 11, 1974, concerning the status of our Federal Register statement and your ANDA for diethylstilbestrol as a postcoital contraceptive.

The final order of the Federal Register statement is currently in the late stages of drafting in my office. We anticipate that the drug will be approved for this indication, although the patient package insert will be modified somewhat from the original proposal of September 26, 1973. Our target date for signing the final order for publication in the Federal Register is three weeks from today, and the final order becomes effective 30 days after it is signed.

Before signing the final order, we will discuss it with Congressman Fountain and his staff if they so desire. As you know, Congressman Fountain's Subcommittee has a continuing interest in diethylstilbestrol, and we consider it prudent to keep him informed of all regulatory matters related to this drug. We do not anticipate at this time a delay in our schedule as a result of this proposed briefing. However, I cannot guarantee that a delay will not occur.

I understand that delays in issuing the final order of this Federal Register statement have placed your firm in an awkward position. I regret that this has occurred. As you know, this particular use of diethylstilbestrol has attracted enormous public attention and we have considered the complex

Issues regarding approval of this drug for this indication with particular care and attention to the public interest. This has simply taken more time than we originally anticipated.

I would be happy to give you an updated status report on the phone if you would call my office in about three weeks.

Sincerely yours,

J. Richard Crout, M.D.
Director
Bureau of Drugs

cc:

HFA-228 (w/incoming lettr.)

Dr. Finkel (HFD-100)

Dr. Seife (HFD-107)

to DH

Tablicaps, Inc.

For Quality Generic Pharmaceuticals

Letter Ref: 10-74-T2-18

October 11, 1974

Richard Crout, PH.D.
Director - Bureau of Drugs
Food and Drug Administration
3600 Fishers Lane
Rockville, Maryland 20852

RECEIVED

OCT 15 1974

OFFICE OF THE DIRECTOR
BUREAU OF DRUGS
FOOD AND DRUG ADMINISTRATION, DHEC

Dear Dr. Crout:

Thank you for the time you took Friday in speaking with me on the telephone, and I do appreciate your interest and concern regarding our postcoital contraceptive ANDA.

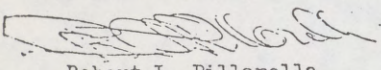
As I mentioned to you, because of the circumstances associated with the final approval on the FDA policy and subsequent approval of our New Drug Application, we at Tablicaps are faced with a credibility gap within our corporation and creditors. We also understand the complexity of having a drug approved, especially one of this nature, and the concern of many given types of people. However, we do believe that this product has a very important place in today's society for that specific purpose for which it is intended.

It would be appreciated if you would send me a letter which I could use to eliminate the credibility gap which we are faced with and, of course, indicating in some way if at all possible, an estimated approval date.

Again, we wish to thank you for the time you have spent on this problem and we anxiously await your reply so that we may fulfill our obligations and retain our operating concepts.

Yours very truly,

TABLICAPS, INC.


Robert L. Pillarella
President

dcp

NDA 83-915

A. F. 42-156 FILE

AUG 21 1973

Tablicaps, Incorporated
Attention: Mr. Richard T. Jackson
P.O. Box 5555
Blackwood Town Road
Franklinville, New Jersey 08322

Gentlemen:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NAME OF DRUG: Diethylstilbestrol Compressed Tablets, 25.0 mg.

DATE OF APPLICATION: August 6, 1973

DATE OF RECEIPT: August 8, 1973

We will correspond with you further after we have had the opportunity to review the application.

We would also like to call to your attention the Federal Register of March 15, 1973 (38 F.R. 7401) regulations establishing procedures for preparation of Environmental Impact Statements (Part 6 - Environmental Impact Considerations). Section 6.1(e) of these regulations requires that the applicant include an environmental impact analysis report as part of any new-drug application. Failure to submit an environmental impact analysis report is grounds for refusing to file or to approve an application (21 CFR 130.5(a)(8) or 130.12(a)(7)).

Please identify any communications concerning this application with the NDA number shown above.

Sincerely yours,

cc: PHI-DO

Dup

BD-69 BD-66 BD-106 BD-310

JLMeyer/2/13/73/skg/8/15/73

ACK

Harvin Seife, M.D.

Director

Generic Drug Staff

Office of Scientific Evaluation
Bureau of Drugs

ADA 83-915

AF None

Tablicaps, Inc.
 Attention: Mr. Richard T. Jackson
 P.O. Box 5555
 Franklinville, NJ 08322

Gentlemen:

Reference is made to your abbreviated new drug application dated August 6, 1973, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diethylstilbestrol Compressed Tablets, 25.0 mg.

This application will not be reviewed until the appropriate Federal Register statement for this therapeutic indication, requiring higher doses than those normally recommended, is published.

The material submitted is being retained as part of your application for this article.

cc:
 NWK-DO
 Dup
 BD-69
 BD-66
 BD-106
 SD-242

VVKarusaitis/JLMeyer/RJWalters/9-6-73
 R/D init. by MSeife/JMeyer/9-10-73
 Final typing/kim/ 9-10-73
 Ack.

Sincerely yours,

Marvin Seife 9/11/73
 Marvin Seife, M.D.
 Director
 Generic Drug Staff
 Office of Scientific Evaluation
 Bureau of Drugs

JMeyer 9/10/73

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

Form Approved
OMB No. 57-R0003

NEW DRUG APPLICATION (DRUGS FOR HUMAN USE)
(Title 21, Code of Federal Regulations, § 130.4)

Name of applicant TABLICAPS, INC.

Address P.O. BOX 5555 BLACKWOOD TOWN ROAD, FRANKLINVILLE, NEW JERSEY 08322

Date AUGUST 6, 1973

Name of new drug DIETHYLSTILBESTROL 25.0 MG. COMPRESSED TABLETS

- ☐ Original application (regulation § 130.4).
☐ Amendment to original, unapproved application (regulation § 130.7).
☒ Abbreviated application (regulation § 130.4(f)).
- ☐ Amendment to abbreviated, unapproved application (regulation § 130.7).
☐ Supplement to an approved application (regulation § 130.9).
☐ Amendment to supplement to an approved application.

The undersigned submits this application for a new drug pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. It is understood that when this application is approved, the labeling and advertising for the drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will contain the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant warnings, hazards, contraindications, side effects, and precautions, as that contained in the labeling which is part of this application in accord with § 1.106(b) (21 CFR 1.106(b)). It is understood that all representations in this application apply to the drug produced until an approved supplement to the application provides for a change or the change is made in conformance with other provisions of § 130.9 of the new-drug regulations.

Attached hereto, submitted in the form described in § 130.4(e) of the new-drug regulations, and constituting a part of this application are the following:

1. Table of contents. The table of contents should specify the volume number and the page number in which the complete and detailed item is located and the volume number and the page number in which the summary of that item is located (if any).

2. Summary. A summary demonstrating that the application is well-organized, adequately tabulated, statistically analyzed (where appropriate), and coherent and that it presents a sound basis for the approval requested. The summary should include the following information: (In lieu of the outline described below and the evaluation described in Item 3, an expanded summary and evaluation outlined in § 130.4(d) of the new-drug regulations may be submitted to facilitate the review of this application.)

- a. Chemistry.
- i. Chemical structural formula or description for any new drug substance.
- ii. Relationship to other chemically or pharmacologically related drugs.
- iii. Description of dosage form and quantitative composition.
- b. Scientific rationale and purpose the drug is to serve.
- c. Reference number of the investigational drug notice(s) under which this drug was investigated and of any notice, new-drug application, or master file of which any contents are being incorporated by reference to support this application.
- d. Preclinical studies. (Present all findings including all adverse experiences which may be interpreted as incidental or not drug-related. Refer to date and page number of the investigational drug notice(s) or the volume and page number of this application where complete data and reports appear.)
- e. Pharmacology (pharmacodynamics, endocrinology, metabolism, etc.).

ii. Toxicology and pathology: Acute toxicity studies; subacute and chronic toxicity studies; reproduction and teratology studies; miscellaneous studies.

e. Clinical studies. (All material should refer specifically to each clinical investigator and to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found.)

- i. Special studies not described elsewhere.
- ii. Dose-range studies.
- iii. Controlled clinical studies.
- iv. Other clinical studies (for example, uncontrolled or incompletely controlled studies).
- v. Clinical laboratory studies related to effectiveness.
- vi. Clinical laboratory studies related to safety.
- vii. Summary of literature and unpublished reports available to the applicant.

3. Evaluation of safety and effectiveness. a. Summarize separately the favorable and unfavorable evidence for each claim in the package labeling. Include references to the volume and page number in the application and in any documents incorporated by reference where the complete data and reports may be found.

b. Include tabulation of all side effects or adverse experience, by age, sex, and dosage formulation, whether or not considered to be significant, showing whether administration of the drug was stopped and showing the investigator's name with a reference to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found. Indicate those side effects or adverse experiences considered to be drug-related.

4. Copies of the label and all other labeling to be used for the drug (a total of 12 copies if in final printed form, 4 copies if in draft form):

a. Each label, or other labeling, should be clearly identified to show its position on the manner in which it accompanies the market package.

b. If the drug is to be offered over the counter, labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to the layman. If the drug is intended or offered for uses under the professional supervision of a practitioner licensed by law to administer it, the application should also contain labeling that includes adequate information for all such uses, including all the purposes for which the over-the-counter drug is to be advertised to, or represented for use by, physicians.

c. If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purposes for which it is intended, including all the purposes for which it is to be advertised or represented, in accord with §1.106(b) (21 CFR 1.106(b)). The application should include any labeling for the drug intended to be made available to the layman.

d. If no established name exists for a new-drug substance, the application shall propose a nonproprietary name for use as the established name for the substance.

e. Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug.

f. No application may be approved if the labeling is false or misleading in any particular. (When mailing pieces, any other labeling, or advertising copy are devised for promotion of the new drug, samples shall be submitted at the time of initial dissemination of such labeling and at the time of initial placement of any such advertising for a prescription drug (see §130.13 of the new-drug regulations). Approval of a supplemental new-drug application is required prior to use of any promotional claims not covered by the approved application.)

5. A statement as to whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

6. A full list of the articles used as components of the drug. This list should include all substances used in the synthesis, extraction, or other method of preparation of any new-drug substance, and in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

7. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed (for example, amount per tablet or per milliliter) and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

8. A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug. Included in this description should be full information with respect to any new-drug substance and to the new-drug dosage form, as follows, in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture, processing, and packing and the described facilities and controls to determine and preserve the identity, strength, quality, and purity of the drug:

a. A description of the physical facilities including building and equipment used in manufacturing, processing, packaging, labeling, storage, and control operations.

b. A description of the qualifications, including educational background and experience, of the technical and professional personnel who are responsible for assuring that the drug has the safety, identity, strength, quality, and purity it purports or is represented to possess, and a statement of their responsibilities.

c. The methods used in the synthesis, extraction, isolation, or purification of any new-drug substance. When the specifications and controls applied to such substance are inadequate in themselves to determine its identity, strength, quality, and purity, the methods should be described in sufficient detail, including quantities used, times, temperatures, pH, solvents, etc., to determine these characteristics. Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the substance may be specified.

d. Precautions to assure proper identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material.

e. Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

f. If the applicant does not himself perform all the manufacturing, processing, packaging, labeling, and control operations for any new-drug substance or the new-drug dosage form, his statement identifying each person who will perform any part of such operations and designating the part; and a signed statement from each such person fully describing, directly or by reference, the methods, facilities, and controls in his part of the operation.

g. Method of preparation of the master formula records and individual batch records and manner in which these records are used.

h. The instructions used in the manufacturing, processing, packaging, and labeling of each dosage form of the new drug, including any special precautions observed in the operations.

i. Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug package to assure their suitability for the intended use.

j. Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

k. Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and, if so, at what stage and by whom it is done.

l. Precautions to check the actual package yield produced from a batch of the drug with the theoretical yield. This should include a description of the accounting for such items as discards, breakage, etc., and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

m. Precautions to assure that each lot of the drug packaged with the proper label and labeling, including provisions for labeling storage and inventory control.

m. The analytical controls used during the various stages of the manufacturing, processing, packaging, and labeling of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components. If the article is one that is represented to be sterile, the same information with regard to the manufacturing, processing, packaging, and the collection of samples of the drug should be given for sterility controls. Include the standards used for acceptance of each lot of the finished drug.

o. An explanation of the exact significance of the batch control numbers used in the manufacturing, processing, packaging, and labeling of the drug, including the control numbers that appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

p. A complete description of, and data derived from, studies of the stability of the drug, including information showing the suitability of the analytical methods used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new-drug substance, for the finished dosage form of the drug in the container in which it is to be marketed, including any proposed multiple-dose container, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed. State the expiration date(s) that will be used on the label to preserve the identity, strength, quality, and purity of the drug until it is used. (If no expiration date is proposed, the applicant must justify its absence.)

q. Additional procedures employed which are designed to prevent contamination and otherwise assure proper control of the product.

(An application may be refused unless it includes adequate information showing that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity in conformity with good manufacturing practice and identifies each establishment, showing the location of the plant conducting these operations.)

9. Samples of the drug and articles used as components, as follows: a. The following samples shall be submitted with the application or as soon thereafter as they become available. Each sample shall consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the application to determine compliance with its control specifications for identity and assays:

i. A representative sample or samples of the finished dosage form(s) proposed in the application and employed in the clinical investigations and a representative sample or samples of each new-drug substance, as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

ii. A representative sample or samples of finished market packages of each dosage form of the drug prepared for initial marketing and, if any such sample is not from a commercial-scale production batch, such a sample from a representative commercial-scale production batch; and a representative sample or samples of each new-drug substance as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

iii. A sample or samples of any reference standard and any used in the procedures described in the application for assaying each new-drug substance and other assayed

components of the finished drug: *Provided, however, that samples of reference standards recognized in the official U.S. Pharmacopeia or the National Formulary need not be submitted unless requested.*

b. Additional samples shall be submitted on request.

c. Each of the samples submitted shall be appropriately packaged and labeled to preserve its characteristics, to identify the material and the quantity in each subdivision of the sample, and to identify each subdivision with the name of the applicant and the new-drug application to which it relates.

d. There shall be included a full list of the samples submitted pursuant to Item 9a; a statement of the additional samples that will be submitted as soon as available; and, with respect to each sample submitted, full information with respect to its identity, the origin of any new-drug substance contained therein (including in the case of new-drug substances, a statement whether it was produced on a laboratory, pilot-plant, or full-production scale) and detailed results of all laboratory tests made to determine the identity, strength, quality, and purity of the batch represented by the sample, including assays. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods used differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

e. The requirements of Item 9a may be waived in whole or in part on request of the applicant or otherwise when any such samples are not necessary.

f. If samples of the drug are sent under separate cover, they should be addressed to the attention of the Bureau of Medicine and identified on the outside of the shipping carton with the name of the applicant and the name of the drug as shown on the application.

10. Full reports of preclinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate preclinical tests by all methods reasonably applicable to a determination of the safety and effectiveness of the drug under the conditions of use suggested in the proposed labeling.

b. Detailed reports of the preclinical investigations, including all studies made on laboratory animals, the methods used, and the results obtained, should be clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short- or long-term administration or whether it is to be used in infants, children, pregnant women, or women of child-bearing potential.

c. Detailed reports of any pertinent microbiological and *in vitro* studies.

d. Summarize and provide a list of literature references (if available) to all other preclinical information known to the applicant, whether published or unpublished, that is pertinent to an evaluation of the safety or effectiveness of the drug.

11. List of investigators. a. A complete list of all investigators supplied with the drug including the name and post office address of each investigator and, following each name, the volume and page references to the investigator's report(s) in this application and in any documents incorporated by reference, or the explanation of the omission of any reports.

b. The unexplained omission of any reports of investigations made with the new drug by the applicant, or

submitted to him by an investigator, or the unexplained omission of any pertinent results of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, whether or not it would bias an evaluation of the safety of the drug or its effectiveness in use, may constitute grounds for the refusal or withdrawal of the approval of an application.

12. Full reports of clinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the labeling.

b. An application may be refused unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

c. Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, full information concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintains adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. An application for a combination drug may be refused unless there is substantial evidence that each ingredient designated as active makes a contribution to the total effect claimed for the drug combination. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

d. Attach a separate section a completed Form FD-1639, Drug Experience Report (obtainable, with instructions, on request from the Department of HEW, Food and Drug Administration, Bureau of Drugs (BD-200) Rockville, Maryland 20852), for each adverse experience or, if feasible, for each subject or patient experiencing one or more adverse effects, described in Item 12c, whether or not full information is available. Form FD-1639 should be prepared by the applicant if the adverse experience was not reported in such form by the investigator. The Drug Experience Report should be cross-referenced to any narrative description included in Item 12c. In lieu of a FD Form 1639, a computer-generated report may be submitted if equivalent in all elements of information with the identical enumerated sequence of events and methods of completion; all formats proposed for such use will require initial review and approval by the Food and Drug Administration.

e. All information pertinent to an evaluation of the safety and effectiveness of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commercial marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application and related drugs. An adequate summary may be acceptable in lieu of a reprint of a published report which only supports other data submitted. Reprints are not required of reports in designated journals, listed in §130.38 of the new-drug regulations, about related drugs; a bibliography will suffice. Include any evaluation of the safety or effectiveness of the drug that has been made by the applicant's medical department, expert committee, or consultants.

f. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of pre-existing information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

g. The complete composition and/or method of manufacture of the new drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in Item 6, 7, or 8 of the application.

13. If this is a supplemental application, full information on each proposed change concerning any statement made in the approved application.

Observe the provisions of §130.9 of the new-drug regulations concerning supplemental applications.

TABLICAPS, INC.

(Applicant)

Per

(Responsible official or agent)

President

(Indicate authority)

(Warning: A willfully false statement is a criminal offense. U.S.C. Title 18, sec. 1001.)

NOTE: This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the applicant must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States.

[Excerpt from Health Subcommittee Hearing, July 20, 1972]

REGULATION OF DIETHYLSTILBESTROL (DES), 1972

THURSDAY, JULY 20, 1972

U.S. SENATE,
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON LABOR AND PUBLIC WELFARE,
Washington, D.C.

The subcommittee met, pursuant to notice, at 9:40 a.m., in room 4232, New Senate Office Building, Senator Edward M. Kennedy (chairman of the subcommittee), presiding.

Present: Senators Kennedy and Javits.

Committee staff present: LeRoy G. Goldman, professional staff member; Dr. Larry Horowitz, professional staff member; and Jay B. Cutler, minority counsel.

Senator KENNEDY. The subcommittee will come to order.

Diethylstilbestrol—DES—is a synthetic estrogen which is widely used in beef cattle and sheep to stimulate more rapid weight gain with less feed.

DES is also, however, a well-recognized carcinogen and has been directly linked to the appearance of vaginal cancer in young women whose mothers had taken large doses of DES during their pregnancy. At significantly lower doses, DES causes cancer in mice.

These two sets of facts present a classic policy dilemma—under what conditions can an economically useful agent, which has some potential to do grave harm to human beings, in this case by causing cancer, be used in the food industry?

The Congress has considered this dilemma in the past, and with administration concurrence, has resolved it very clearly.

The Delaney clause of the Food, Drug, and Cosmetic Act forbids the appearance of any residues of known cancer-causing agents in the food people eat.

That fact is not in dispute. The law does not require that cattle, for example, not be fed cancer-causing agents. But it does require that all such agents be completely eliminated from those cattle by the time they are slaughtered and sent to market.

The intent of Congress here is clear—whether by banning such substances or by assuring their disappearance before slaughter, cancer-causing agents must not be found in the meat that appears on America's dinner tables.

We are here today because DES, a known cancer-causing agent, is appearing on thousands of American dinner tables. It appears four times more frequently today than it did 6 months ago. The latest figures released by the Department of Agriculture this past Tuesday show that 2.27 percent of all cattle tested contained DES residues after slaughter. Considering that we slaughter in excess of 30 million

cattle each year, that means that more than 660,000 head of cattle probably reach American dinner tables, in various forms, with a known cancer-causing agent in them.

The Food and Drug Administration is the regulatory body which is responsible for controlling DES. Six months ago, when the reported incidence of DES was 0.5 percent, FDA took the position that the residues could be eliminated by tightening administrative procedures. They did just that, extending the period for withdrawal of cattle from DES to 7 days from the previous 2-day period. At that time, FDA Commissioner Charles C. Edwards stated:

The FDA will not permit DES residues in the food supply. Should the new control procedures prove unsuccessful in application—we are prepared to ban its use entirely from animal feeds.

There was considerable controversy 6 months ago about whether the new control procedures could be successful. Dr. Roy Hertz, senior physician at the Rockefeller University, formerly of the National Cancer Institute, said:

I think that administratively, this would be totally impractical. I think the hazards of additional exposure would be increased by such a practice rather than reduced, and I believe that on the face of it, knowing regulatory practices, particularly on a national scale, notwithstanding the possibility of criminal action against violations, that the impracticability of protecting the public from exposure to these materials in foodstuffs is very, very great and really a foolhardy undertaking. What has been proposed by * * * FDA is unfeasible and impractical and ill-advised.

It now seems that the control procedures are unenforceable. In 6 months, the incidence of DES has risen from 0.5 to 2.27 percent. And yet, DES is, at the present moment, still not banned and still is part of many Americans' daily diet.

FDA has called for public hearings to "gather all the facts" in this matter. To do that, it has explained that the only mechanism available is to propose a formal action to withdraw approval of the drug which would automatically, in their words, "* * * bring about an opportunity for an official hearing." Such hearings have in the past, however, been far from automatic—on March 31, 1971, 15½ months ago, FDA published a similar hearing notice for Nihydrzone and there has still been no hearing.

The facts in this case are clear. So clear that 21 countries, including the two leading cattle producers, Argentina and Australia, have banned DES; and Sweden and Italy have banned the importation of U.S. meat from cattle fed with DES.

The law is also clear. What is not clear is why the FDA has not followed the friendly advice of Dr. Frank L. Rauscher, the Director of the National Cancer Institute, who has said he would ban the use of DES in cattle feed now, and then, if warranted, conduct hearings.

My distinguished colleague, Senator William Proxmire of Wisconsin, is the principal sponsor of S. 2818, which would bar DES from use in animal feed. At this point we will enter a copy of the bill, S. 2818.

(A copy of S. 2818 follows:)

92^d CONGRESS
1st SESSION

S. 2818

IN THE SENATE OF THE UNITED STATES

NOVEMBER 8, 1971

Mr. PROXMIRE (for himself, Mr. BAYH, Mr. CASE, Mr. MCGOVERN, Mr. MOSS, and Mr. RIBICOFF) introduced the following bill; which was read twice and referred to the Committee on Labor and Public Welfare

A BILL

To amend the Federal Food, Drug, and Cosmetic Act to prohibit the administration of the drug diethylstilbestrol (DES) to any animal intended for use as food, and for other purposes.

1 *Be it enacted by the Senate and House of Representa-*
2 *tives of the United States of America in Congress assembled,*

3 That section 301 of the Federal Food, Drug, and Cosmetic
4 Act (21 U.S.C. 331) is amended by adding at the end
5 thereof a new subsection as follows:

6 “(q) The administering of the drug diethylstilbestrol
7 (commonly known as DES) to any animal intended for
8 use as food or to any animal the product of which is intended
9 for use as food.”

1 SEC. 2. Section 409 (a) of the Federal Food, Drug, and
 2 Cosmetic Act (21 U.S.C. 348 (a)) is amended by inserting
 3 “(1)” immediately after “SEC. 409. (a)” ; by redesignating
 4 clauses (1) and (2) as clauses (A) and (B), respectively;
 5 and by adding at the end of such section a new paragraph
 6 (2) as follows:
 7 “(2) A food shall be deemed to be unsafe for the pur-
 8 poses of the application of clause (2) (C) of section 402 (a)
 9 if it contains the drug diethylstilbestrol (commonly known
 10 as DES).”

Senator KENNEDY. This morning's hearing will consider the implications of S. 2818 and the entire DES question.

Senator Javits.

Senator JAVITS. Thank you, Mr. Chairman.

First I would like to state my support of the chairman in calling these hearings and my gratification for his having agreed to have as the opening witness FDA Commissioner Edwards who will express his views, which I understand are to be that DES is safe if used as directed and, as to the question of “imminent hazard” and whether the evidence is adequate to support that legal requirement.

For myself, I believe, with my colleagues, that if DES residues cannot be eliminated—and that seems to be the evidence of the Department of Agriculture—then we have to prohibit the introduction of DES into the food supply, unless we are shown some very good reason why not;

I am very gratified, Mr. Chairman, that we are having these hearings, and we will get right down to business on the practicalities of the situation.

Mr. Chairman, I would like at this moment to express my appreciation for the appearance here of a top scientific witness, Dr. Peter Greenwald, director of the Cancer Control Bureau of the New York State Department of Health.

His tremendous background, training, and experience concerning this issue, and his investigations relating to the possible cause-and-effect relationship between DES administered to pregnant women and cancer of the vagina, to which the chairman referred, occurring years later in their daughters.

This will be discussed with us, and I am sure will have a great bearing on how we handle this matter in the future.

I want to mention also my appreciation for the appearance of Dr. Rauscher of the National Cancer Institute, who has shown a remarkable sensitivity to the need to deal with this issue in a most decisive way.

(The prepared statement of Senator Javits follows:)

PREPARED STATEMENT OF HON. JACOB K. JAVITS, A U.S. SENATOR
FROM THE STATE OF NEW YORK

Mr. Chairman, it is a matter of great scientific importance and serious social implication as to whether we should ban the use of diethylstilbestrol—commonly known as DES—a synthetic drug. While DES promotes rapid weight gain in beef cattle with its cost savings and better quality meat for the consumer, it has been determined to be a carcinogen capable of causing cancer in experimental animals and is also reportedly linked to human cancer.

Dr. Frank J. Rauscher, Jr., the Director of the National Cancer Institute, which has as its mission the conquest of cancer, recently indicated that the prudent course is to prohibit DES in livestock feed pending the outcome of the FDA public hearings on the matter.

Dr. Rauscher has publicly defined his mission as Director of the National Cancer Institute as being "to protect the people from cancer." I believe our commitment as legislators is to help him fulfill that goal. If legislatively reasonably possible, we should eliminate from the environment anything that increases man's carcinogenic burden.

Apparently the FDA voluntary regulatory control program—withdrawal of DES from livestock feed for greater periods prior to slaughter, for example, from 48 hours to 7 days—has not been successful; the DES detection rate has increased. I understand FDA Commissioner Edwards views DES safe if used as directed and at this point does not believe there is sufficient evidence to declare it an "imminent hazard" which would enable the Secretary to ban the use of DES pending the outcome of the FDA hearings. However, I believe that if DES residues cannot be eliminated—and that appears likely according to the evidence found by recent Agriculture Department samplings of beef and lamb livers—then we would have to prohibit the introduction of DES into the food supply.

In closing, Mr. Chairman, I am pleased to welcome as a witness Dr. Peter Greenwald, director of the Cancer Control Bureau of the New York State Department of Health. Dr. Greenwald has an outstanding background of training and experience concerning this issue and has investigated the possible cause-and-effect relationship between DES administered to pregnant women and cancer of the vagina occurring years later in their daughters.

Senator KENNEDY. I want to welcome this morning as our first witness Senator Proxmire, who is perhaps best known for his very effective work as Chairman of the Joint Economic Committee.

He introduced this legislation a number of months ago. I believe it was on November 8 of 1971, so he was very much aware of this problem and concerned about it a long time ago, before it was really brought forth for a full airing.

**STATEMENT OF HON. WILLIAM PROXMIRE, A U.S. SENATOR FROM
THE STATE OF WISCONSIN, ACCOMPANIED BY TOM VAN DER
VOORT AND DAVID EPSTEIN**

Senator PROXMIRE. Thank you, Mr. Chairman.

I have with me Tom van der Voort and David Epstein of my staff.

Let me first thank you very much for you and your Subcommittee on Health convening these hearings; and I see that you and Senator Javits have both anticipated part of what I intend to say this morning, and I appreciate that very much.

Congress must devote serious attention to a cancer-causing drug which has shown up in the food supply of the American people with alarming frequency in recent months.

My reading of the record indicates that Congress has, on numerous occasions in the past, devoted its serious attention to this very issue, and has already resolved it through the Delaney amendment.

According to that provision, no residue-producing carcinogens may be added to American food supplies. But for whatever reasons, the FDA has not seen fit to apply the Delaney amendment to DES.

Accordingly, I have proposed specific legislation on that subject.

To my knowledge, no one expresses the slightest doubt that DES is carcinogenic. An expert from the National Cancer Institute told Congressman Fountain's Intergovernmental Relations Subcommittee that DES is "one of the chapters in a textbook" on cancer.

Laboratory experiments have proven it to be carcinogenic to animals. And a 1970 study established a clear link between use of DES by pregnant women and vaginal cancer in their daughters.

Yet, DES is currently being added to livestock feed to increase the growth rates of cattle and sheep.

To the best of my knowledge, more than half of our beef is being fed DES.

Residues of DES have been detected in beef and lamb tissue samples tested by the Department of Agriculture since 1965. As of last December, residues were being found in about one-half of 1 percent of samples tested.

At that time, the Food and Drug Administration claimed that these residues were attributable only to violations of the procedural guidelines set down for use of DES.

Therefore, the agency made their guidelines mandatory, lengthened the period for withdrawal of livestock from DES-medicated feed from 2 to 7 days, and promised stricter enforcement.

At that time, the FDA was confident that this would solve the problem of the persistent one-half of 1 percent residue rate. But FDA Commissioner Edwards repeatedly assured Congressman Fountain's House Subcommittee about FDA's intentions if the new controls failed.

On page 203 of the hearing record, he said:

Should the new control procedures prove unsuccessful in application, or should new evidence on DES be developed, we are prepared to ban its use entirely from animal feeds.

And on page 251:

The fact of the matter is, if we find that our new program is not working, there is just one recourse for us and that is to ban its use totally.

The new procedures went into effect January 1. What has happened since that time?

From the beginning of January to the middle of April, the residues continued at about one-half of 1 percent. But between April 15 and the most recent report on July 8, the residues showed up at a startling average rate of 3.60 percent. That is over seven times higher than the old figure.

If that rate continued for a year, it would mean over 1,200,000 cattle would be slaughtered in this country with residues of DES. This rate, I remind you, is with the new FDA procedures in effect. I do not believe anyone would deny that these controls are, to use the Commissioner's phrase, "unsuccessful in application."

As it happens, April 15 was the date that the USDA began reporting results of more sensitive tests which detect DES levels below two parts per million. So part of the increase is attributable to improved detection—but only part of the increase.

To be precise, 2.06 percent of the samples showed residues under two parts per million; and the other 1.54 percent showed residues over two parts per million.

This means two things: first, the lower level residues were presumably present before April. So there were in the past more residues than we had known about.

Second, the residues above two parts per million have themselves tripled; which means that regardless of measuring techniques, the absolute number of DES residues seems to have increased markedly. Neither of those conclusions is at all comforting.

With a 7-year history of residues, why hasn't the FDA banned DES under the Delaney clause?

The answer they gave last winter was to insist that there is in theory no reason for there to be residues. The FDA said its experiments persuaded it that DES, used in accordance with the regulations, leaves no residue. Therefore, even though there was no evidence of procedural violations in a number of the cases the FDA reported to the House subcommittee, they argued that if there were residues, there must have been procedural violations.

If the problem is indeed one of enforcement, it is no less a problem. I understand that at the present time, the FDA has filed one court case and has two more in process. There have been 54 residues reported since January. This subcommittee should find out what has happened in each of those cases.

If FDA thinks the regulations can be enforced, why are not violators prosecuted?

But frankly, I will not be satisfied if FDA manages to bring a few more cases to trial. The purpose of controlling DES is to protect American consumers; and even a more vigorous prosecution program will not achieve this. The primary grounds for prosecution rests on finding DES residues.

The USDA inspection program for DES tests about one out of every 10,000 cattle slaughtered each year. That is apparently enough to give us an idea of how widespread DES residues are.

But that also means that the chance of an individual violation being detected and prosecuted is extremely small.

Many violations are apparently unintentional, resulting from cross-contamination of feed supplies, human error, or animals uncooperatively eating feed intended for other animals. Even under laboratory conditions, according to the testimony of Dr. Roy Hertz, it is difficult to prevent accidental contamination with an agent as potent as DES.

Unintentional violations, in all but the tiniest fraction of cases, will not even be called to the farmer's attention. And there is certainly no particular incentive to scrupulously follow the regulations. The point is that such a plan of controls is simply unworkable. It will continue to detect the presence of residues in our food, but it will do almost nothing to stop the residues.

It is not enough for the FDA to assert that their procedure should prevent all residues. It cannot comfort Americans to know that their meat is uncontaminated in theory, while it, in fact, may contain carcinogenic residues.

Whether the FDA regulations are inadequate, or whether they are adequate but violated—in either case, the result is residues of a carcinogen in livestock destined for American dinner tables. In either case, it is unacceptable. In either case, the solution is a ban on the use of DES.

Some who have opposed a ban on DES have managed to be quite equivocal in their assessment of its dangers. The FDA throughout last winter's hearings insisted that it agreed with the Delaney clause that no amount of carcinogenic residue in meat is tolerable.

But again and again they explained that, well, if there just happened to be a little bit that slipped through, it wouldn't be so intolerable. But experts agree that there is no level that can be called safe for a carcinogen—nor do we know how to go about establishing such a level.

For this reason, Congress has again and again resolved that no carcinogen may be added to our food supply. According to FDA internal staff memoranda, even our most advanced techniques do not have anything near the sensitivity required to detect significant levels of residue. In fact, in one memorandum, two top FDA scientists recommended that consideration be given to "withdrawing DES from use in medicated feed until such time that an analytical method sensitive to one part per trillion is developed."

The two largest beef producing nations outside the United States—Argentina and Australia—have already banned the use of DES—and you can imagine the economic price that this constitutes with respect to those nations that depend far more on beef than we do as far as their balance of trade is concerned—as have the Common Market nations.

I recently received a letter from a spokesman from Canada's National Farmer's Union, indicating that organization's advocacy of a ban in Canada.

I am fully aware of estimates claiming that a ban on DES would cost the American consumer an additional \$3.85 a year. That is not a trivial amount, but it is not extravagant, either.

The total national cost is less than the Federal Government will spend for the National Cancer Institute this year. It is a drop in the bucket of our gross national product.

This assessment of cost, I believe, also reflects a limitation of imagination. There should be an intensive effort to explore alternative

means of cutting the costs of producing wholesome—and I emphasize the word “wholesome”—meat. Getting our meat cheaply but with the potential of causing cancer is a bad bargain. By banning DES, we would provide the consumer with a bargain his dollars cannot now buy—the assurance that the beef and lamb he eats is uncontaminated by an artificial carcinogen.

Mr. Chairman, in great part owing to your leadership, our Nation has resolved to combat cancer. Surely controlling the hazards of carcinogens in our food supply is a necessary part of that effort.

For 7 years, we have permitted residues of DES to reach the American consumer. We will not know the full impact on the health of our people for many years, if we will know then. But with the evidence about DES we already have, a ban on the use of this drug in livestock feeds is simply a matter of prudence.

Mr. Chairman, I addressed a beef producers' meeting in Wisconsin on this subject a few months ago. You can imagine that there was a natural concern about this and an opposition to banning DES on the part of the beef producers.

At that meeting, the Lilly Co., which is the largest present producer of DES, was represented; as was the Department of Agriculture of the State of Wisconsin, and the U.S. Department of Agriculture.

What I found was that the beef producers find themselves in a competitive situation. As long as DES is permitted, they are almost compelled to use it because they are in competition. If an individual beef raiser should not use it, his losses are considerable under these circumstances.

If it is banned, however, there is not any question that within a short time their collective situation will be adjusted to the market, and their losses would not be significant; and I found that they understood that.

I talked to a number of them privately about this, and they told me if DES were found to be cancer producing, they certainly wanted it banned.

Senator KENNEDY. Thank you very much, Senator Proxmire.

Your last comment is certainly very interesting. Your feeling then is that if the meat producers themselves were convinced that inclusion of DES in the feed would significantly threaten the health and well being of the American people, they would not want a part of it?

Senator PROXMIRE. Yes, indeed; but, as I say, they are in a position where they have to continue feeding DES because of the competitive situation.

Senator KENNEDY. Yes; but if it were banned and no one could use it, at least they could recognize the value of that step if they were convinced that it did pose a threat.

In the FDA release of June 16, they point out a beef animal will reach a market weight of about 1,000 pounds 35 days sooner using 500 pounds less feed than a comparable animal not fed DES.

That is in their Department press release. That seems to be to be an economic issue, not an FDA issue.

Senator PROXMIRE. That is true; but you also have a situation where this is not an economic problem for the country as a whole because we have a surplus of feed. In fact, we have a situation where we have to store it, take it off the market, in order to hold up the price.

Senator KENNEDY. I thought FDA was going to be looking at the health issues rather than the economic. It seems to me the Department of Agriculture would be making that argument rather than the Food and Drug Administration, which is charged with protecting the health and well-being of the people.

Tell me, what is your reaction to the Delaney amendment? Do you think that is strong enough? Do you agree with me that with the passage of the Delaney amendment by the Congress, the Congress thought it was doing the job that we want to be done in this circumstance; or do you think that it is full of loopholes?

Senator PROXMIRE. In this case, it seems to be a very clear loophole. It is obvious to me this is not being administered in the spirit in which Congress intended it, at least not in the spirit which this Senator intended.

There is not any question that DES is a carcinogen; there is not any question the purpose of the Delaney amendment was to prohibit or prevent meat or food containing carcinogens from being sold to the public, and they are being sold to the public.

Senator KENNEDY. I want to thank you again for your appearance here. You are a real leader in the Congress on this issue.

I think particularly that because you come from a meat-producing State, you have shown a considerable amount of courage on this issue, as well as on many others.

Senator PROXMIRE. May I add, Mr. Chairman, there are, I think, three issues which might arise on the part of those who oppose this amendment, and I would like to leave the answers to some of the questions with you.

One claim is that DES residues are only apparent in livers. Since what we eat is mostly muscle tissue, why worry? Why not just ban the livers?

I have some very interesting information indicating that DES residues are present in other parts of the animal.

Senator KENNEDY. Certainly if it is in the blood stream it would naturally contaminate the other parts of the animal.

Senator PROXMIRE. Yes, indeed; and we found when we got this more sensitive test it is at a somewhat lower level, one-quarter to one-ninth of the concentration that is found in the liver, but is found in the kidneys, the musculature.

A second claim is that DES produces more healthful meat because it reduces the amount of fat.

The answer there, I think, is a convincing answer, but as far as health is concerned, DES makes no contribution that is significant.

The third claim is that estrogenic hormones are naturally present in the human body as well as in many plants and animals which humans eat, and the answer is that natural hormones are vastly different from DES in level and potency.

I have this documented, and I would appreciate it if this information could be included in the record.

Senator KENNEDY. It will be included in the record.

(The information referred to follows:)

LIVERS--FEED SURPLUS

Claim: DES residues are only apparent in livers. Since ~~we~~ what we eat is mostly muscle tissue, why worry? Why not just ban the livers?

First, liver is a useful nutritious food. Why ban it?

Second, in the two cases where DES residues were found in parts of the carcass other than the liver (the musculature and the kidney) it was at levels $1/4$ and $1/9$ the concentration in the liver. Thus if we assume, conservatively, that DES occurs in the musculature at $1/10$ th the levels in the liver it would show up in the musculature at a level of $1/5$ th part per billion when it was present in the liver at 2 parts per billion. This one-fifth level is too low to be detectable but too high to be acceptable according to FDA's own scientists who urge withdrawal of DES until it can be detected at one part per x trillion.

FATS

Claim: The use of DES produces more healthful meat because it reduces the amount of fat.

Reply:

A study in the Journal of Animal Science, November 1960, reported that DES-fed cattle actually had more fat at age 6 months than cattle not fed DES.

A USDA study in 1955 (number 2444-55 (42)) concluded that while the non-DES cattle were slightly fatter than the DES-fed cattle, there was no difference between the two groups in either marbling or intra-muscular fat. This is important, since external, removable fat is not eaten. The only fat with any relation to the healthfulness of the meat is that which is found within the meat itself. And the USDA study found no difference in the amount of internalized fat between DES and non-DES cattle.

HORMONES PRESENT IN THE HUMAN BODY

Claim: Estrogenic hormones are naturally present in the human body, as well as in many plants and animals which humans eat.

Reply: Those natural hormones are vastly different from DES in level and potency.

- (1) ALL plant hormones are significantly lower in activity than DES. One of the most potent, coumestrol, found in alfalfa and clover, has 1/10,000th the activity of DES.

- (2) The estrogen naturally present in animals and humans is estradiol. Since it is natural in man, it is rapidly metabolized and excreted. But DES is a synthetic estrogen having ten times the potency of estradiol and is much more slowly metabolized and excreted.

- (3) Recent studies* have quantified the estradiol level in meat.
In the serum, total estrogens range from
0.5 to 10 parts per trillion
rising just before the onset of estrus to
20 to 30 parts per trillion.
Even that highest figure is 1/17 the lowest level of
DES that has been detected. And bear in mind that
DES is 10 times as potent.

- (4) The estradiol level in post-menopausal women is about
15 parts per trillion
Assuming one of these women ate 4 ounces of liver
containing 1 part per billion DES, this could be the
equivalent of almost tripling the physiological level of
estradiol on a body weight basis, or assuming these
estrogens exist only in the blood, of raising the level
to 22 times normal.

In short, introduction of DES is clearly on quite a different scale than naturally-present hormones. Indeed, it would be quite surprising if the results were otherwise, since DES dramatically stimulates livestock growth, it surely should be expected to have other dramatic effects.

*Hendricks, et.al., Endocrinology, Vol. 89, No. 6, December 1971
and Dr. Hafs, Michigan State University, unpublished data.

EXPLANATION OF STATISTICS

RESIDUES

"From the beginning of January to the middle of April, the residues continued at about one half of one percent."

January 1 - April 15 1046 samples, 5 residues = .48%

"But between April 15 and the most recent report of July 8, the residues showed up at a startling average rate of 3.60 percent."

April 15 - July 8 1360 samples, 49 residues = 3.60%

NOTE: Latest data thru July 15: 1504 samples, 53 residues = 3.52%
This data leaves the ~~residues~~ succeeding statements unchanged.

"If that rate continued for a year, it would mean over 1,200,000 cattle would be slaughtered in this country with residues of DES."

35,354,000 cattle slaughtered in 1970 (USDA statistics)	
<u>3.60 %</u>	
1,272,744 (or using 3.52, 1,244,461)	
<u>both exceed 1,200,000.</u>	

"2.06% of the samples showed residues under 2 parts per billion; and the other 1.54% showed residues over 2 parts per billion."

April 15 - July 8	1360 samples	
	28 under 2ppb	= 2.06%
	<u>21 over 2ppb</u>	<u>= 1.54%</u>
	49 total	= 3.60%

ARE THE STATISTICS SIGNIFICANT?

Yes. The weekly report figures are subject to fluctuation due to bunching of results. But a USDA spokesman agreed that analysis of trends over several months is possible. Our figures from April to July include 12 weeks of results, and more than 1300 samples, easily enough to be significant.

FDA MEMORANDUM. From Leo Friedman, Ph.D., Director, Division of Toxicology, To: Dr. Virgil O. Wodicka, Director, Bureau of Foods, February 8, 1972

Dr. V. O. Wodicka

page 2.

The dose of DES, 0.1 mg twice weekly, represents about 2 µg/kg at the time of administration and on a weekly basis averages about 0.5 to 0.6 µg/kg/day. Considered in terms of dietary intake, this is approximately 20 ppb of the total daily diet.

1) PLANT HORMONES

Comments have been made that we are continually exposed to naturally occurring exogenous and endogenous hormones in greater amounts than we would encounter from DES. The plant hormones which may be concerned are either man or animal very widely in estrogenic effect but all are significantly lower in activity than DES. One of the most potent plant hormones, coumestrol, found in clover and alfalfa, has only 1/10,000th of the activity of DES. Genistein and genistin, estrogenic compounds derived from clover and soybeans, have about 1/300,000th the potency of DES.

2) ESTRADIOL IN MEAT

The principal source of estradiol and its metabolites in our foods would be from meat. Data currently available (Hendricks et al., Endocrinology, Vol. 89, No. 6, December 1971), using a radio-immunoassay has, for the first time, really quantified this source. His data indicate that in the bovine female, total estrogens present in serum range from 0.5 to 10 parts per trillion in the diestrus state, and rises to between 20-30 parts per trillion about 24 to 48 hours prior to the onset of estrus, then falls rapidly (during the 6-8 hour period) following the onset of estrus. We have no reason to believe muscle levels would be above these amounts and would more likely be somewhat less than the serum levels. It is interesting to note that a 250 lb heifer needs only an increase of approximately 300 nanograms within the whole volume of her circulating blood to go into heat. A kilogram of liver with 1 ppb would contain 1000 nanograms. (Dr. Rafe, of Michigan State University, unpublished data, has checked the serum level of estradiol in steers and finds it in the same range as has been published by Hendricks for the diestrus female).

3) DES PERSISTS IN MAN LONGER THAN ESTRADIOL.

Estradiol is a natural hormone in man, and the metabolic pathways are already established so that in the event any is absorbed, it will be rapidly metabolized and excreted. DES, on the other hand, is a synthetic estrogen having ten times the potency of estradiol and is much more slowly metabolized and excreted, thus exerting its effect on target organs for a much longer period of time. Dr. Umberger has estimated the half-life of DES to be 12 hours, while Hendricks' (Clemson University) work would indicate the half-life of estradiol is much less, probably somewhere between 6 and 8 hours.

4) NATURAL LEVEL OF ESTRADIOL IN HUMANS

The level of circulating estradiol in serum of post-menopausal women is about 15 parts per trillion (Korenman et al, Journal of Clinical Endocrinology, 29:879, 1969). Assuming one of these women ate 4 oz. of liver containing 1 ppb DES, she would consume about 0.125 mg of

0.0025 mcg/kg body weight, which is equivalent to 2.5 parts per trillion. Since DES has ten times the activity of estradiol, this could be the equivalent of adding 25 ppt estradiol to that already normally present, almost tripling the physiological level on a whole body weight basis. If we assume that the DES and estradiol exist only in the circulation blood, the increase would be 22 times normal.

If violations of the 7-day withdrawal period should occur, the probability that muscle as well as kidney and liver, will be above what we now would consider an "acceptable" level, would be real. Furthermore, one must consider that such exposures would not be limited to an occasional piece of liver or that they would be equivalent to the natural exposure from the occasional slaughter of a pregnant cow, because:

1. Many people buy meat in quantity and store it in lockers or home freezers.
2. Liver is still considered a hematonic and, in some cases, consumed daily.
3. If violations of the withdrawal period do occur, it would not be limited to a random animal, but would more likely involve all the cattle marketed at that time by that producer.
4. Until sufficient time has elapsed to clear the animal's metabolic pool of DES, we are dealing with a population of hyperestrogenized animals that cannot be considered normal in this regard. We should like to have better evidence than we have now to conclude that 7 days are sufficient time to reduce the DES to the low physiological levels of estrogenic activity normally found.

The study by Mitchell et al in Agriculture and Food Chemistry, Vol. 7, No. 7, July 1959, is practically the only evidence to support the 7-day withdrawal period. By our current standards, this study is weak scientific justification for the conclusion:

1. Only one animal was used in this study.
2. Only a single dose of tritium labeled DES was given. The animal had not been equilibrated by feeding unlabeled drug.
3. Only 51% of the administered drug was recovered in urine and feces (29.3% in feces and 21.8% in urine), while 49% of the administered drug was not accounted for. Yet when untreated fecal material was spiked with radioactive material, from 73% to 83% could be recovered.

Senator KENNEDY Thank you very much, Senator Proxmire.

I want to welcome now Dr. Charles Edwards, the Commissioner of the Food and Drug Administration.

Dr. Edwards, I think you are aware of the order of scheduling witnesses. We had you a little later in the morning in order to hear from some of the scientific witnesses first.

I recognize full well the procedures controlling the hearing of administration witnesses first. I always feel it is sometimes better to have some of the information laid out before we get the final position.

I followed that procedure with the Refugee Committee business.

We did not intend any disrespect either for you or for the position you hold, and we welcome you here. We hope you will be able to remain so that in the course of the morning if there are some questions, which I am sure there will be, we will be able to have an opportunity to gather your comments on those questions.

We welcome you now; and I want the record to be quite clear on why we had arranged the order we had.

STATEMENT OF CHARLES C. EDWARDS, M.D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION; ACCOMPANIED BY DR. HENRY SIMMONS, DIRECTOR, BUREAU OF DRUGS, PETER HUTT, ASSISTANT GENERAL COUNSEL, FOOD, DRUGS, AND ENVIRONMENTAL HEALTH DIVISION, DR. C. D. VAN HOUWELING AND GERALD F. MEYER, DIRECTOR, OFFICE OF LEGISLATIVE SERVICES, FOOD AND DRUG ADMINISTRATION

Dr. EDWARDS. Thank you, Senator.

I do appreciate this opportunity of appearing after Senator Proxmire, because I think it is important that we get the "real" FDA position on the table in the course of your deliberations this morning.

Senator KENNEDY. Good.

Dr. EDWARDS. At any rate, we do appreciate this opportunity to appear before you to discuss the Department of Health, Education, and Welfare's position on S. 2818, which would prohibit the administration of diethylstilbestrol (DES) to food-producing animals and provides that food containing DES shall be "adulterated" under the Federal Food, Drug, and Cosmetic Act.

Diethylstilbestrol is a synthetic drug with estrogenic activity which was first approved for use in animal feed in 1954. It effectively causes cattle and sheep to grow more rapidly and with less feed consumption. For example, a beef animal will reach a market weight of about 1,000 pounds, 35 days sooner using 500 pounds less feed than a comparable animal not fed DES. Additionally, this increase in body weight is reflected in additional protein and less fat in edible tissues.

DES has been shown to induce tumors in certain species of laboratory animals when included in their diets for extended periods of time. Some reports have recently been developed which show an apparent association of vaginal cancer in girls whose mothers were treated with large doses of DES over a period of weeks or months to prevent a threatened abortion.

I would first like to address myself to those specific aspects of the use of DES, which are the responsibility of and subject to the legal actions of FDA.

As I am sure you know, Mr. Chairman, the 1958 Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act included the so-called Delaney clause, which prohibits the use in the food supply of any food additive found to produce cancer in man or animals.

The 1962 Drug Amendments, however, exempted from the Delaney clause those drugs or chemicals added to animal feed, which are shown to be safe for the animal, and which leave no residue in edible tissue at the time of slaughter if used in accordance with label directions that are "reasonably certain to be followed in practice."

It should be pointed out that Congress enacted this exemption from the Delaney clause explicitly to permit the use of DES in cattle and sheep. DES was the major subject of the congressional debate. At the time, Congress knew that DES was a carcinogen and that misuse could result in illegal residues.

The data submitted in support of a regulation providing for the use of from five to a maximum of 20 milligrams of DES per day for beef cattle establish that no DES residues were detectable in edible animal tissues when the medicated feed is withdrawn 48 hours prior to slaughter. This determination was made using the officially approved assay method which is sensitive to at least two parts per billion. The regulations authorizing the use of DES, therefore, required that it be withdrawn at least 48 hours prior to slaughter.

It should be noted that, under the Delaney clause, as amended, the finding of residues of DES in the livers of some animals does not, in itself, require disapproval of the drug. Illegal residues should result in enforcement action and punishment of the offender if misuse of the drug is proven, rather than withdrawal of approval of the new animal drug application. Such withdrawal is indicated only if it is determined that the label directions are not—and I quote from the law—"reasonably certain to be followed in practice."

As I am sure you know, because of reports of misuse of DES resulting in illegal residues, more than 6 months ago, the U.S. Department of Agriculture and the Food and Drug Administration instituted new controls over the use of DES in animal feed to further assure that DES residues would not be found in the livers of animals fed DES. No new restrictions were instituted for DES administered by implant because no violations were or have been found when used in that way. Livers are the only edible tissue in which DES has been detected after misuse of medicated animal feed. This is so even though the USDA examines flesh tissues whenever a positive liver sample is found.

These controls were instituted after USDA's monitoring program disclosed DES residues in approximately one-half of 1 percent animal liver samples collected in 1971. At that time, we extended the withdrawal period for DES to 7 days before slaughter. The additional withdrawal period was believed to be more practical and offered an additional margin of safety. USDA, at the same time, established a mandatory certification program, requiring livestock producers to provide written certification that they complied with the 7-day withdrawal period.

Despite these precautionary steps, USDA has continued to detect residues of DES in the livers of animals offered for slaughter. During the first 6 months of 1972, DES residues have been found in 58 livers or 2.3 percent of samples analyzed. These tests show that the drug is not always being used as required by the regulations.

Mr. Chairman, there has been substantial publicity and confusion concerning FDA's position with respect to DES. When we instituted our new controls earlier this year, I stated unequivocally that if the new and increased restrictions failed to reduce the incidence of violative residues of DES, FDA would withdraw approval for the use of DES in animal feeds. On finding the incidence of violations increasing, late last month we commenced appropriate proceedings to withdraw the approval for the use of DES.

Senator KENNEDY. Does that mean you have banned it or not banned it?

Dr. EDWARDS. I will explain that as I move along, Mr. Chairman. We have proposed withdrawing approval of the new animal drug applications which in essence will be to ban the use of the drug in animal feeds.

Senator KENNEDY. Can they feed the animals today or can they not?

Dr. EDWARDS. They can feed DES to animals today.

Senator KENNEDY. How long will they continue under the procedures to be able to feed animals DES?

Dr. EDWARDS. We proposed withdrawing approval for DES. Under the procedures, there is a 30-day period for comments, and this period expires as of Friday of this week.

After evaluating the comments that are received by the manufacturers, we have to make a determination of whether or not to ban or whether there is sufficient evidence that has been adequately explored to call for a hearing on it.

Senator KENNEDY. The Secretary could declare it an imminent hazard, could he not, and stop it today?

Dr. EDWARDS. That is correct. If we found and so advised the Secretary that DES was an imminent hazard, it could be banned immediately.

Senator KENNEDY. And halt it right away?

Dr. EDWARDS. That is correct.

Senator KENNEDY. And you are not prepared to make that recommendation to the Secretary?

Dr. EDWARDS. We are not, nor is the National Cancer Institute, nor any of the authorities we have consulted, willing to categorize this as an imminent hazard.

Senator KENNEDY. In spite of all the information and the research and the studies that have been made to indicate there is an increase in DES residues in the liver of cattle generally? You are still not prepared to make such a recommendation to the Secretary that it is an imminent hazard?

Dr. EDWARDS. That is right, Mr. Chairman, because we have absolutely no evidence that the use of DES in animal feed has caused harm to human health.

Senator KENNEDY. Your hearing procedures have taken up to 15 months, have they not, before a final decision was made, and they have been taking that long in the past in some instances?

Dr. EDWARDS. There have been some prolonged hearings. But I assure you, if the hearing route is the way we go, it will not take 15 months. We anticipate the hearings lasting somewhere between 2 and 3 months.

Senator KENNEDY. When you say in your testimony, "We commenced appropriate proceedings to withdraw the approval for the use of DES," you really have not taken the final step, have you, Mr. Commissioner, the final step being the urging of the Secretary to ban it? You are unwilling to take that final step?

Dr. EDWARDS. We have not taken that step under the route we are going. We have to allow time for comment.

Senator KENNEDY. If you made the recommendation that he ban it, he could ban it within the law.

Dr. EDWARDS. If we declared it an imminent hazard; that is correct.

Senator KENNEDY. But you are either not sufficiently concerned or the evidence presented to you is not sufficiently convincing to the point you think you ought to take that important step. This is just so I understand your position.

Dr. EDWARDS. I would not want to suggest for one moment we are not concerned, but we feel there are many, many hundreds of other chemicals in which we have equal concern.

Senator KENNEDY. How often have they done that in the past? How often has the Food and Drug Administration recommended to the Secretary that he ban a drug?

Dr. EDWARDS. As an imminent hazard, you mean?

Senator KENNEDY. Yes.

Dr. EDWARDS. I am not sure. Maybe Mr. Hutt can answer that.

Mr. HUTT. Senator, we would have to provide that information for the record. Neither of us has been here long enough to go back in history.

The Food and Drug Administration cannot identify any occasion in which the Secretary of the Department of Health, Education, and Welfare immediately banned a drug under the "imminent hazard" to health provisions of the Federal Food, Drug, and Cosmetic Act.

Senator KENNEDY. You must have made a study of this. This ought to be one of the alternatives that you were considering in your recommendations to the Commissioner.

Mr. HUTT. We certainly did consider it.

Senator KENNEDY. What were the factors that you considered?

Mr. HUTT. The question of whether something is an imminent hazard is a scientific determination involving the danger to human health. It is specifically laid out in the statute.

We consulted the scientists, as the Commissioner mentioned. We talked to the National Cancer Institute. No one thus far has been able to come up with a rationale for saying DES is an imminent hazard to health.

Senator KENNEDY. As I understand from reading the newspaper reports, the head of the Cancer Institute said it would be prudent to ban it now.

Mr. HUTT. Senator, we have talked to Dr. Rauscher about that. He obviously will speak for himself on that. He has informed us that at the time he made that statement, he obviously had no information about the legal requirement for a finding of imminent hazard.

Senator KENNEDY. Wait a minute. The legal? What about the health? Are we getting bottled up on legalities, or are we talking about the health issue to the American people?

Mr. HUTT. There is a requirement in the law that there be a determination by health authorities that there is an imminent hazard to health. As a health authority, the Commissioner has no evidence on which to base such a determination; therefore, as a matter of law, we cannot order a ban pending a hearing.

Senator KENNEDY. You mean as a health issue, you would like to ban it, but somehow the legalities of the statute under which you are operating do not give you the power to do so? Is that what we are presenting to the American people?

The head of the Cancer Institute will speak for himself, and you feel he would recommend that it be banned; but you cannot find the legal justification to do so?

Mr. HUTT. Senator, no; that is incorrect. If there were no statutory requirements for finding an imminent hazard to health—if in short one could just arbitrarily say that DES is a chemical we would just as soon not have in the food supply—I think anybody would say let us take it out.

However, the statute which Congress enacted specifically precludes us from doing that unless there is a finding of imminent hazard to health, and neither he nor the others with whom we have consulted have been willing to go that far.

Senator KENNEDY. I did not understand his statement to be, "We would just as soon not have it." I thought he said in his statement if it were up to him as a health issue—as a health issue—as the person who is in charge of the National Cancer Institute, he would ban it.

As I understand from your point of view, he was unaware of the legal acrobatics that had to be gone through; therefore, as a health issue, he would like to ban DES but because of the legalisms, either you do not feel you have the power to do so or the legal justification therefore, it is not being done; we are following this other procedure.

Mr. HUTT. Senator, just to recap, he has advised us in his judgment there is no imminent hazard to health.

Now, he must speak for himself, and he will apparently testify shortly.

Senator KENNEDY. But he still recommended that it be banned as a health matter, did he not?

Dr. EDWARDS. I think Dr. Rauscher should speak to this.

Senator KENNEDY. We will get back to that.

All right; do you want to continue?

Under the Federal Food, Drug, and Cosmetic Act, there are two possible courses for withdrawing DES from use in food animals. If an "imminent hazard" to health can be demonstrated, the Secretary of the Department of Health, Education, and Welfare, can issue an immediate ex parte ban on the shipment of DES in interstate commerce. It should be noted that in this case, an opportunity for an expedited hearing must be provided to the affected parties.

A decision that DES is an "imminent hazard" would require immediate removal from the market of all meat from animals fed DES and all feed containing DES.

An "imminent hazard" under the Federal Food, Drug and Cosmetic Act is defined as being a condition so hazardous that the article involved cannot continue on the market during the pendency of administrative proceedings. There is no evidence of harm to humans from the use of DES as a growth promotant in food animals, and conse-

quently, we cannot substantiate a finding that it constitutes an "imminent hazard" to health.

Senator KENNEDY. How much of a hazard is it—not "imminent"—legally?

Dr. EDWARDS. At this point in time, Mr. Chairman, I think all we can say is that it represents a potential hazard.

Senator KENNEDY. If you had a piece of steak in front of you right now, would you let your wife eat it if it had 0.5 percent residues of DES?

Dr. EDWARDS. Absolutely.

Dr. SIMMONS. Mr. Chairman, I think it is important to point out that the hazard we are talking about here is small compared to other hazards which are around us all the time.

Dr. EDWARDS. Mr. Chairman, speaking of the steak, I think the potential hazard in eating a charcoal broiled steak is much greater than the hazard posed by these DES residues, which are minimal, to say the least.

Dr. SIMMONS. There also is evidence, Mr. Chairman, if your wife were going to eat steak, it would probably be better to eat steak with DES in it since DES produces a meat with less fat.

A meat with less fat, when broiled, may produce less of a substance which is a potent carcinogen.

Senator KENNEDY. We will hear from some others on that.

Dr. EDWARDS. Mr. Chairman, I might say at this point that this is an extremely complex issue.

Senator KENNEDY. Everything is complex.

Dr. EDWARDS. That is right.

Senator KENNEDY. If we just leave it to the experts, we will be all right.

Dr. EDWARDS. I think the experts likewise have a responsibility to look at all aspects of all the problems. Unfortunately, I do not think this has always happened.

Continuing, however, thus the only alternative available is to follow the formal procedures of the act to withdraw approval of applicable new animal drug applications—NADA's. This has been done.

As required by law, FDA published a notice of opportunity for a hearing on DES in the Federal Register on June 21, 1972. This notice initiated the procedure to withdraw approval for use of DES in food-producing animals. I would like to insert that proposal at this point in the record.

Senator KENNEDY. It will be included.

(The information referred to follows:)

[From the Federal Register, vol. 37, No. 120—Wednesday, June 21, 1972]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

FOOD AND DRUG ADMINISTRATION

[Docket No. FDC-D-494; NADAs 9525, etc.]

ELANCO PRODUCTS CO. ET AL.

Diethylstilbestrol; Notice of Opportunity for Hearing on Proposal To Withdraw Approval of New Animal Drug Applications

Substantial public interest has been raised about the continued approval of diethylstilbestrol for use as a growth-promotant for cattle and sheep. A Subcommittee of the Committee on Government Operations of the House of Represent-

atives held extensive hearings on this matter during 1971. The Natural Resources Defense Council has filed a lawsuit to compel the Food and Drug Administration to withdraw approval of diethylstilbestrol. In December 1971 the Food and Drug Administration and the U.S. Department of Agriculture instituted a joint program to extend the withdrawal period for diethylstilbestrol containing feeds from 2 days to 7 days and to require written certification of withdrawal (36 F.R. 23292, 24928). At the same time, a new and more sensitive method of detecting diethylstilbestrol was put into widespread use. Using this more sensitive method, the number of reported illegal residues of diethylstilbestrol in animal livers has increased rather than decreased.

In light of this increase in reported diethylstilbestrol residues the Commissioner of Food and Drugs is considering whether it is appropriate to withdraw approval of diethylstilbestrol, to institute new more effective restrictions to reduce illegal residues, or to take other action. The Commissioner has concluded that, prior to making a final decision as to the appropriate course of action to be taken, additional information is needed from all segments of the public, including consumer organizations, the animal husbandry industry, the pharmaceutical industry, the academic community, members of Congress, and other governmental agencies and departments.

The Commissioner has concluded that the most appropriate forum for public consideration of this matter is a public hearing, to develop on the public record the information necessary for a conclusion as to the proper handling of this matter. Under section 512 of the Federal Food, Drug, and Cosmetic Act, an opportunity for a hearing on a proposal to withdraw approval of a new animal drug application is provided to the holder of the application. The Commissioner has discretion in permitting other interested individuals and organizations to participate in any subsequent hearing. Accordingly, the Commissioner has concluded that it would be appropriate to propose withdrawal of the approval of the new animal drug applications for diethylstilbestrol in order to utilize the hearing mechanism provided in the statute for this purpose.

The Commissioner has not yet concluded that withdrawal of approval for diethylstilbestrol is the appropriate course of action. Requests for a public hearing may be accompanied by proposals for additional and more effective restrictions on diethylstilbestrol that would obviate such withdrawal of approval. Alternative restrictions that could be considered include prohibition of use for human food of livers from animals receiving diethylstilbestrol, or requiring such livers to be tested prior to marketing, or requirements limiting the persons who may use the drug.

In the event that a hearing is held, the Commissioner will wish to obtain data and information from all interested persons with respect to such relevant matters as the current rate of illegal residues and ways in which this might be reduced, the potential effect upon the public health and safety of a low rate of illegal diethylstilbestrol residues, the likely effect on the environment of withdrawing approval of diethylstilbestrol, the availability of alternative growth-promotant drugs and their safety and effectiveness as compared with diethylstilbestrol, the need for growth-promotant drugs in the animal husbandry industry, differences or similarities between administration of diethylstilbestrol by feed or by implant with respect to the potential for residues, the accuracy and reliability of present detection methods for diethylstilbestrol, the potential availability of more sensitive detection methods for diethylstilbestrol and the likely result of their use, and any other relevant information.

Accordingly, notice is hereby given to the following listed holders of new animal drug applications that the Commissioner of Food and Drugs proposes to issue an order under section 512(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360(e)) withdrawing approval of the following listed new animal drug applications which provide for use of diethylstilbestrol as a growth promotant for cattle and sheep:

Elanco Products Co., Post Office Box 750, Indianapolis, IN 46206. NAD Nos. 9525, 11090, 42162.

Pfizer, Inc., New York, N.Y. 10017. NADA Nos. 9757, 9783, 11356, 9770.

Walnut Grove Products, Division of W. R. Grace Co., Atlantic, Iowa 50022. NADA No. 10132.

Dawes Laboratories, Chicago, Ill. 60632. NADA Nos. 10421, 11485, 34916.

Simonsen Manufacturing Co., Quimby, Iowa 51049. NAD No. 10566.

Vineland Laboratories, Inc., Subsidiary of Damon, Vineland, N.J. 08360. NADA No. 10964.

Hess & Clark, Division of Rhodia, Inc., Ashland, Ohio 44805. NADA Nos. 11295, 12553, 44344, 45982, 45981.
 Peter Hand Foundation, Inc., Waukegan, Ill. 60085. NADA No. 14773.
 O. M. Franklin Serum Co., Denver, Colo. 80216. NADA No. 15274.
 Fort Dodge Laboratories, Fort Dodge, Iowa 50501. NADA No. 31446.
 Thompson-Hayward Chemical Co., Kansas City, Kans. 66106. NADA Nos. 35019, 35017.
 Feed Additives, Inc., Fremont, Nebr. 68025. NADA Nos. 36313, 37869.
 Dale Alley Co., St. Joseph, Mo., 64501. NADA Nos. 36671, 36554.
 Standard Chemical Manufacturing Co., Omaha, Nebr. 68103. NADA Nos. 36976, 34735.
 National Oats Co., East St. Louis, Ill. 62205. NADA Nos. 37148, 37541.
 Texas Nutrition & Service Co., Fort Worth, Tex. 76108. NADA Nos. 38507, 38510, 39509.
 Bresley-Koelling, Inc., Ord, Nebr. 68862. NADA No. 39491.
 Feed Products, Inc., Denver, Colo. 80211. NADA Nos. 39716, 39718, 39717, 39715.
 Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, N.J. 07065. NADA Nos. 39772, 42840, 10261.
 Chemetron Corp., Chicago, Ill. 60611. NADA No. 42355.
 Farmland Industries, Kansas City, Mo. 64116. NADA No. 42702.
 Western Farmers Association, Seattle, Wash. 98111. NADA No. 44526.
 E. R. Squibb & Sons, New Brunswick, N.J. 08902. NADA No. 11365.
 Western Feed Supplements, Ellensburg, Wash. 98926. NADA No. 40014.
 Ultra Life Laboratories, Inc., East St. Louis, Ill. 62201. NADA No. 38682.
 Square Deal Fortification Co., Kouts, Ind. 46347. NADA No. 39161.
 Falstaff Brewing Corp., St. Louis, Mo. 63166. NADA No. 44795.
 Feed Products, Inc., Denver, Colo. 80211. NADA No. 39715.
 American Cyanamid Co., Princeton, N.J. 08540. NADA No. 10259.
 S. B. Penick Co., New York, N.Y. 10008. NADA No. 36479.

The Commissioner, based on an evaluation of new information before him with respect to such drugs together with the evidence available to him when the applications were approved, concludes that there is a question as to whether the drugs are shown to be safe under the conditions of use upon the basis of which the applications were approved.

Information available to the Commissioner establishes that use of such drugs has resulted in illegal residues of diethylstilbestrol in animal livers.

In accordance with the provisions of section 512 of the act (21 U.S.C. 360b), the Commissioner hereby gives the applicants an opportunity for a hearing at which time such persons may produce evidence and arguments to show why approval of the above listed new animal drug applications should not be withdrawn. Promulgation of the proposed order would cause any such drug containing diethylstilbestrol to be a new animal drug for which no approved new animal drug application is in effect. Any such drug or any animal feed bearing or containing such drug then on the market would be subject to regulatory proceedings.

Within 30 days after publication hereof in the Federal Register, such persons are required to file with the Hearing Clerk, Department of Health, Education, and Welfare, Office of the General Counsel, Food, Drug, and Product Safety Division, Room 6-88, 5600 Fishers Lane, Rockville, Md. 20852, a written appearance electing whether:

1. To avail themselves of the opportunity for a hearing; or
2. Not to avail themselves of the opportunity for a hearing.

If such persons elect not to avail themselves of the opportunity for a hearing, the Commissioner, without further notice, will enter a final order withdrawing approval of said applications.

Failure of such persons to file a written appearance of election within 30 days will be construed as an election by such persons not to avail themselves of the opportunity for a hearing.

The hearing contemplated by this notice will be open to the public except that any portion of the hearing concerning a method or process that the Commissioner finds is entitled to protection as a trade secret will not be open to the public, unless the respondent specifies otherwise in his appearance. Interested persons who are not parties may intervene to present evidence and file pleadings, and may cross-examine witnesses when in the judgment of the hearing examiner their interests are not adequately protected otherwise or it is required for a full and true disclosure of the facts.

If such persons elect to avail themselves of the opportunity for a hearing, they must file a written appearance requesting the hearing and giving the reasons why the approval of the new animal drug applications should not be withdrawn together with a well-organized and full-factual analysis of the data they are prepared to prove in support of their opposition to the Commissioner's proposal. A request for a hearing may not rest upon mere allegations or denials but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. When it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact which precludes the withdrawal of approval of the applications, the Commissioner will enter an order stating his findings and conclusions on such data. If a hearing is requested and is justified by the response to this notice, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence.

Responses to this notice may be seen in the Office of the Hearing Clerk (address given above) during regular business hours, Monday through Friday.

Pending consideration of responses to this notice, no action will be taken on the notice of opportunity for hearing pertaining to diethylstilbestrol liquid premixes, published in the *FEDERAL REGISTER* for March 11, 1972 (37 F.R. 5264). Both notices will be acted upon at the same time.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 512, 82 Stat. 343-51; 21 U.S.C. 360b) and under authority delegated to the Commissioner (21 CFR 2.120).

Dated: June 16, 1972.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

Dr. EDWARDS. Our proposal to withdraw approval of DES must by law allow time for affected parties to submit objections and request a public hearing. Requests for a hearing must be justified on the basis of a genuine and substantial issue of fact. If no hearing is requested, or if objections filed do not support the need for a hearing, prompt action will be taken to issue a final order withdrawing approval for use of DES in food-producing animals. Time for objections and requests for a hearing will end on July 21, 1972—this Friday.

If a request for a hearing is justified based on reasonable grounds establishing genuine issues of fact relevant to this decision, we will immediately proceed to announce and schedule the hearing. If a hearing is held, a final decision must be based on evidence adduced at the hearing. It would, of course, be inappropriate for me to further address the question of whether or not a hearing should be held, or DES banned, until I have had the benefit of reviewing the data submitted in response to our proposal.

Senator KENNEDY. You have had a pretty good opportunity. Tomorrow is the last day.

Dr. EDWARDS. That is correct.

Senator KENNEDY. You must have examined all of these data pretty well if you have only 1 more day.

Has anything come in to date that you can tell us about?

Dr. EDWARDS. Mr. Hutt is more familiar with this aspect.

Mr. HUTT. We have received no formal objections as of yesterday noon. The way the time limit runs under the regulations they must be mailed with a postmark no later than midnight Friday.

It is quite often the case that all the objections are mailed on the last day, and we would therefore not receive them until next Monday. In any event, we have received none as of yesterday.

Senator KENNEDY. You have not received any?

Mr. HUTT. None. If none is received, that will be the end of the matter.

Senator KENNEDY. What do you mean by that?

Mr. HUTT. There would be an immediate order issued withdrawing approval of the drug, and it could no longer be used.

Senator KENNEDY. By when? When would you know? If your mail does not come in on Monday, will we get something Monday afternoon?

Mr. HUTT. The notice would have to be drawn up, and we would have to go through the proper procedures, Senator. But it would certainly be an expedited matter, I assure you.

Senator KENNEDY. Help us out a little.

Mr. HUTT. A week.

Senator KENNEDY. Why does everybody wait until the end?

Mr. HUTT. Presumably, Senator, we have made it clear that we are not going to grant a hearing unless there is good cause shown. We have made that very clear, as the Commissioner has said.

Therefore, the industry is on notice if they do wish to have a hearing—and we do not know that at this moment—they must do a first-rate job on their presentation.

Senator KENNEDY. They have not indicated to you, though, that they want a hearing at this time?

Mr. HUTT. There was an initial press release that one company would submit objections. That was when we initially announced the opportunity for the hearing.

Senator KENNEDY. Can one company delay this?

Mr. HUTT. Yes. Let me qualify that. The notice in the Federal Register lists a number of new animal drug applications. If any one of the individuals involved does not submit an objection and request for a hearing, we may withdraw that particular NADA if any hearing is to be held on the other NADA's.

Senator KENNEDY. If you do not get any mail tomorrow, can you tell us whether you are planning to ban it?

Mr. HUTT. If we get no mail whatever?

Senator KENNEDY. Yes.

Mr. HUTT. We will ban it.

Dr. EDWARDS. Even if we get mail, as Mr. Hutt has pointed out, and as I did in my testimony, the respondents to our proposal have to demonstrate some reasonable issues on which to hold a hearing, or we will obviously ban it.

Mr. Chairman, let me now shift for just a moment from the specific issue of DES to other subjects of broader concern which I also believe are pertinent to this hearing.

Quite candidly, judging the safety of any substance used in food is not a simple matter. A number of considerations and issues cannot be ignored in determining whether a substance is suitable for use in food.

In making a judgment to withdraw approval for a useful substance in food, we must be mindful of other ramifications which can result from such action. A theoretical or potential risk to the public health may well be sufficient reason for moving against a particular food ingredient.

On the other hand, where the use of a substance substantially increases the availability of a food, affects its nutritional value, or

lessens the possibility of other hazards to health, a potential problem may not be sufficient to justify completely removing the product from the market.

We are concerned about the extent to which our decisions may affect the nutritional value of our food supply, and I am certain this committee and every consumer is concerned with the impact of decisions which may influence the availability of nutritious food to large segments of our population.

Many decisions affecting our food supply may also have a significant impact on the environment, and could present as difficult a health problem as the potential direct effect of ingesting minute traces of the substance. Indeed, under the National Environmental Policy Act, we are required to consider the environmental effect of our actions.

Perhaps the most critical scientific consideration is the as yet unresolved question as to whether extremely low levels of a substance actually represent a potential risk for the induction of cancer in man. It is this concern that was a preeminent consideration in our decision to develop the research resources at Pine Bluff, Ark., the National Center for Toxicological Research.

All of these factors are considerations for which the answers are extremely difficult to obtain; and in certain instances, we are only able to give them limited attention because of the law.

For example, the all-or-nothing philosophy of the Delaney clause sounds eminently reasonable to the consumer because he wants absolute assurance that no harm will come from anything he eats. And yet, we must regulate in the certain knowledge that absolute safety is impossible and science nearly always incomplete. We are certainly opposed to carcinogenic substances entering our food supply, as well as other harmful substances. We must keep in mind, however, that a statistical association of substances causing tumors in experimental animals may not have any relationship to the induction of cancer in humans. This must be considered for many substances both natural and synthetic that enter man's environment.

Mr. Chairman, DES will not be the only substance to generate these kinds of issues. This is why we cannot recommend enactment of S. 2818. We do not believe piecemeal legislation directed at any given substance is appropriate for making regulatory decisions that are to be based on scientific evidence. We now have sufficient regulatory authority to act effectively on behalf of the consumer. In this sense, S. 2818 is unnecessary.

I do appreciate the opportunity to discuss these issues with your committee, and I will be pleased to answer any questions you or members of your committee believe will be helpful.

Senator KENNEDY. I do have some questions, but what I would like to do is hear from our next witnesses. Then I would have some brief questions and release you. We will not delay you terribly long.

I would like next to welcome Dr. Peter Greenwald, Director of the Cancer Control Bureau of the New York State Department of Health.

Dr. Greenwald received his M.D. from the State University of New York at Syracuse, his M.P.H. from the Harvard School of Public Health. He is also clinical assistant professor of medicine at Albany Medical School.

STATEMENT OF PETER GREENWALD, M.D., DIRECTOR OF THE
CANCER CONTROL BUREAU, NEW YORK STATE DEPARTMENT OF
HEALTH

Dr. GREENWALD. In New York State, nine teenage girls are known to have developed vaginal cancer 15 to 19 years after their mothers took DES or another synthetic estrogen during pregnancy. Six of these girls have died of advanced disease.

I plan to summarize our study of these nine patients, present the reasons we believe there is a cause-and-effect relationship between DES and vaginal cancer, and briefly discuss our continuing studies of DES in relation to other human tumors.

Physicians, hospitals and laboratories throughout New York State, exclusive of New York City are required by State law to report all patients with cancer to a registry maintained by the health department.

Senator KENNEDY. Do you think there ought to be a national registry maintained?

Dr. GREENWALD. Yes.

Senator KENNEDY. Why do you believe this?

Dr. GREENWALD. I believe it is essential for a number of reasons.

One is that we have to have detailed information, as much as possible, on what the risk is, the number of people exposed; and in this instance with DES the details about the dosage, and whatever we can learn as to how to prevent cancer, and the best mode of treatment.

There have been some steps taken in this direction, although this has not been formalized.

Senator KENNEDY. Registration of this kind of research would be extremely difficult, would it not? It would be virtually impossible?

Dr. GREENWALD. That is right.

The initial observation is possible, but to completely follow through on it as completely as we might wish would be impossible.

New York City was recently added to our State reporting system. Among their many uses, cancer reporting systems allow for rapid identification of people with specific tumors for study of possible causative factors.

In this instance, we believe that all diagnosed vaginal tumors in women under 30 years old and from a wide geographic area—upstate New York and Long Island—were reported for further study.

The nine patients were studied in detail for history of drug use by their mothers during pregnancy. DES therapy was definitely given to mothers of seven patients. Obstetricians used the therapy to prevent threatened spontaneous abortion.

The mother of the eighth patient told us herself that she had received therapy during pregnancy in order to avoid "a miscarriage like the last time."

Destruction of records, however, prevented definite ascertainment of whether DES was used. The ninth patient took another synthetic estrogen, dienestrol, which is very similar to DES.

Details on dosage, the period during which DES was taken by the mothers, and the age and year at diagnosis in the daughters are shown

in table 1 appended Place of birth varied widely with four patients being born in upstate New York, four in New York City, and one in Pennsylvania

All patients were single and had no children. Their menstrual periods 1 year before the first symptoms were described as normal, and none had hormone or contraceptive therapy before the onset of first symptoms.

I believe that the following facts demonstrate the cause-and-effect relationship between therapeutic use of DES by mothers and vaginal cancers in their daughters:

(1) The mothers of all patients studied had definitely or probably taken DES or another synthetic estrogen during pregnancy;

(2) None of the mothers of a comparison group of girls had taken DES. This difference between patients and a comparison group of girls of the same age and born at the same hospitals is statistically significant;

(3) All nine patients were born during the period 1951 through 1955, the time of peak clinical use of DES to prevent miscarriages;

(4) There is an absence of vaginal cancer in girls of this age group born before the time of common use of DES;

(5) The rather uniform microscopic pattern of these tumors supports the possibility of a common cause;

(6) The observations are consistent with our biologic knowledge of DES, and particularly with the fact that DES can be shown to produce cancer in a variety of animals; and

(7) Similar observations were made by two independent investigators. Our studies confirmed and expanded upon those by Doctors Herbst, Ulfelder, and Poskanzer in Boston.

It should be pointed out that I believe, as do most cancer investigators, that cancer is generally not the result of a single cause, but rather of a chain or web of causes which interplay with each other.

By "cause-and-effect relationship," I mean that the DES was a necessary factor, and the cancer would not have developed without it. There are undoubtedly additional factors affecting susceptibility and resistance, which are yet to be uncovered.

It should also be noted that as we have studied all vaginal cancer patients in the State, and as the mothers of all had been treated therapeutically, there is no reason to suspect that DES in food caused any of the tumors.

The depth of the investigation was important here. In one instance, neither the obstetric nor the hospital record showed evidence that DES had been taken. It was only after a local pharmacist had searched his records from 1952, which he had fortunately maintained, that we could demonstrate that this mother had been prescribed 100 5 mg DES tablets at 2½ weeks of gestation, and 50 25 mg DES tablets at 11 weeks of gestation.

Senator KENNEDY. Does this not really show just on another issue, a quality-of-care issue, the importance of maintaining a record of all prescriptions?

Dr. GREENWALD. Yes; this was very valuable.

Senator KENNEDY. This is certainly not required now, and I would assume it would be a serious administrative burden to the pharmacists all over the country. Probably that is a burden on which they ought

to get some kind of assistance or relief; but it does raise the quality-of-health issue, which I think all of us are trying to deal with. This is a good example of the importance of maintenance of records.

Dr. GREENWALD. It is very dependent on records. A retrospective study such as this always is, and we felt we were just lucky that this pharmacist kept this record.

Senator KENNEDY. What is his name; do you remember?

Dr. GREENWALD. No; he is from the town of Lyons, N.Y.

As for other tumor types, in persons of both sexes, we have obtained prenatal drug use histories on mothers of all females born after 1947—when DES began to be used to prevent miscarriage—reported with cancers of the breast, uterine cervix—adenocarcinoma—uterine corpus, fallopian tubes and urethra, and all males born in the same period with cancers of the breast, prostate, penis, epididymis, spermatic cord and urethra.

A number of patients with cancers of the ovary, testis, bladder, and kidney were also studied. These sites were chosen primarily because they derive embryologically from the same general area as the vagina or because they are hormone-dependent organs.

DES was taken during pregnancy by the mother of only one patient, an 18-year-old girl with adenocarcinoma involving both the cervix and vagina; she is case No. 6 on the table.

Time trends in incidence for the 0 to 24 year age group, born at a time when DES might have been used in pregnancy, were compared to the unexposed 25 to 34 year age group. There were no increases that could be attributed to DES use. There is thus far no indication that maternal use of DES contributes to the development of tumors other than those of the lower female genital tract.

Dr. Hollis S. Ingraham, our State commissioner of health, 1 full year age took the lead in responding to this evidence of DES and vaginal cancer.

Dr. Ingraham alerted all of the State's physicians to this problem, and suggested that the Food and Drug Administration do likewise on a national scale. We are recommending intravaginal examination of girls whose mothers were treated with DES, and are helping mothers who aren't sure whether they received DES to find out if they were so treated and the dosage level.

Senator KENNEDY. Do you know what the results of Dr. Ingraham's request of the Food and Drug Administration were? Do you know what response he received?

Dr. GREENWALD. Yes.

We wrote the Food and Drug Administration in June of last year, and then there were Congressman Fountain's hearings the following fall.

About that time, the Food and Drug Administration did alert all the physicians in the country. I am not sure to what degree our own information caused the action, but they did follow through.

With respect to DES in foods, it is difficult to assess the relative significance of large therapeutic doses as compared to the trace levels in foods. My personal opinion—and it is an opinion—is that it would be prudent to insure that DES is not in food when it reaches the table.

Past actions on sweetening agents—cyclamates—and pesticides may also have some bearing on the DES question, and incidentally, we

used the New York State Cancer Registry to evaluate both cyclamates and pesticides.

I have some reluctance in comparing different situations, but it is clear that with DES we have direct evidence of a cancer-producing effect in humans, while with the other compounds, we do not.

Senator KENNEDY. Are you saying that there is more evidence available that DES causes cancer in human beings than was available on cyclamates?

Dr. GREENWALD. Yes.

As far as I know, there is no evidence whatsoever that cyclamates cause cancer in humans.

Senator KENNEDY. They have been banned; have they not?

Dr. GREENWALD. Yes; but with diethylstilbestrol there is evidence in humans. I did not comment on whether the ban on cyclamates was the right action, but in a comparative sense, the DES is more of a threat to humans, to pregnant women.

Senator KENNEDY. As a researcher or as one who has studied this area, you are convinced there is more evidence that DES causes cancer in human beings?

Dr. GREENWALD. Yes; and I would say evidence is limited to ingestion by pregnant women at this point.

Senator KENNEDY. Very good.

Thank you very much.

(Additional information supplied by Dr. Greenwald follows:)

Table 1. Vaginal Cancer and Maternal Use of Synthetic Estrogen in Patients Reported in the New York State Cancer Registry, 1950-1972.

Case No.	Date of Birth	Age (Year) at Diagnosis	Maternal Synthetic Estrogen Therapy During Pregnancy		
			Time Started*	Time Ended*	Drug & Dose
1	2/9/51	15 (1966)	5 wk	Delivery	Stilbestrol (oral), 5 mg/day initially, increased 5 mg/wk to 125 mg/day
2	4/5/52	19 (1971)	2½ wk	3½ - 4 mo	Stilbestrol (oral), 5-mg tablets initially & 25-mg tablets later (exact dose unknown)
3	9/28/52	15 (1968)	Conception	Delivery	Stilbestrol (oral), 0.1 mg/day until 3d week, then 5 mg/day to 100 mg/day
4	10/2/52	17 (1970)	3 mo	6 mo	Dienestrol (oral), 5 mg/day; also estrone (intramuscularly) for 2 doses at 3d mo; progesterone & thyroid 3d mo to delivery
5	4/20/53	17 (1970)	2½ mo	5 mo	Stilbestrol (oral), possibly 65 mg/day; also, 28 "estrogen" shots from 2½ mo to 4½ mo
6	4/5/52	18 (1970)	2½ mo	5½ mo	Stilbestrol (oral), 25 mg/day; from 2½ mo to 5½ mo
7	8/18/53	17 (1971)	3 mo	Delivery	Possibly stilbestrol, dosage unknown
8	2/3/52	19 (1971)	3 mo	9 mo	Stilbestrol (oral), 75 mg/day from 3 mo to 7 mo, decreased beginning 7 mo to 50 mg/day and at middle of 8 mo to 25 mg/day
9	-/-/55	17 (1972)	3 mo	9 mo	Stilbestrol (oral), dosage unknown

*Time of gestation

Senator KENNEDY. We welcome Dr. Arthur L. Herbst, head of the department of gynecology at Massachusetts General Hospital.

STATEMENT OF ARTHUR L. HERBST, M.D., ASSISTANT PROFESSOR OF OBSTETRICS AND GYNECOLOGY, MASSACHUSETTS GENERAL HOSPITAL, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

Dr. HERBST. Thank you, Senator Kennedy.

At the outset, I would like to acknowledge the invaluable contributions to these studies of Dr. Howard Ulfelder, professor of gynecology; Dr. Robert E. Scully, professor of pathology; and Dr. David C. Poskanzer, who serves as our epidemiologist. All are from the Massachusetts General Hospital and Harvard Medical School.

Prior to 1966, there had not been one case of adenocarcinoma of the vagina in a woman under age 25 years at our hospital, and only a very few rare case reports existed in the medical literature.

Then between 1966 and 1969, six women under 25 years of age with adenocarcinoma of the vagina were seen and treated at the Vincent Memorial Hospital, Department of Gynecology, Massachusetts General Hospital.

During that period, we had the opportunity to review the findings of a seventh similar case treated elsewhere. These young girls had sought medical advice because of excessive vaginal bleeding and were found to have vaginal cancers.

Six of the seven young patients were able to be treated and all six are living and well today.

The seventh patient had advanced disease when first seen and has since died. During this time, we also heard of an eighth identical case treated at another Boston hospital and these eight cases were more than had been reported in the medical literature up to that time.

A case control retrospective epidemiologic study was carried out to compare in detail the patients with carcinomas and other families with an appropriate control group of young ladies of similar age who did not have these cancers.

Four matched controls were obtained for each patient with carcinoma by examining the birth records of the hospitals in which the patients were born.

Females were identified who were born within 5 days of each girl with carcinoma, and we then contacted the women who gave birth to the daughters closest in time to each of our patients with carcinoma. In this way, 32 control families; that is, four for each patient with cancer, were obtained whose replies to our detailed epidemiologic questionnaire were compared to the replies of the families of the girls with carcinoma.

There was no significant differences to the replies obtained from these two groups for most of the topics covered. However, there was a highly significant association between the treatment of the mothers with diethylstilbestrol during pregnancy and the subsequent development of adenocarcinoma of the vagina in their young daughters years later.

Other factors found to be significant were bleeding during the study pregnancy and a history of previous pregnancy losses. The fact that

these were so-called high-risk pregnancies was the indication for stilbestrol administration.

Six of the seven mothers interviewed volunteered the information that stilbestrol had been prescribed for them. The seventh was uncertain, but her physician identified the drug as diethylstilbestrol.

For one of the eight mothers, whose daughters had this carcinoma, there was no evidence that stilbestrol was administered during pregnancy. She had not experienced prior pregnancy loss or bleeding during the study pregnancy. As mentioned previously, these tumors were known to occur, though very rarely, in women of this age group prior to the availability of stilbestrol. It is thus possible that factors other than maternal stilbestrol ingestion are operative in the development of these cancers.

After the publication of our findings last year, we heard of additional cases of cancer identical to the ones that we studied; and you have already heard a description of some of these by Dr. Greenwald.

Because it was obvious that many more of these tumors would develop in the future, and since definitive statements on tumor behavior and therapy are not yet warranted, my colleagues and I established a registry for clear-cell adenocarcinoma of the genital tract in young women to help centralize this important information and rapidly obtain data on a large number of cases.

Senator KENNEDY. Do you think it would be worth while to have a national registry on this?

Dr. HERBST. That is exactly what we are trying to do. We have been in touch with physicians all over the country in the medical centers, and in the departments of obstetrics and gynecology, in order to study this.

Senator KENNEDY. Is there a role for the Federal Government in this on developing legislation?

Dr. HERBST. For legislation?

Senator KENNEDY. Yes.

Dr. HERBST. I think accurate records could be kept, and we are making data from our records available to the Food and Drug Administration so that they can carry through with what additional record-keeping they want.

Senator KENNEDY. Maybe you can think about that and let us know if you think there is a need for this at the national level. I am convinced of the importance of it, and we would welcome your thoughts about a role that we might be playing in this.

Dr. HERBST. The registry contains varying amount of information on over 80 cases of adenocarcinoma of the vagina or cervix in young women under age 25 years.

This information has been made available to the registry thanks to the generous cooperation of many physicians throughout the United States. The details of a few of these cases have been published in the medical literature by different investigators, and I have cited that in the references in the prepared statement, in Nos. 1, 2, 3, 4, and 5.

Maternal histories are not available in all cases entered in the registry, but stilbestrol, dienestrol, or hexestrol have been implicated in most of the cases for which we have been able to obtain a history.

Dienestrol and hexestrol are chemically similar to stilbestrol. All three are potent nonsteroidal synthetic estrogens. Thus far, we know

of no cases which have been associated with steroidal estrogens. It must be remembered, however, that the nonsteroidal compounds were the ones most frequently prescribed to support pregnancies in the past.

We have, from the beginning of our investigations, been interested in the relation of the dosage and time of administration of stilbestrol during pregnancy to the appearance of these cancers. Our information in these categories obviously varies depending upon the mother's recollection of past medication, the availability of doctors' records, et cetera.

Such data are often difficult to obtain since we are dealing with pregnancies that for the most part occurred 15 to 25 years ago.

Nevertheless, we do know of one case for which the record indicates the mother received only 1.5 milligrams of stilbestrol daily. Her daughter developed cancer.

In a different case, the patient's record reports the use of stilbestrol for only 12 days during the first trimester of pregnancy.

It is my impression that there is wide variation both of the doses used and the duration that the mothers of the girls with cancers were treated. I do not think we can define with confidence the smallest dose or shortest duration of exposure to these compounds that might endanger the fetus.

Senator KENNEDY. Really, we cannot define the smallest safe dose for a carcinogen either, can we?

Dr. HERBST. That is right; I do not believe we can.

Our studies to the present time do not permit us to estimate the risk of cancer development in any young girl whose mother took stilbestrol during pregnancy.

We do not know the number of women in this country or elsewhere who have been treated with stilbestrol or similar drugs during pregnancy. It probably is many thousands or perhaps even millions.

Only a few cases of carcinoma have been uncovered so far. Although we cannot specify the risk of cancer development, present status suggests the risk is small. Nonetheless, the results of our study indicate that intrauterine exposure to stilbestrol and similar compounds increases the risk of development of these adenocarcinomas years later.

Senator KENNEDY. Very good. I have just a few questions, Doctor. In your study, do you consider DES to have been a major factor in the development of vaginal cancer?

Dr. HERBST. A major factor? Yes, we do.

Senator KENNEDY. Would you be concerned if pregnant women were exposed to trace levels of DES in food over the course of their pregnancies?

Dr. HERBST. As I mentioned during my testimony, I do not think we can find what levels of exposure would be safe. I just do not think we know.

Senator KENNEDY. As I understood, you could not determine what would be dangerous, but you cannot say either what would be safe?

Dr. HERBST. That is correct. I would agree with that.

Senator KENNEDY. Nonetheless, you are satisfied that some DES—and you are not prepared to state at what level—is also a factor in development of vaginal cancer?

Dr. HERBST. Yes.

Senator KENNEDY. In your medical opinion, is there a possible risk to humans if they are continually exposed to trace levels of DES in their daily diet for over a long period of time?

Dr. HERBST. From our studies, one really cannot answer that question because we are dealing with a limited situation; namely, a woman who is pregnant with a female fetus.

I think if she is exposed to stilbestrol in her diet, the risk of development of cancer increases, and our studies up to the present time have not yet related the increase in risk to dosage.

It has occurred with high doses, small doses, long exposure, and short exposure; so I would have to say we do not know.

Senator KENNEDY. Can you give us any help as to what the parameters are regarding high dosage, low dosage? What can you tell the laymen?

Dr. HERBST. The high doses that were used and were often publicized in the medical literature would go up to as much as 125 milligrams a day in the latter part of pregnancy.

As I mentioned, the lowest dose we know is 1.5 milligrams per day. These are doses where there is definite association with carcinoma development, so there is really a wide difference of dosage associated with carcinoma development.

I have to again emphasize we have a small number of cases where the dosage of stilbestrol is known.

Senator KENNEDY. But you are satisfied that with trace levels over a period of time in pregnant women, the incidence of cancer is increased?

Dr. HERBST. We have documented it for 1.5 milligrams. Whether a dosage smaller than that can do it, we obviously do not know.

Senator KENNEDY. Thank you very much.

If your wife were pregnant, would you have any reluctance in seeing her take DES for the period of pregnancy?

Dr. HERBST. I would not want her to take DES if she were pregnant.

Senator KENNEDY. Dr. Edwards, could you come back?

We are going to vote at 11. I think we could recess just very briefly, and we will go over and vote and then come back.

I would like to have your own thinking about the administrative procedures that can be followed.

I do not think we will be gone a long period of time. We will recess for about 10 or 12 minutes.

(Short recess.)

Senator KENNEDY. Mr. Commissioner, you appeared before the Fountain committee several months ago. You indicated, in response to a question:

We will investigate all reported residues. Immediately upon receipt of such reports, appropriate legal action will be taken against offenders if residue reports are substantiated by field investigation; and should these measures prove unsuccessful, we will be prepared to ban its use entirely in animal feed.

Do you remember that comment?

Dr. EDWARDS. Absolutely; yes.

Senator KENNEDY. Can you tell us about how many cases have actually been prosecuted?

Dr. EDWARDS. With your permission, I would like to have our General Counsel speak to that.

Mr. HUTT. There is one criminal suit that has been filed against a person who used the product illegally, resulting in an illegal residue.

There were a number of criminal investigations that were terminated at an earlier stage—18 in number, I believe—for failure of the Department of Agriculture to keep the necessary duplicate samples which, under our statute, are required to be given to any defendant, so that he may conduct appropriate tests himself.

There have been, I believe, five new citations recently, although Dr. Van Houweling can correct me on the precise number, and an additional two that are in a stage of investigation right now.

What we have done, Senator, is instead of bringing a criminal citation under section 305 of the act, which is an order to show cause why the individual should not be criminally prosecuted, in every instance of an illegal residue, we have first sent out investigators to determine whether it appears that there was illegal activity.

If there is an appearance of illegal activity, then we institute the so-called section 305 citation.

Senator KENNEDY. How many reports have been brought to your attention?

Mr. HUTT. Dr. Van Houweling, I believe, can answer that.

Dr. EDWARDS. Dr. Van Houweling, Mr. Chairman, is Director of our Bureau of Veterinary Medicine.

Dr. VAN HOUWELING. I believe the USDA has reported residues in 58 instances up to the present time.

We have reports from investigations of 34 at the present time. There are 24 that we have not yet received a report.

Senator KENNEDY. Just so I understand, there have been 58 allegations or charges; is that right?

Dr. VAN HOUWELING. No. For the record, we should state that the U.S. Department of Agriculture does the sampling. They have reported 58 instances where they detected DES in the liver of slaughtered animals.

Senator KENNEDY. They detected it in 1958. You must have investigated all of those, did you not?

Dr. VAN HOUWELING. They are all under investigation. We have received the reports of the investigations on 34.

Senator KENNEDY. And you are waiting for the others?

Dr. VAN HOUWELING. They are in process.

Senator KENNEDY. The other 24?

Dr. VAN HOUWELING. When we received the notification from Agriculture by telephone that they have liver in which they found DES residues, we immediately phone our field office, and the investigation is begun. We follow this up with TWX instructions.

Senator KENNEDY. So you have received back investigative reports on 34, and 24 you are waiting for; is that right?

Dr. VAN HOUWELING. That is right.

Senator KENNEDY. Of the 34 that you have received, how many of those did you decide to move ahead with criminal prosecution?

Dr. VAN HOUWELING. As Mr. Hutt indicated, we have filed one case.

Senator KENNEDY. When was that filed?

Mr. HUTT. Approximately 3 weeks ago.

Senator KENNEDY. So you have filed that one case. What about the other 33?

Dr. VAN HOUWELING. There are four more in which we are still considering prosecution. They are in various stages of evaluation, either in our Bureau or in the General Counsel's office.

As we indicated, we have two other citation instructions we are considering at the present time.

Senator KENNEDY. So you are considering four more; is that right?

Dr. VAN HOUWELING. That is right.

Senator KENNEDY. What about the other 29?

Dr. VAN HOUWELING. The reports have not been completed, and we have not received the final recommendation from the field as a result of their investigation.

Mr. HUTT. Senator, perhaps I could clarify that.

Are you referring to the other 24 that are still in the field, or are you referring to the 29?

Senator KENNEDY. Let us take the 29.

Mr. HUTT. There were a number, as I mentioned, 18 of which I am aware of, and there may well have been all 29, in which we concluded that the case was legally defective and that we could not file, or where investigation showed that there was no history of use of DES by the individual involved that we could determine.

Senator KENNEDY. What do you mean by "legally defective"?

As I understand, there was DES in the liver.

Mr. HUTT. Yes. To the best of our methodology, yes. But the difficulty was, as I stated earlier, that the Department of Agriculture did not retain a sample of the illegal liver.

The Federal Food, Drug and Cosmetic Act provides that we provide a duplicate sample to the potential defendant.

This problem has been overcome. The Department is now retaining the samples.

Senator KENNEDY. You mean because they did not have a duplicate sample, you could not move ahead on the prosecution?

Mr. HUTT. That is entirely correct. It is unfortunate.

Senator KENNEDY. Are there other reasons besides the duplicate sample?

Mr. HUTT. That was the controlling reason.

As I mentioned, there were some cases where the duplicate sample issue was moot because our investigation indicated that there was no wrongdoing on the part of the individual.

Senator KENNEDY. You mean the people are feeding DES to cattle and you cannot prove the wrongdoing even though they are feeding it? You cannot halt it or you are not equipped to halt it?

Mr. HUTT. No.

Perhaps I can break these cases down once again.

Senator KENNEDY. Before you do, I apologize, but the last vote was 46 yeas and 46 nays, and there is another vote now.

I do not want this next one to be 46 to 45. We are going to have to recess and take a vote and come back.

(Recess.)

Senator KENNEDY. The subcommittee will come to order.

We were talking about the number of cases that were brought to the attention of the FDA and the procedures that they followed to investigate the various cases and what action had been taken.

And as I remember, we saw that one of the cases had been filed for criminal prosecution, and there were four others, I believe, that were under immediate consideration for filing.

There were 34 that had been investigated and returned and there were 24 still under investigation.

Mr. HUTT. I perhaps should correct that record somewhat. Of the 58, it is correct, one was filed; it was in the latter part of May, which was about 6 weeks ago now.

Four were recommended for prosecution to my office, and the criminal information is in the process of being put together and typed up for transmittal to the U.S. attorney.

In two, the section 305 citation has been recommended, and that will go forward through our field offices.

In 27, there has been only a preliminary report from the field, not a final report, and thus, at this moment, no prosecution, citation, or anything has been recommended. And in 24 there has been no report whatever because it has been too recent to even get a preliminary report.

Senator KENNEDY. Now, as I understand, you indicated previously that one of the principal limitations in carrying forth a filing for prosecution was the fact there had not been a reserve sample that had been retained and that the procedure had been changed now so they will maintain—

Mr. HUTT. Yes, sir.

Senator KENNEDY. Were there any other reasons?

Mr. HUTT. There was the basic reason, other than the possibility that in some instances, we have not found any use of DES whatever by the individual involved, in which case our investigation leads us to the conclusion that it was a false positive, or naturally occurring estrogen may have been picked up through the chemical analysis, or cross contamination of a kind that we are unable to track down in any way and certainly not the fault of the farmer himself.

Senator KENNEDY. Was another reason that the chemical method was not legal?

Mr. HUTT. No, sir.

We considered whether that would be a legal disability and concluded it would not prevent us from filing prosecutions.

Indeed, the one prosecution filed depends upon the new chemical method. We did consider, as I mentioned, from a legal standpoint, whether it would be permissible to use the new method even though it is not yet the formal legal requirement, and we concluded that we could do so.

Senator KENNEDY. You remember the February 9 memorandum which you offered, in the fourth paragraph, that although the former section 305 hearing was not in itself a legal impediment, the lack of 70T samples, especially in light of the fact that the residues were not determined by the method legally designated in regulations, required the conclusion that prosecution must be refused as legally defective.

Can you explain that to me?

Mr. HUTT. Yes; there were two factors.

Senator KENNEDY. Let me just tell you how it appears to me and maybe you can indicate to me why the methods which you were using to detect this were, you felt at that time, legally defective in a criminal prosecution.

Am I wrong in that interpretation?

Mr. HUTT. I believe, Senator, the conclusion was, as I mentioned, there were two factors involved there.

One was a lack of a sample. The other was the question of the test methodology.

We concluded the lack of the sample was the critical factor that prevented the prosecution. We have concluded that the test methodology is not controlling and will not prevent filing of a criminal information or successful prosecution.

Senator KENNEDY. Well, the courts ruled——

Mr. HUTT. The courts in the past have ruled that a sample is required, a duplicate sample. The courts have not ruled on the question of the methodology and we believe we can be sustained on that.

Senator KENNEDY. Why should there be any confusion about methodology? Why can you not have a valid means for the testing?

Mr. HUTT. Well, what we have been trying to do before publishing this new method, official method, in the Federal Register is to validate it with a collaborative program involving the Food and Drug Administration and the U.S. Department of Agriculture.

We have preliminary results back from that validation, which indicate that we can go ahead now and publish it in the Federal Register.

Senator KENNEDY. Isn't part of the reason that there has not been a greater administration oversight on this, is because you did not have a validated procedure for the investigators?

Mr. HUTT. To my knowledge, no, sir.

Senator KENNEDY. Did you have one?

Mr. HUTT. Yes, we do.

Senator KENNEDY. Was it published in the Federal Register?

Mr. HUTT. It is not yet——

Senator KENNEDY. Is it legal?

Mr. HUTT. It is not a disability for a prosecution, Senator. As to whether it is the official method——

Senator KENNEDY. Let us talk about the health of the American people on this. You were using a system that had not been validated, had not followed the Administrative Procedures Act?

Mr. HUTT. Senator, I think we had better step back one step and go through the history of this.

Senator KENNEDY. I am just reading from your memorandum here, so you understand.

Mr. HUTT. I understand.

Senator KENNEDY. I am going to include the memorandum, and maybe you can explain your way out of it, and I am glad to hear the explanation. In an earlier paragraph, you said: "With the result we cannot corroborate the DES residue." That is part of it.

In the fourth full paragraph on the first page, you point out: "Were not determined by methods legally designated in the regulations."

Mr. HUTT. That is correct. We have concluded that that is not a disability of our prosecuting an individual where there is an illegal residue.

Senator KENNEDY. How about the part where it is refused as legally defective?

Mr. HUTT. That was based upon the conclusion that there was not statutorily required reserve sample, which the courts have held is a legal disability. The courts have not said that the failure to use the

method specified in the Federal Register precludes us from prosecution where there is an illegal residue by any method.

Senator KENNEDY. In the next paragraph: "This underscores the fact that the new chemical method must immediately be validated and promulgated in the Federal Register."

Mr. HUTT. Yes. We are proceeding to do this in order to bolster our case.

Again, it is our legal conclusion it is not necessary. Let me explain the reason for the methodology. The reason for the methodology is set out in section 512 of the Federal Food, Drug, and Cosmetic Act.

Senator KENNEDY. Well, this memorandum is dated February 9, and the date today is July 20. Were they ever put into the Federal Register?

Mr. HUTT. It has not yet been put in the Federal Register.

Senator KENNEDY. Why not?

Mr. HUTT. The validation process is in its final stages now. I would like to ask Dr. Van Houeweling how close it is to publication. I am uncertain about that.

Dr. VAN HOUEWELING. We have concluded in this collaborative study that the sensitivity of the method is two parts per billion.

We have another study underway to be concluded in about 2 weeks. If it turns out to be successful, we will be able to publish shortly thereafter. There is general agreement that it is capable of detecting DES at two parts per billion.

Mr. HUTT. I would like to return to the reason for the methodology.

The methodology does not establish whether we may prosecute for illegal residue. The methodology is required under section 512 of the act as a means of establishing the level at which no residue may be found in order to determine whether the drug should remain on the market or not.

If there is any residue by any legal method or unpublished method, then it is a violative article.

I might add that whenever we find a residue by any method whatever that is in our opinion a permissible method scientifically, all of the meat involved is immediately embargoed by the U.S. Department of Agriculture and will never reach the consumer.

Senator KENNEDY. Well, I will leave this, Mr. Counsel. I wish I could be more understanding of your position. I will let the record and the memorandums speak for itself.

Mr. HUTT. Very good, sir.

(The information referred to follows:)



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

OFFICE OF THE SECRETARY

ROCKVILLE, MD. 20852

OFFICE OF THE
GENERAL COUNSEL

OCT 3 1972

Honorable Edward M. Kennedy
Chairman, Subcommittee on Health
Committee on Labor and Public

Welfare
United States Senate
Washington, D. C. 20510

Dear Senator Kennedy:

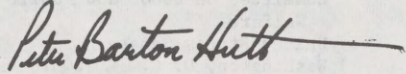
During the hearings on diethylstilbestrol on July 20, 1972, you were concerned that the fact that the new GLC method has not yet been published in the Federal Register as the official methodology for detecting DES might inhibit enforcement action against violators. As I testified at that time, it is our legal opinion that prosecution of violators is neither precluded nor inhibited by the fact that this method has not yet been published.

Section 512(d)(1)(H) of the Federal Food, Drug, and Cosmetic Act requires that methodology be published in regulations in order to determine whether residues of the drug will be found, for purposes of determining whether a new animal drug application for the drug may be approved. If, under the methodology contained in the published regulations, no residues are found, the drug may properly be approved.

The enforcement procedures, however, are entirely different, and are found in separate sections of the Act. Section 402(a)(2)(D) provides that a food is adulterated, and hence illegal, if it contains a new animal drug which is unsafe within the meaning of section 512. Section 512(a)(1)(B) in turn states that a new animal drug is unsafe unless its use conforms to an approved application. DES has been approved for use in animal feed and implants with a zero tolerance, that is, on the condition that it not be found in any edible portion of the animal. There is no requirement in these provisions of the statute that any particular methodology must be used in determining if an illegal residue is present. Accordingly, it is our opinion that the GLC method, and indeed any other scientifically valid method, may properly be used in determining residues, and residues so found may properly be the basis for enforcement action under the law.

The February 8 memorandum to which you referred during the hearing relied upon the failure to retain a duplicate liver sample as the controlling factor in determining that 18 cases could not be prosecuted. The fact that FDA was using new methodology was mentioned as a contributing factor, but was not regarded at the time as controlling. The February 8 memorandum was not intended as a full exposition of the subject, but rather simply as a means of summarizing our legal conclusion to the Bureau of Veterinary Medicine. This is corroborated by the fact that we have, since then, initiated enforcement action based upon the GLC method. We are confident that this enforcement action will be upheld in the courts.

Sincerely yours,



Peter Barton Hutt
Assistant General Counsel
Food, Drugs, and Product
Safety Division

Senator KENNEDY. What about the two dairy cow violations? How does DES—why does DES appear in dairy cows?

Dr. VAN HOUWELING. I believe it is a common practice in many areas when a cow has been stopped being used for milk production, they are put in feed lots and fed for a period of time along with beef cattle being fed for slaughter. The Department of Agriculture is screening these dairy cattle along with the steers and the fed heifers.

Senator KENNEDY. Are you prepared to say the two cases were not milk-producing cattle?

Dr. VAN HOUWELING. I am confident they were not.

Senator KENNEDY. I mean, tell me now. You have investigated it. You know these cases.

Dr. VAN HOUWELING. We can supply the details for the record. I do not have them with me, sir.

Since January 1, 1972, the U.S. Department of Agriculture reported to FDA positive DES findings in two cows, the breed of which are normally used for milk-producing purposes. FDA's investigation, however, disclosed that neither instance involved dairy cows being used for such purposes.

In the first case, 2.85 parts per billion DES was found in a liver sample collected by USDA in April 1972. FDA's followup investigation revealed that the animal was an adult Holstein cow that had been raised in a feed lot. In this lot, cows were purchased from dairies as cull animals and fattened a short time prior to slaughter. Investigation disclosed that a withdrawal feed may have been cross-contaminated with DES.

The other case involved a liver sample collected in June 1972 by USDA in which was detected a residue of .9 part per billion DES. FDA's investigation divulged that the dairy cow was not a lactating animal but had been fattened for slaughter. A preliminary report of investigation disclosed a possibility that the mixing equipment was not being adequately cleaned to prevent DES contamination of the withdrawal feed.

Senator KENNEDY. It certainly seems to me to be inexcusable in a dairy cow. I am not an agriculture expert; but I know it was prohibited, as I understood, for dairy cows. You cannot give us assurance now that those were not milk producing, can you—can you or can you not?

Have you got anybody here? There must be somebody here with preparation that has reviewed these cases.

Dr. VAN HOUWELING. I do not have detailed records with me. I know there was one case that was alleged to have been fed to a dairy cow and the investigation was found to be a false report, and I do not have the detailed information. I will supply it with the other case.

Senator KENNEDY. We had some of the samples of field reports. There have been a number of samples, one from Mr. Graham, dated December 6. I will make this a part of the record; but here is the second paragraph, and I quote:

Mr. Ringhausen's visit to Iroquois, South Dakota, was for the sole purpose of verifying these facts, prior to issuance of notice of hearing; and Mr. Ringhausen's visit did disclose the man's name was Mr. X and this individual had offered sheep for slaughter and not cattle.

It has Iroquois, S. Dak., as the middle of nowhere. We have no man in the State. Consequently, further followup would place undue burden on existing * * * and manpower. We do not believe the situation warrants any more work.

Dr. EDWARDS. I have no immediate explanation to that.

As you probably know, Senator, we have a tremendous manpower problem in the Food and Drug Administration. We have some 200 inspectors to monitor the food supply in this country, as a result of which we do have to establish priorities. Apparently the decision regarding investigation of the incident was based on the judgement of the Regional Director in accord with priorities he had established.

Senator KENNEDY. How can you give the assurances then, Mr. Commissioner, to the Congress, that that is just what you are going to do? Why are you not saying to the Congressman, throwing it right back up to Congress, telling us you cannot do the job we are charged to do because you have not got the manpower and resources?

Dr. EDWARDS. This is just exactly what we have done.

Senator KENNEDY. You did not do it through the Fountain Committee on this problem?

Dr. EDWARDS. We have told the Fountain Committee this on a number of occasions. Just because the Fountain Committee has not listened does not mean we have not said it.

Senator KENNEDY. You gave assurances?

Dr. EDWARDS. That is right.

Senator KENNEDY. How can you give assurances if you do not do the job?

Dr. EDWARDS. In considering the benefit-to-risk ratio, we believe the assurances we have given are justifiable.

Senator KENNEDY. Well, another report from the Minneapolis district, January:

It appears that we have reached the end of the line here, so to speak, as is the usual result in this type of case. We therefore request your concurrence to place the subject number in permanent abeyance.

Dr. VAN HOUWELING. I think that is an investigation of one of these reports received last year.

As we indicated, we have greatly speeded up our reporting procedure and our request for investigations.

Last year there was quite a timelag in some instances from the time we got the report from Agriculture, before we were able to get out and make the investigation.

In some instances it was quite a timelag from the time the sample was collected until the report was given to us. Some of these were complicated last year by those time lags.

There was a considerable period of time from the time the samples were collected until the investigation was conducted.

Senator KENNEDY. We have other samples. We are running too late to go through them, but there are other examples that I would think certainly does not satisfy any reasonable investigating procedures that I have been aware of.

How do you, Mr. Commissioner, consider the benefit-risk ratio? Is this a proper function for the Food and Drug Administration?

Mr. EDWARDS. I think very definitely. In order to put this in proper perspective, Senator, I would like to ask Dr. Simmons if he would

speak to the risk-benefit ratio, particularly as it relates to some of the subjects being discussed by some of the scientific experts this morning namely, the therapeutic use of DES and compare that with the rather different problem that goes with the use of DES in feed.

Dr. SIMMONS. Mr. Chairman, there are really a number of facts which are vital in an objective public record on this issue; so I apologize for the length of what I have to say to answer your question; but we do consider them very important.

I will have to start by going back to some of the specific things we have talked about today, starting with the Herbst study on human carcinogenesis.

We consider the Herbst study extremely important, and we hope for the benefit of all of science that it will be confirmed or rejected. It must be understood, certainly, by the Congress and the scientific community and the public that the Herbst study presented an association of diethylstilbestrol and vaginal cancer in offspring of mothers treated with that particular drug.

An editorial appearing with the article published in the New England Journal stated that it was an association which would have to be confirmed and certainly we would concur with that. That is one thing that it is important to consider.

Senator KENNEDY. I do not remember the doctor saying anything like you have said here.

Dr. SIMMONS. I am not talking about Dr. Herbst making that point. I am talking about others making an assumption that there is a causal effect. That is not so at present.

It is necessary to consider another control group that would substantiate that.

In the interest of science, we hope it will be followed up further. This is what Dr. Herbst is doing now and what we will be doing in some other studies.

Senator KENNEDY. Do you think it is bona fide carcinogen——

Dr. SIMMONS. Animal, not human.

Senator KENNEDY. How can you be so sure it is not human?

Dr. SIMMONS. I have no evidence.

Senator KENNEDY. Can you say it is not because——

Dr. SIMMONS. I have no evidence.

Senator KENNEDY. How can you give assurance?

Dr. SIMMONS. I am not giving you assurance. I am telling you I have no evidence that it is a human carcinogen.

Senator KENNEDY. There are researchers who believe that it is.

But continue.

Dr. SIMMONS. All right.

The other thing is, it is important to keep in mind that the dosage that was given in this association with females during pregnancy was thousands of times higher than may occasionally be found in an occasional liver and given at a crucial time in genesis. The risk even at that comparatively massive exposure was extremely small.

I think it is important for the public's benefit to remember that.

Now, to put things in further perspective.

Diethylstilbestrol is not a carcinogen, period. It is an estrogen. And it and other estrogens are carcinogens in certain instances.

Estrogens are also vital to life.

You, Senator, right now, are producing in your body 100 times more estrogenic substance every day than you are likely to eat in a piece of liver which you eat at any time or your family. That is the magnitude we are talking about.

Estrogen is vital to life, and with a very high dose it can be carcinogenic. It has not been demonstrated in humans to be carcinogenic at a normal dose.

In addition, as you know, in some instances, estrogens are actually treatment for carcinoma. There are carcinogens, Senator, all around us, every day, from the moment we are born; and they are now in the smoke in this room and they are in the atmosphere of Washington. We are exposed to them in the sun, in the soil, in our crops, and in a heavier concentration than we are likely to get in occasional liver. You know the figures on the environmental pollution, but every day in a city like Los Angeles, there are 1,000 to 2,000 tons of hydrocarbons thrown into the air, which contain carcinogens. Every time we burn an organic substance, we are likely to generate carcinogenic substances.

Everyone is aware of that in cigarette smoke and auto exhaust but few realize that carcinogens can be generated each time we burn food or fuel or cook our meats, especially charcoaling or grilling steaks.

And again, in higher exposure than we are speaking of here.

So, Senator, in answer to your original question, when we eat steak that is grilled, I think the honest answer is if there is an imminent hazard, it is more in charcoal grilled steaks and fires than DES residue in liver.

Senator KENNEDY. They have a choice as to whether they grill or broil. You are not offering them a choice when they pick up some meat at the market.

Dr. SIMMONS. Senator, any time we eat organic substances, we have the possibility of producing carcinogen. There is no way to prepare our meat supply without that possibility. In that respect, it is not a judgmental voluntary thing.

As I said, the other thing that we know about is that 5 to 41 percent less fat is produced in the meat on cattle fed diethylstilbestrol. There are people who would suggest that that also would produce less carcinogen, such as when heated.

In that respect, you might say it is beneficial. I am not going to make that judgment, but it should be considered.

And the other thing I think it is important to point out is that cholesterol is also shown to be a carcinogen in animals. This is another substance vital to human life.

Now, to go further to speak of the dose, the more important perspective that is important for all of us considering this issue is the dosage of diethylstilbestrol we are talking about.

In two parts per billion, in occasional liver samples, we are talking about a half microgram in a half-pound of liver.

As I said before, normal males and females produce every day about 100 to 200 times that estrogenic substance every day. Every day there are 8 million American women taking oral contraceptives which contain estrogens, again about 100 to 200 times the dose of diethylstilbestrol they may occasionally be exposed to.

The question I am really placing into the public record is what is the carcinogenic burden we are talking about? And that is what needs to be kept in perspective.

As far as the chance of exposure, when we testified before Congressman Fountain, we gave some interesting figures there.

You might be interested to know that your chance of eating liver that has two parts per billion diethylstilbestrol 4 days in a row are one in 706 million. That is the risk that we are talking about, about being exposed to this in the food supply as it currently exists.

Senator KENNEDY. You cannot give us these assurances now. The Commissioner just indicated the inadequacy of investigating manpower. We have just reviewed some of these investigations.

Before you give us assurances about what Americans can or cannot eat or what they can expect, I think you have to have a good deal more confidence in the kinds of investigating reports that say here that in Iroquois, S. Dak., is in the middle of nowhere, and you have no man in the State so consequently any further followup would place undue burden.

So before you start giving assurances to the American people, I think we ought to have a greater degree of confidence in what you can assure people about.

Dr. EDWARDS. I would like to correct the record on that one, Senator. We were talking earlier about our investigation. Once a positive is found it is on a responsibility to brake a follow-up investigation. The U.S. Department of Agriculture, on the other hand has the responsibility for testing the meat. I think the sampling that they are doing is statistically valid, and we can assure on the basis of this sampling. If we do not follow up adequately, that is a separate issue.

Senator KENNEDY. Why have 21 nations of the world banned DES to feed cattle? What do they know about it that we do not?

Dr. VAN HOUWELING. The use of DES in animal feed is particularly important when you are feeding cattle to fatten them for slaughter. This is done to a very limited extent in other countries.

Senator KENNEDY. Why do they ban it if it is done very limitedly?

Dr. VAN HOUWELING. There is no advantage to its use, so it is very easy to ban it.

Senator KENNEDY. Because they do not use much of it, it is easy to ban, and if they use a lot of it, it is more difficult to ban? Why is that?

Dr. VAN HOUWELING. They do not feed cattle for slaughter as we do in the United States.

Senator KENNEDY. Why did they ban it?

Dr. VAN HOUWELING. I started to finish by saying—

Senator KENNEDY. Do they know why they ban it? Do these 21 nations know why they ban it?

Dr. VAN HOUWELING. We have not been able to determine why they ban it.

The methods for feeding beef cattle and sheep in many countries are different than what is used in the United States and Canada. Cattle are range-fed in these countries and not fattened in a feedlot immediately prior to slaughter. DES is not considered to be effective in cattle that are exclusively range fed. FDA will contact each of the 21 countries that have reportedly banned DES and ask for more definitive information. This will be provided to the committee at a later date.

Senator KENNEDY. But they have been able to determine it.

Thank you very much.

We are going to recess briefly, because there is another vote; and then we will take up our other witnesses.

Thank you very much.

(Short recess.)

The subcommittee will come to order.

The next witness is Dr. Frank J. Rauscher, Director, National Cancer Institute, National Institutes of Health.

Dr. Rauscher, I welcome you and look forward to your testimony.

STATEMENT OF DR. FRANK J. RAUSCHER, JR., DIRECTOR, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH

Dr. RAUSCHER. Thank you, Mr. Chairman.

My presentation, Mr. Chairman, is essentially a synopsis of scientific data, some of which was presented this morning and, in part, other data that NCI has provided to the FDA.

First of all, in terms of its carcinogenicity in animals, DES has been shown to be carcinogenic in mice of both sexes since the late 1930's. DES along with other estrogens has been widely used as an experimental carcinogen. All have been shown to produce a variety of tumor types in several species.

The structure of DES and its main tumor responses are tabulated in appendixes 1 and 2. They include tumors of several endocrine-related organs but also tumors of other tissues such as kidney tumors.

Dose-response studies have shown that the carcinogenic effect is retained at low levels of administration. In addition, a combined effect of X-irradiation and DES which results in the potentiation of mammary carcinogenesis in rats was recently reported by various workers.

Further work along these lines, using progressively lower doses of radiation combined with DES, is underway in Dr. Segaloff's laboratory under contract from the National Cancer Institute.

A point that needs to be made is that all the types of tumors induced by DES can also be similarly induced by natural estrogenic hormones. However, DES is chemically different from natural estrogens and we do not know its molecular mechanism of action.

CARCINOGENICITY IN HUMANS

DES is used in therapy for its marked estrogenic activity in men and women. In this context, since estrogenic stimulation is well known as a causative factor of human cancers, DES, as an estrogen, must be considered a potential human carcinogen.

In addition, specific effects of DES have been recognized. Herbst et al., recently reported in *New England Journal of Medicine*, 284: 878-881, 1971, the development of adenocarcinoma of the vagina—an otherwise very rare type of cancer—in young women who had been exposed to DES during fetal life after their mothers were treated with DES during pregnancy.

This association has also been reported by Greenwald in previous testimony.

These tumors appeared at a very early age—late teens and early twenties—and they may therefore represent just the first manifesta-

tion of the carcinogenic effect which usually is manifested after a long latent period.

It is unfortunately quite possible that the population of women and men who have been exposed to DES during fetal life will represent a high-risk group for cancer, possibly at different sites—for example, breast, testes, pituitary, adrenals.

Therapeutic use of much higher doses of DES in male patients, in the therapy of prostatic cancer, also leads to the growth of mammary tissue in men and in some cases to the development of mammary cancers.

Finally, it has been known for many years that occupational exposure to estrogenic hormones—in laboratories and in manufacturing plants—can lead to growth of mammary tissue in men.

In conclusion, it can be stated that DES is definitely a carcinogenic substance for several animal species and apparently for the human.

Senator KENNEDY. You are satisfied it is also a carcinogenic substance for human beings?

Dr. RAUSCHER. The data we have right now, largely through the two studies reported this morning, are highly indicative that this is true. It is difficult to answer your question directly.

As a scientist, we know that the only real direct way of doing this is to inoculate test people and of course this would never be done. Rather than do that, we rely on epidemiologic information such as that presented this morning.

Senator KENNEDY. I suppose there is always more information that one could glean from additional research and testing. But as I understand, just from the available information, you believe that there is a reasonable presumption to assume that it is carcinogenic—

Dr. RAUSCHER. In my judgment; yes. Certainly with high doses, it is very reasonable to assume and—

Senator KENNEDY. You are not prepared at this time to give the degree or the quantities that would be necessary to induce cancer?

Dr. RAUSCHER. No; that is one of the problems. As the Commissioner mentioned this morning, we have to do far more at very low doses. But this is time consuming to the point of many years, frankly.

Senator KENNEDY. You cannot say at what levels, over what periods of time it will induce certain cancers. But then we cannot say that because there are some traces for a period of time that it will not mean that there is an increase in instances of cancer—

Dr. RAUSCHER. That is right; we cannot. I do not think we can say that about any compound. Of the thousand chemicals known to be cancer causing in animals, about 20 or 22 of these are known to be cancer causing in men.

I do not think that for one of these we can answer that question with any definitions. Part of the problem is that we are such a heterogeneous population. It depends on who is exposed at what time and what other factors he is exposed to. This is part of my concern about a presumed chemical carcinogen in man. It is not only that chemical, but it may be the chain reaction it contributes to which may eventually result in cancer. It is almost impossible, therefore, to pin down which chemical and at which dose.

Senator KENNEDY. Doctor, you are the chief, the distinguished head of the Institute. Just as a matter of conviction, if you felt there were some means of reducing any sort of exposure to DES, even if we do not know the precise amount which might cause cancer, it is still advisable to reduce that exposure to such—

Dr. RAUSCHER. Mr. Chairman, my job is to prevent people from getting cancer and to prevent the continuation of cancers. When I see any data that may be with reasonableness assigned to a potential carcinogenic role, I think the prudent course is to try to remove that possible carcinogenic stimulus from the environment.

Senator KENNEDY. As you point out, I suppose you have to balance that viewpoint against the other economic implications—

Dr. RAUSCHER. This must certainly be considered. For instance, in my own field, just to stay within cancer, we know that certain estrogens are potent chemotherapeutic agents for the treatment of men with prostatic cancers. So here clearly it is a balance, but our judgment is—and I think this is borne out by many studies now—that the use of that particular drug, although it may be carcinogenic, is far more valuable in warding off or controlling that particular tumor that the person has now. There is a risk-benefit ratio.

Senator KENNEDY. As I understand, the example you gave, Doctor, is a medical consideration and not an economic consideration.

Dr. RAUSCHER. That is right.

Senator KENNEDY. You are more sympathetic to considering the medical implications of it, I suppose, as a researcher.

Dr. RAUSCHER. Other economic or other kinds of considerations clearly must be considered. Additional studies may show or may not show that low doses of a particular chemical contribute to man's carcinogenic burden. In the case of DES, if this can be shown—and many more studies need to be done, admittedly—but if it is shown that way, I do not think the other economic benefits would outweigh removing a cancer causer from our environment, if in fact it is shown to be that.

Senator KENNEDY. As I understand further, you think that, although we cannot tell exactly the danger that is provided, at least we ought to determine that first before continuing even with the low distribution of DES.

Dr. RAUSCHER. I think these are testable hypotheses, and additional data will put us on more firm ground.

Senator KENNEDY. How long would that really take, do you think? I know it is always difficult to predict and project, but would your agency be willing to help in the research and cooperation with the Food and Drug—

Dr. RAUSCHER. Yes, indeed.

Senator KENNEDY (continuing). To try and make that determination, so if it really is not a danger, we could reinstitute it?

Dr. RAUSCHER. Absolutely. We are doing that now. Some of the studies you heard this morning were, in part at least, supported by the National Cancer Institute. The problem here, which I think is essential to much of the discussion that you heard this morning, is that with most drugs that you might consider toxic or hazardous to man, you know that it is toxic within 10 minutes to 10 days to 2 weeks; at least, very soon. With cancer causers—and we already have this information—it can take 20, 30, or more years.

There is evidence that tumors occur, for instance, in mammary cancer at a peak age in women between 25 to 45. Something happens in the first years of the life which eventually shows up as cancer. This may be the very thing we are talking about, with very low doses of a chemical like DES.

It could take another 10 or 20 years. The only way to determine that is to survey large numbers of the population, and this we are doing and continuing to do in collaboration with our colleagues in the FDA.

Senator KENNEDY. That is being done by research laboratory rather than experimenting with our own people?

Dr. RAUSCHER. The whole Nation is a research laboratory when it comes to this kind of population survey; yes.

Senator KENNEDY. Can you tell me whether in your own research or your own knowledge, why some of these other countries have banned DES? The Cancer Institute has tremendous contact with other nations and countries, and some research—

Dr. RAUSCHER. I do not know the specific answer to that question, but I have been told by some of my staff that these nations must be concerned about the knowledge that we have had for 30 years that DES is a carcinogen in animals. Certainly they are aware, as we are, of the literature—studies provided by my two colleagues this morning—that pregnant women put their female daughters at risk. I am concerned and I am impressed, frankly, with the fact that not only have other nations banned it, but two nations have banned the import of meat from our country. I can only presume they are concerned about DES as a potential health hazard.

As far as I know, neither they nor we have any direct evidence that DES causes cancer in people when they eat it at levels now being detected in the few samples of meat or liver in which it has been found. We have no direct evidence; and to that extent, my colleagues that appeared before me are absolutely correct.

Senator KENNEDY. But they do have good evidence that it does not?

Dr. RAUSCHER. That is right.

Senator KENNEDY. And that there has been research which would indicate that DES in other amounts has been at least to the satisfaction of these researchers, a primary cause for—

Dr. RAUSCHER. That is right. There is critical information that we do not have now, but which we are trying to get.

For instance, we know that DES is a chemical structure which is different from the naturally occurring hormones. Does this mean that it is a more potent carcinogen? We do not know yet, but we can find out. We do not know, for example, whether very young children exposed to this may have a higher response rate than you and I as adults. There are examples of this in cancer literature which show if you are young, you respond more quickly than if you are old. We do not have enough of this kind of information. Until we get it, I think the prudent course is the position I have taken before.

Senator KENNEDY. Which is to ban it?

Dr. RAUSCHER. Which is to insure, again in cooperation with the FDA, that man is not exposed to this material.

Would you like me to continue?

Senator KENNEDY. Yes.

Dr. RAUSCHER. Now, in terms of the extent of exposure in the population, far higher exposures of individual people to DES occur as a result of its drug use and of occupational exposure.

The administration of DES has recently been recognized by the FDA as contraindicated during pregnancy. The annual production as an animal feed additive is approximately 50,000 pounds per year.

The extent of occupational exposure is largely dependent on the large-scale production of DES for use in animal feed. A survey of occupational sources of exposures and an epidemiologic study of the exposed populations is highly recommended and is being done.

Finally, we come to the use of DES as a feed additive. Current use practice is reported to lead to the presence of detectable residues in over 1 percent of the samples of beef liver that have been analyzed. The doses that are present in such residues have been of two parts per billion or more. In a single 150-gram serving of beef liver, at two parts per billion, the intake would be about 0.3 micrograms. It should be noted that DES has not been detected, as far as I know, in any other edible portion of animals in which DES was detected in the liver.

The extent of use of liver in the diet varies, but liver is an item of large consumption.

The main reasons for concern over this environmental carcinogenic hazard are the following.

Individual doses of about one microgram of DES, ingested at long intervals, could add to the existing carcinogenic burden for the population. However, as long as the use of DES in feed is allowed to continue, there could occur instances of even higher contamination.

As mentioned above, another reason for concern about DES use is the occupational hazard to those people exposed to it continuously for long periods of time during the manufacture of the large amounts of DES required by the feed industry.

Finally, Mr. Chairman, and in order to put this testimony in objective perspective, I must say that at the present time, our data do not incriminate DES as a human carcinogen when ingested at levels currently being detected in beef liver.

This fact, however, will not allow us to forget our concern when you recall that DES has been used for only approximately 15 years as an additive to feed grain; even with the relatively high doses used in the treatment of pregnant women it has taken 14 to 20 years to determine that cancers were induced in young women whose mothers received this drug during pregnancy.

My point here, to deviate just a moment, is we simply do not have enough years under our belt to determine whether even low doses have any carcinogenic effect or not in man.

It is certainly true, as has been stated by some, that there is far more chemical substance capable of causing cancer in tobacco smoke or smoke which is generated during the process of charcoaling meat than there is in the occasional sample of liver found to be contaminated with DES.

Nonetheless, it is important also to point out that exposure to these sources of carcinogens are largely matters of personal choice and can therefore be avoided.

In conclusion, therefore, DES is (a) a potent carcinogen for animals, and (b) an apparent carcinogen for man under specific circumstances.

These are the facts that we provided to the FDA.

Senator KENNEDY. Doctor, you have been enormously helpful today on this matter, as you are on some of the others.

The Cancer Institute, knows the full commitment of the Congress and the President on this whole area, and I think it is in excellent hands. You have been enormously valuable to us here this morning.

You have given us a very balanced and valuable comment. I understand from your conclusions that purely from a health consideration, given what you know about this, you would like to reduce even the limited exposure of American people to DES.

Dr. RAUSCHER. I think until we know more about it, this would be the prudent choice.

(The prepared statement of Dr. Rauscher follows:)



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

STATEMENT

BY

FRANK J. RAUSCHER, JR., Ph.D.

DIRECTOR, NATIONAL CANCER INSTITUTE

NATIONAL INSTITUTES OF HEALTH

ON DIETHYLSTILBESTROL (DES)

BEFORE THE

SUBCOMMITTEE ON HEALTH

SENATE COMMITTEE ON LABOR AND PUBLIC WELFARE

JULY 20, 1972

Mr. Chairman and Members of the Subcommittee:

I appreciate the opportunity to appear before you to present the scientific data on the carcinogenic hazards of diethylstilbestrol (DES).

A. Evidence of Carcinogenicity

1. Carcinogenicity in Animals. DES has been shown to be carcinogenic in mice of both sexes since the late 1930's. DES along with other estrogens has been widely used as an experimental carcinogen. All have been shown to induce a variety of tumor types in several species. The structure of DES and its main tumor responses are tabulated in Appendices 1 and 2. They include tumors of several endocrine-related organs but also tumors of other tissues such as kidney tumors. Dose-response studies have shown that the carcinogenic effect is retained at low levels of administration. In addition, a combined effect of X-irradiation and DES which results in the potentiation of mammary carcinogenesis in rats was recently reported at Segaloff et al (Cancer Research 31:166-168, 1971). Further work along these lines, using progressively lower doses of radiation combined with DES, is under way in Dr. Segaloff's laboratory under contract from the National Cancer Institute (NIH-NCI-E-71-2131).

A point that needs to be made is that all the types of tumors induced by DES can also be similarly induced by natural estrogenic hormones. However, DES is chemically different from natural estrogens and we do not know its molecular mechanism of action.

2. Carcinogenicity in Humans. DES is used in therapy for its marked estrogenic activity in men and women. In this context, since estrogenic stimulation is a well-known causative factor of human cancers, DES, as an estrogen, must be considered a potential human carcinogen. In addition,

specific effects of DES have been recognized. Herbst et al. recently reported in New England Journal of Medicine 284: 878-881, 1971, the development of adenocarcinoma of the vagina (an otherwise very rare type of cancer) in young women who had been exposed to DES during fetal life after their mothers were treated with DES during pregnancy. This association has also been reported by Greenwald (Hearings before the Subcommittee on Government Operations, House of Representatives, "Regulation of Diethylstilbestrol," November 11, 1971, pp. 9-20, and New England Journal of Medicine 285: 390-392, 1971). These tumors appeared at a very early age (late teens and early twenties), and they may therefore represent just the first manifestation of the carcinogenic effect which usually is manifested after a long latent period. It is unfortunately quite possible that the population of women and men who have been exposed to DES during fetal life will represent a high-risk group for cancer, possibly at different sites (e.g., breast, testes, pituitary, adrenals). Therapeutic use of much higher doses of DES in male patients, in the therapy of prostatic cancer, also leads to the growth of mammary tissue (gynecomastia) and in some cases to the development of mammary cancers. Finally, it has been known for many years that occupational exposure to estrogenic hormones (in laboratories and in manufacturing plants) can lead to growth of mammary tissue in men.

In conclusion, it can be stated that DES is definitely a carcinogenic substance for several animal species and apparently for the human.

B. Extent of Exposure in the Population

Far higher exposures of individual people to DES occur as a result of its drug use and of occupational exposure. The administration of DES has

recently been recognized by the FDA as contraindicated during pregnancy. The annual production as an animal feed additive is approximately 50,000 pounds per year.

The extent of occupational exposure is largely dependent on the large-scale production of DES for use in animal feed. A survey of occupational sources of exposures and an epidemiologic study of the exposed populations is highly recommended. Such a suggestion has been forwarded to the National Institute of Occupational Safety and Health.

Finally, we come to the use of DES as a feed additive. Current use practice is reported to lead to the presence of detectable residues in over 1% of the samples of beef liver that have been analyzed. The doses that are present in such residues have been of 2 ppb or more. In a single 150 g serving of beef liver, at 2 ppb, the intake would be about 0.3 microgram. It should be noted that DES has not been detected in any other edible portion of animals in which DES was detected in the liver. The extent of use of liver in the diet varies, but liver is an item of large consumption.

The main reasons for concern over this environmental carcinogenic hazard are the following:

Individual doses of about 1 microgram of DES, ingested at long intervals, could add to the existing carcinogenic burden for the population. However, as long as the use of DES in feed is allowed to continue, there could occur instances of higher contamination.

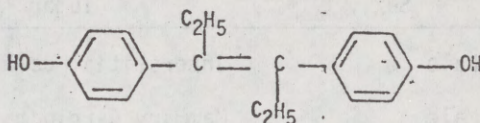
As mentioned above, another reason for concern about DES use is the occupational hazard to those people exposed to it continuously for long periods of time during the manufacture of the large amounts of DES required by the feed industry.

Finally, Mr. Chairman, and in order to put this testimony in objective perspective, I must say that at the present time our data do not incriminate DES as a human carcinogen when ingested at levels currently being detected in beef liver. This fact, however, will not allow us to forget our concern when you recall that DES has been used for only approximately 15 years as an additive to feed grain; even with the relatively high doses used in the treatment of pregnant women it has taken 14 to 20 years to determine that cancers were induced in young women whose mothers received this drug during pregnancy. It is certainly true as has been stated by some that there is far more chemical substance capable of causing cancer in tobacco smoke or which is generated during the process of charcoaling meat than there is in the occasional sample of liver found to be contaminated with DES. Nonetheless, it is also important to point out that exposure to these sources of carcinogens are largely matters of personal choice and can therefore be avoided.

In conclusions, therefore, DES is (a) a potent carcinogen for animals, and (b) an apparent carcinogen for man under specific circumstances. These are the scientific facts that are being weighed by the FDA in exercising its regulatory responsibilities.

APPENDIX I.

1. Structural Formula for DES:



2. Accepted Chemical Abstract Registry Name and Number:

4,4'-Stilbenediol, α,α' -diethyl (#56,531)

3. Synonyms for DES:

alpha, alpha'-Diethyl-4,4'-stilbenediol	Milestrol
Bio-des	Neo-Oestrano 1
3,4-Bis(p-hydroxyphenyl)-3-hexene	Oestrogenine
Comestrol estrobene	Oestromenin
Cyren A	Oestromensyl
DEB	Oestrogenin
Di-Estryl	Palastrol
trans- α,α' -Diethyl-4,4'-stilbenediol	Perocetrine Oestrogenique Iscovesco
α,α' -Diethylstilbenediol	Serral
α,α' -Diethyl-4,4'-stilbenediol	Sexocratin
Diethylstilbestrol	Sibol
Diethylstilbestrol	Stil
trans-Diethylstilbestrol	4,4'-Stilbenediol, 2,2'-diethyl-
4,4'-Dihydroxy- α,α' -diethylstilbene	Stilbestrol
3,4'(4,4'-Dihydroxyphenyl)hex-3-ene	Stilbestrol, diethyl-
Domestrol	Stilbatin
Estilbin "MCO"	Stilboestroform
Estrobene	Stilboestrol
Estrosyn	Stilkap
Fonatul	Stil-Rol
Grafestrol	Synestrin
3-Hexene, 3,4-bis(p-hydroxyphenyl)-	Synthoestrin
HiBestrol	Syntofolin
Micrcest	

APPENDIX 2

Strain	MOUSE	
	Sex	Tumor Type
BALB/C3H	Male	Interstitial Cell Tumor
C3H	Male	Mammary Carcinoma
	Castrate Male	Mammary Carcinoma
Strain A	Castrate Male	Mammary Carcinoma
	Female	Mammary Carcinoma
--	Male	Testicular Tumors

Strain	RAT	
	Sex	Tumor Type
--	Female	Pituitary (Hanno-Luteotrophic)
	Male	Pituitary (Hanno-Luteotrophic)
Sprague-Dawley	Female	Ovarian
		Uterine
--	Female & Male	Bladder
--	Female & Male	Adrenal

Strain	HAMSTER	
	Sex	Tumor Type
--	Male	Renal Tumor
	Male	Pituitary Chromophobe Adenomas

MAIN TUMOR RESPONSES TO DES

Senator KENNEDY. Thank you very much.

Well, I have another vote on the floor of the Senate.

We have one more witness, and we will come back and hear the witness.

(Short recess.)

Senator KENNEDY. The subcommittee will come to order to hear Dr. Duane Flack, chairman, Task Force Committee on DES, American National Cattle Association.

STATEMENT OF DUANE E. FLACK, D.V.M. CHAIRMAN, TASK FORCE COMMITTEE, DES, AMERICAN NATIONAL CATTLE ASSOCIATION

Dr. FLACK. Thank you, Senator.

On behalf of the American National Cattlemen's Association, thank you for this opportunity to present comments relative to the current interests and proposals concerning the use of diethylstilbestrol—DES—in animal feeds.

It is my understanding that the purpose of this hearing is to discuss the proposed banning of DES by the Food and Drug Administration—FDA—and pending hearings associated with that proposal.

I am sure there is concern in this committee in what would appear to be an increased incidence in the occurrence of DES residues in liver samples. The question is undoubtedly implied, if not stated, why not ban DES now? I am privileged and happy to speak to these points.

The use of this efficiency promoting additive has been a commonly accepted practice for nearly two decades. It has been estimated that 80 to 90 percent of the cattle on feed receive DES or similar hormonal products in one form or another.

Its advantages have been available to all segments of the industry. Simple calculations would indicate that DES is responsible for the production of literally billions of pounds of wholesome, pure beef per year.

If the efficiencies realized in just the finishing phase of cattle production were to be lost, sirloin steak would be 10 to 15 cents per pound higher than it is today.

That could be expanded against the number of pounds consumed today to equate \$200 million to \$400 million added food bill to this Nation's consumers.

Senator KENNEDY. As I understand, the Department of Agriculture studies estimate that the average cost would be 3 cents per pound, with a total of \$3.65 per year per person eating 110 pounds of the meat—I am just wondering if you had a chance to examine those studies which they have done on this subject; and if you have had a chance to do so, what is your reaction to those studies?

Dr. FLACK. Yes, sir; I have.

I read through the report prepared for the USDA on this subject. The report was designed on three hypothetical circumstances that then led to conclusions that \$3.85 per person would be the added cost.

The figure I am using, 10 to 15 cents per pound at retail level for cuts of sirloin steak, is based upon studies and investigations we have conducted ourselves, by taking groups of cattle, placing them on

feed, without use of any additive, following those cattle through the entire feeding period and calculating the measurable cost against those of comparable cattle using the drug.

You will come up with a cost of approximately 3 to 5 cents a pound, on a live cattle basis.

To convert that to 60-percent yield in the packing plant and apply the formula for various cuts of meat—all meat is not priced the same throughout the carcass—you come up with very legitimate estimate of 10- to 15-cent increase in cost for higher priced cuts of beef, such as sirloin steak.

In a marketplace that is today as concerned as it is about the high price of beef, I think this is pertinent. If for no other reason, doesn't this make it important not to ban the use of DES unless it is truly necessary? Is it?

DES has been used with unquestioned confidence in its safety and efficiency. It has only been in the last year, and more specifically in the past several months, that we have heard accusations, claims and counterclaims, reports of increased residue instances, and widespread publication of each.

These events have brought confusion and disagreement among the regulatory agencies, scientific and commercial representatives, the cattle industry itself, and most crucial of all, that ubiquitous group known as the consumer.

To the best of my knowledge, never has a residue of DES been detected in carcass beef even though samples are tested from the same animals from which other tissues are submitted. I have not heard of the first case to be identified of a human illness of any kind caused by the ingestion of DES in the form, the manner, or quantity represented in the residues identified in a few isolated liver samples.

I understand that chemicals of comparable estrogenic activity are present in many common natural foods at relatively much higher levels.

I also understand that DES specifically is commonly used for the therapeutic treatment of several conditions in men and women at tremendously high levels as compared to those we are discussing.

This is where it appears some problem has occurred. But surely some kind of dose to effect; and benefit-to-risk ratio should be applied. This is certainly the practice with any other therapeutic drug. The relation between therapeutic dose and tissue residue level are ridiculously far apart.

These facts being true, I find it alarming that there is being generated an impression that this Nation's meat supply is contaminated when, in fact, this simply is just not the case.

Right in this room today, we have heard references made to meat specifically, or steak. To date, all monitoring testing done by the USDA has not identified a residue of this chemical in carcass meat.

The beef cattle industry is concerned.

The ANCA has appointed the ad hoc committee which I represent today. Ours is a multi-billion-dollar industry. I think we rightfully have more sincere interest in the wholesomeness, purity, and quality of our product than all the scientists and legislators you could gather to discuss the subject.

Senator KENNEDY. On your committee, what is the makeup of that committee? How many members?

Dr. FLACK. It is a committee of four people, represented from throughout the Western part of the United States.

We have Dr. Jim Nofziger, consultant nutritionist from California; there is myself as cattle feeder and veterinarian; a man from Idaho, Mr. Tom Hovenden, executive secretary, and director of Idaho Cattle Feeders; Tom Herrick, president of the Texas Cattle Feeders Association.

Senator KENNEDY. You have got a researcher and yourself, a veterinarian, who would be evaluating the scientific information?

Dr. FLACK. Yes, sir; although the real purpose of the task force is not a research committee.

The committee was formed by ANCA for the specific purpose to act as liaison between regulatory agencies and the cattle feeding industry in the proper use and control of the product, not in the technical investigation or scientific aspects of the product itself.

We have heard comments concerning the use of DES in foreign countries.

I might just touch on that.

Specifically, there is some confusion as to what really constitutes a product that is being banned.

From one standpoint, you could refer to it as a specifically outlawed product where a legislative mandate has been passed, that this product will not be used.

On the other side of the picture, and I think much more commonly, the circumstances you have been referring to as far as the 21 countries, it just merely has not been approved for use.

In this, it is significant at least to point out that the husbandry and the cattle production practices of the rest of the world and the countries specifically that you are referring to are certainly much different than those in the United States today.

We probably have the only place in the world where cattle are under confinement, fed high concentrates for finishing of the beef to the condition that the American consumer desires and demands.

We can always take a great deal of pride in the amount of respect that our product has and the demand for our type of beef throughout the world.

Senator KENNEDY. Even though what you are really saying there is that they do not use it, still they banned it; why have they banned it?

Dr. FLACK. I think in many of the cases—I am not experienced or well versed in all phases of international law or regulatory services of the various countries—but I think in many of the countries it has not been banned. It has not been approved. This has really been a test of contention here in this country.

In some circumstances it has been legislatively banned, as I understand it. Many of these bannings go back many, many years before even the common use of the drug in animal feeds. I think there has probably—and I cannot speak for the legislative actions of other countries—has been a fear, so to speak, of just the classification “hormone”—there have been some other cases specifically, at least where the claim has been made that this has been used as a means of a nontax trade barrier for restriction of importation of American beef.

Senator KENNEDY. Argentina was in 1961; that is official bulletin; that is the list here. I am not going to take up your time by going through it.

I will make the list of the countries, what countries have undertaken the ban, included in the record at the appropriate place, so as not to interrupt the witness' testimony.

There are, of course, two countries which banned the importation of American beef because they used DES: Sweden and Italy. I am not sure they were great importers of beef, but they have taken that action.

Dr. FLACK. Here again, I cannot speak for this action or the reason why. It has been reported by industry people here that this has been done as a means of a trade barrier.

The apparent increased instances of residue identifications do not appear to be due to produce abuse. It does seem to be due to an accelerated monitoring program and simultaneous application of a much more highly sophisticated assay technique.

I am advised by competent authorities that the reliability of the gas liquid chromatographic—GLC—technique is questionable at levels less than one part per billion.

The availability of competent people and facilities to conduct GLC determinations are extremely limited. The industry needs a capability to monitor its own program. It takes time to develop these services.

I feel confident in saying that management practices and control of DES have improved significantly over the past year. This has been stimulated by an awareness that a problem does exist.

What happened, then, when residues have been identified? I feel that it would be erroneous to imply that some cases of failure to comply with the regulatory laws have not occurred. Where this is shown to be the case, the full weight of the law should be applied.

Intentional abuse or disregard of withdrawal regulation has not been a significant factor, however.

Inadvertent cross-contamination, for one reason or another, seems to have been the most common cause. Carelessness has happened, human error, poor management or manufacturing practices, have been identified. These are problems which are identifiable and manageable; they are not the exotic, profound, and mysterious.

Other questions of a more technical nature are also arising. The carcinogenicity of DES has been legitimately challenged.

Senator KENNEDY. Why do you think the incidence has been—you think the incidence has been increasing; you have given some of the ways and reasons; but you say they are controllable; yet, we find from those reports there has been some increase—

Dr. FLACK. There are two factors. No. 1, there have been a lot more tests run. We have larger total number tests.

No. 2, the tests or the specificity of the tests critical to two parts and below per billion really are levels that by prior methods would have been considered zero.

Senator KENNEDY. But the total numbers are higher, as I understand; the figures, the percentages, are higher than we were a year ago?

Dr. FLACK. Yes, sir; and for that reason, because of the increased ability of the test, to detect very, very small levels, which was not the case a year ago, or previously.

Senator KENNEDY. Do you think as the tests get better that it is going to show other increases?

Dr. FLACK. That would be a matter of conjecture on my part. I cannot answer that. I think without a doubt the industry is responding to this. In other words, take the case of the individual user, the man on the farm who has been using this product, or others, in full confidence that his management practices were sufficient and now with the new test, which is pointing out that we do have a residue problem below levels previously detectable, we are finding a very extreme interest in the industry to improve management techniques and manufacturing practices.

I feel confident it will be done. The biological significance of these ultramminute traces, or the relationship to previously identified levels, has not been established.

I would quote—and this itself has actually been repeated by several different people this morning—one of the witnesses this morning, Dr. Greenwald, did state that, "It has been noted that as we have studied vaginal cancer patients in the State and mothers all treated therapeutically, there is no reason to suspect that DES in food caused any of the tumors." This is a point we feel needs a great deal more investigation and explanation.

What is the importance of the fact that residues have only been identified in a small percentage of liver and a few kidneys? What is the relationship of this to our total beef supply?

Are other means available to monitor and control potentially contaminated livers? Not all routes of original administration have been identified with residue problems?

The fact that DES is widely used, and yet well over 97 percent of the Government's objectively collected samples have shown no residue, bears undisputable evidence that the product is being safely used. We need to determine, then, what management and manufacturing practices need to be applied in those isolated instances to insure that no residues will occur in violation to regulation.

And, finally, what constitutes none? It has been stated on many occasions by competent scientific investigators that mankind, our environment, Mother Nature, herself, could not comply with an absolute zero attitude on anything.

These are not answers for me to determine. These are topics and discussions that need to be heard. For this reason, ANCA heartily endorses the efforts of FDA to bring this matter out in the open before taking further action.

We feel confident that these hearings will bring to light opportunities to solve problems and allow continued use of this tool. Take away a tool responsible for a 10-percent advantage in efficiency of production, and that cost will be reflected throughout the chain of production all the way to the consumer.

On the other hand, the unquestioned confidence of the consumer is the most valuable asset of the American agricultural producer. DES or any other product is of no value if it hinders product quality, wholesomeness, or safety. Such determination, however, must be based on fact, not emotion; true relevance, not speculative potentiality; and, above all, reason, not politically motivated and unfounded accusations.

Senator KENNEDY. Thank you very much, Dr. Flack, for your testimony. We have heard that there is a potential hazard to workers exposed to cattle using DES. Are you aware of this, concerned about it, or is your committee going to consider this as well?

Dr. FLACK. We have had no indications where any apparent problems have arisen. In my own schooling and experience as a veterinarian, prior to becoming directly involved in the feeding industry, I have heard reports of several problems of this nature, originating clear back with the original use of the product. Some of the investigators at laboratories that were under very close exposure over a period of time may have had some problem. I do not know of any reported problems of this nature since then, and it is not something we have considered as a problem in the feeding industry.

Senator KENNEDY. Do you plan to file an objection with the Food and Drug Administration?

Dr. FLACK. We are not a licensed manufacturer, so we are therefore not in a position to do so. We are a user, not a licensee.

Senator KENNEDY. You do not have the ability to do so under the regulations?

Dr. FLACK. No, sir. I understand it is merely the licensed manufacturer of the product who is in a position to file with the FDA.

Senator KENNEDY. Though I have some reservations about your position, I think you ought to be entitled to make those recommendations.

Dr. FLACK. I can assure you that we are confident these are being filed.

Senator KENNEDY. All right.

If this were to be banned, would it work an economic hardship on some cattle feeders more than others, or would the ban be served as an economic hardship equitably across the board, so to speak?

Dr. FLACK. The point was made earlier today in testimony, the comparison or the relative position of feeder against feeder, big and small.

This would, the banning of the product, totally taken completely out of use, put the feeding industry on an equal basis across the board; so there would be no advantage or disadvantage. I would like to extend on that a little bit.

The problem would come and it would be one that would be hard to identify who is going to pay the bill.

If we take a product which originates as calf on a ranch that has a value, and we end with a piece of meat on a consumer plate, and we reduce by a factor of approximately 10 percent, the efficiency of the production of that product, that cost has to be paid, whether it is less money for the original calf or whether it is more money for the eventual piece of meat, or if it is merely a decreased quantity which is to be consumed, a big concern of the cattlemen in this country.

Calendar No. 256

94TH CONGRESS
1ST SESSION

S. 963

[Report No. 94-264]

IN THE SENATE OF THE UNITED STATES

MARCH 5, 1975

Mr. KENNEDY (for himself and Mr. SCHWEIKER) introduced the following bill; which was read twice and referred to the Committee on Labor and Public Welfare

JULY 3, 1975

Reported, under authority of the order of the Senate of June 26, 1975, by Mr. KENNEDY, from the Committee on Labor and Public Welfare, with amendments

[Strike out all after the enacting clause and insert the part printed in italic]

A BILL

To amend the Federal Food, Drug, and Cosmetic Act to prohibit the administration of the drug diethylstilbestrol (DES) to any animal intended for use as food, and for other purposes.

- 1 *Be it enacted by the Senate and House of Representa-*
- 2 *tives of the United States of America in Congress assembled,*
- 3 ~~That section 301 of the Federal Food, Drug, and Cosmetic~~
- 4 ~~Act is amended by adding at the end thereof the following~~
- 5 ~~new subsections:~~
- 6 ~~“(q) The administering of the drug diethylstilbestrol~~
- 7 ~~(DES) to any animal intended for use as food or any animal~~
- 8 ~~the product of which is intended for use as food.~~
- 9 ~~“(r) The introduction or delivery for introduction into~~

1 interstate commerce the drug diethylstilbestrol (DES) for
2 use as a postcoital contraceptive for a one-year period begin-
3 ning on the date of the enactment of this subsection”.

4 *TITLE I—CANCER PREVENTION*

5 *SEC. 101. Section 301 of the Food, Drug, and Cos-*
6 *metic Act is amended by adding at the end thereof the fol-*
7 *lowing new subsection:*

8 “(q) The introduction or delivery for introduction into
9 interstate commerce of the drug diethylstilbestrol (DES)
10 for purposes of administering the drug to any animal in-
11 tended for use as food or to any animal the product of which
12 is intended for use as food.”.

13 *SEC. 102. Section 502 of the Food, Drug, and Cosmetic*
14 *Act is amended by adding at the end thereof the following*
15 *new subsection:*

16 “(q)(1) If it is, or purports to be, or is represented
17 as a drug composed wholly or partly of diethylstilbestrol
18 (DES), unless—

19 “(A) its label bears the following statements:

20 “(1) WARNING—THIS DRUG MAY
21 CAUSE CANCER;

22 “(2) THIS DRUG MAY NOT BE USED
23 AS A CONTRACEPTIVE AFTER SEXUAL
24 INTERCOURSE EXCEPT IN CASES OF

1 RAPE OR INCEST OR A COMPARABLE
2 MEDICAL EMERGENCY;

3 “(3) THIS DRUG MAY NOT BE TAKEN
4 UNLESS A PATIENT OR PATIENT’S
5 LEGAL GUARDIAN HAS GIVEN HIS
6 WRITTEN CONSENT AFTER FULL VER-
7 BAL DISCLOSURE BY THE ATTENDING
8 PHYSICIAN OF THE RISKS, BENEFITS,
9 AND ALTERNATIVE METHODS OF
10 TREATMENT; and

11 “(B) each and every capsule or tablet is pre-
12 packaged, by the drug producer, in units which contain
13 the appropriate number of capsules or tablets for the
14 desired course of treatment and the statements required
15 by subsection (q)(1)(A) of this section are con-
16 spicuously placed on the label next to the capsules or
17 tablets so as to permit the patient an opportunity to read
18 the statements during the entire prescription period. The
19 letters contained in the statements required by subsection
20 (q)(1)(A) of this section are twice as large in size as
21 any other words and statements required by this Act; and

22 “(C) there is a multi-copy ‘informed consent form’
23 which is deemed part of the label for the purpose of this
24 Act; and

1 “(D) a copy of each and every executed informed
2 consent form and a written record of each and every at-
3 tending physician’s prescription for such drug is sub-
4 mitted by the attending physician to the Secretary at such
5 times and in such form as the Secretary may require but
6 not less than four times a year. Each and every executed
7 informed consent form and prescription record sub-
8 mitted to the Secretary shall contain both the attending
9 physician’s license number and the name of the State
10 which issued such license number; and

11 “(E) a copy of each and every prescription for
12 such drug which has been presented to a pharmacist is
13 submitted by the pharmacist to the Secretary at such
14 time and in such form as the Secretary may require and
15 not less than four times a year. Each and every prescrip-
16 tion submitted to the Secretary shall contain both the
17 attending physician’s license number and the name of
18 the State which issued such license number.

19 “(2)(A) For the purpose of this subsection an ‘in-
20 formed consent form’ means a form issued by the Secretary
21 and approved by the National Commission for the Protection
22 of Human Subjects of Biomedical and Behavioral Research
23 (hereinafter in this subsection referred to as the ‘Commis-
24 sion’) and is fully explained by the attending physician to
25 the patient and is thereafter executed by the attending

1 physician and patient or the patient's legal guardian. If the
2 Commission fails to take action within sixty days after the
3 Secretary submits the proposed informed consent form, it
4 shall be deemed approved.

5 “(B) Drug producers shall not be held liable for mis-
6 branding under subsection (g)(1) (D) and (E) of this
7 section.

8 “(C) No patient names or other identifying information
9 shall appear on any informed consent form, prescription, or
10 report submitted to the Secretary. No patient name or other
11 identifying information shall be submitted to or collected by
12 the Secretary.

13 TITLE II—FOOD AND DRUG ADMINISTRATION

14 SHORT TITLE

15 SEC. 200. This title may be cited as the “Food and Drug
16 Administration Act”.

17 ESTABLISHMENT OF FOOD AND DRUG ADMINISTRATION

18 SEC. 201. The Federal Food, Drug, and Cosmetic Act
19 (21 U.S.C. 301 et seq.) is amended by adding at the end
20 thereof the following new sections:

21 “FOOD AND DRUG ADMINISTRATION

22 “SEC. 903. (a) There is hereby established within the
23 Department of Health, Education, and Welfare an agency
24 to be known as the Food and Drug Administration (herein-
25 after referred to as the ‘Administration’).

1 “(b) The Administration shall be headed by a Com-
2 missioner of Food and Drugs (hereinafter referred to as the
3 ‘Commissioner’) who shall be appointed by the President,
4 by and with the advice and consent of the Senate, for a term
5 of five years. A Commissioner is eligible for reappointment
6 only once. The Commissioner shall be responsible for the
7 effective administration of the laws subject to his jurisdiction.

8 “(c) The President shall appoint by and with the ad-
9 vice and consent of the Senate a Deputy Commissioner and
10 General Counsel for the Administration for terms of five
11 years each.

12 “POWERS OF THE COMMISSIONER

13 “SEC. 904. (a) In order to fulfill his duties under the
14 laws subject to his jurisdiction, the Commissioner is em-
15 powered to—

16 “(1) direct and supervise all personnel of the
17 Administration,

18 “(2) employ experts and consultants in accordance
19 with section 3109 of title 5, United States Code, and
20 compensate individuals so employed for each day (in-
21 cluding traveltime) at rates not in excess of the maximum
22 rate of pay for grade GS-18 as provided in section 5332
23 of title 5, United States Code, and, while such experts
24 and consultants are so serving away from their homes or
25 regular place of business, to pay such employees travel

1 *expenses and per diem in lieu of subsistence at rates au-*
2 *thorized by section 5703 of title 5, United States Code,*
3 *for persons in Government service employed intermit-*
4 *tently;*

5 *“(3) appoint advisory committees composed of such*
6 *private citizens and officials of the Federal, State, and*
7 *local governments as he deems desirable to advise him*
8 *with respect to his functions under the law subject to*
9 *his jurisdiction, and to pay such members (other than*
10 *those regularly employed by the Federal Government)*
11 *while attending meetings of such committees, or other-*
12 *wise serving at the request of the Commissioner, com-*
13 *pensation and travel expenses at the rate provided for*
14 *in paragraph (2) of this subsection with respect to ex-*
15 *perts and consultants;*

16 *“(4) promulgate such regulations as may be neces-*
17 *sary or appropriate to carry out the functions vested in*
18 *him and for the efficient enforcement of the laws subject*
19 *to his jurisdiction;*

20 *“(5) utilize, with their consent, the services, person-*
21 *nel, and facilities of other Federal agencies and of State*
22 *and private agencies and instrumentalities with or with-*
23 *out reimbursement therefor;*

24 *“(6) enter into and perform such contracts, leases,*
25 *cooperative agreements, or other transactions as may be*

1 *necessary or appropriate in the conduct of the work of the*
2 *Administration and on such terms as the Commissioner*
3 *may deem appropriate, with any agency or instrumental-*
4 *ity of the United States, or with any State, territory, or*
5 *possession, or any political subdivision thereof, or with*
6 *any public or private person, firm, association, corpora-*
7 *tion, independent testing laboratory, or institution;*

8 “(7) accept gifts and voluntary and uncompensated
9 services, notwithstanding the provisions of section 665
10 (b) of title 31, United States Code;

11 “(8) designate representatives to serve or assist
12 on such committees as the Commissioner may determine
13 to be necessary or appropriate to maintain effective liai-
14 son with Federal agencies and with State and local
15 agencies and independent standard-setting bodies carry-
16 ing out programs and activities related to the protection
17 of consumers against injury resulting from the use of
18 products subject to his jurisdiction;

19 “(9) construct such research or test facilities as
20 may be necessary to carry out the purposes of the laws
21 subject to his jurisdiction, (A) after fully utilizing the
22 personnel, facilities, and other technical support avail-
23 able in other Federal agencies, (B) when authorized by
24 the Congress to plan, design, and construct such facilities,

1 and (C) subject to the appropriation of funds for this
2 purpose by the Congress;

3 “(10) conduct public hearings anywhere in the
4 United States to further the purposes of the laws subject
5 to his jurisdiction;

6 “(11) prescribe personnel policies for the Admin-
7 istration, including selecting, appointing, fixing compen-
8 sation of, hiring, firing, promoting, and transferring of
9 employees, subject to the civil service and classification
10 laws;

11 “(12) undertake such other activities as are inci-
12 dental to enforcement of the laws subject to his jurisdic-
13 tion; and

14 “(13) except as provided in section 905(a)(2)
15 delegate any of his functions and duties under the laws
16 subject to his jurisdiction to other officers or employees
17 of the Administration.

18 “(b) Nothing in this section shall be construed to prevent
19 the Commissioner from undertaking any activities previously
20 performed by the Secretary through the Food and Drug
21 Administration.

22 “FUNCTIONS OF THE COMMISSIONER

23 “SEC. 905. (a)(1) All functions of the Secretary of
24 Health, Education, and Welfare administered through the

1 *Food and Drug Administration are transferred to the*
2 *Commissioner of Food and Drugs.*

3 “(2) *Functions of the Secretary to suspend the approval*
4 *of an application because of an immanent hazard to health,*
5 *pursuant to sections 505(e), 512(e), and 512(m) are trans-*
6 *ferred to the Commissioner of Food and Drugs and shall not*
7 *be delegated.*

8 “(b) *The Secretary of Health, Education, and Welfare*
9 *may by regulation delegate such additional functions to the*
10 *Commissioner as he from time to time deems appropriate.*

11 “(c)(1) *All personnel, property, records, obligations,*
12 *commitments, and unexpended balances of appropriations,*
13 *allocations, and other funds, which are used primarily with*
14 *respect to any office, agency, bureau, or function transferred*
15 *under the provisions of this section are transferred to the*
16 *Commissioner of Food and Drugs. The transfer of personnel*
17 *pursuant to this subsection shall be without reduction in*
18 *classification or compensation for one year after such trans-*
19 *fer, and this provision shall not be construed to impair the*
20 *authority of the Commissioner to assign personnel during this*
21 *period to carry out the functions of the Administration most*
22 *effectively.*

23 “(2) *Any commissioned officer of the Public Health*
24 *Service who, upon the day before the effective date of the*
25 *Food and Drug Administration Act, is serving as such officer*

1 primarily in the performance of functions transferred by
2 that Act to the Commissioner may, if such officer so elects,
3 acquire competitive status and be transferred to a competitive
4 position in the Administration subject to paragraph (1) of
5 this subsection, under the terms prescribed in section 15(b)
6 (3)-(8)(A) of the Clean Air Amendments of 1970 (84
7 Stat. 1676; 42 U.S.C. 215).

8 “(d) The Civil Service Commission shall establish cri-
9 teria in consultation with the Commissioner when preparing
10 competitive examinations for positions in the Administration.

11 “(e) All laws relating to any office, agency, bureau,
12 or function transferred under the Food and Drug Admin-
13 istration Act shall, insofar as such laws are applicable,
14 remain in full force and effect. And orders, rules, regula-
15 tions, permits, or other privileges made, issued, or granted
16 by any office, agency, or bureau or in connection with any
17 function transferred by that Act, and in effect at the time
18 of the transfer, shall continue in effect to the same extent as
19 if such transfer had not occurred until modified, superseded,
20 or repealed. No suit, action, or other proceeding lawfully
21 commenced by or against any office, agency, or bureau of
22 any officer of the United States acting in his official capacity
23 shall abate by reason of any transfer made pursuant to
24 that Act.”

1 *COMPENSATION: ADDITIONAL POSITIONS*

2 *SEC. 202. (a)(1) Section 5314 of title 5, United*
3 *States Code, is amended by adding at the end thereof the*
4 *following new paragraph:*

5 *“(60) Commission of Food and Drugs.”.*

6 *(2) Section 5315 of title 5, United States Code, is*
7 *amended by adding at the end thereof the following new*
8 *paragraphs:*

9 *“(98) Deputy Commission, Food and Drug*
10 *Administration.*

11 *“(99) General Counsel, Food and Drug Admin-*
12 *istration.”.*

13 *(b) Section 5108(c) of title 5, United States Code, is*
14 *amended by—*

15 *(1) striking out the word “and” at the end of*
16 *paragraph (10):*

17 *(2) striking out the period at the end of paragraph*
18 *(11) and inserting in lieu thereof a semicolon and the*
19 *word “and”; and*

20 *(3) by adding immediately at the end of such sub-*
21 *section the following new paragraph:*

22 *“(12) The Commissioner of Food and Drugs, with-*
23 *out regard to this chapter (except section 5114), may*
24 *place twenty-five positions in the Food and Drug Admin-*
25 *istration in GS-16, GS-17, and GS-18.”*

1 *EFFECTIVE DATE; INITIAL APPOINTMENT OF OFFICERS*

2 *SEC. 203. (a) This Act shall take effect ninety days*
3 *after the Commissioner first takes office, or on such prior date*
4 *after enactment of this Act as the President shall prescribe*
5 *and publish in the Federal Register, but in no event later*
6 *than one hundred and eighty days after enactment of this Act.*

7 *(b) Any officers provided for in this Act may (notwith-*
8 *standing subsection (a)) be appointed in the manner pro-*
9 *vided for in this Act at any time after the date of enactment*
10 *of this Act. Such officers shall be compensated from the date*
11 *they first take office at the rates provided for in this Act.*
12 *Such compensation and related expenses of their offices shall*
13 *be paid from funds available for the functions to be trans-*
14 *ferred to the Commission pursuant to this Act.*

Amend the title so as to read: "A bill to protect the public health by amending the Federal Food, Drug, and Cosmetic Act to prohibit the introduction or delivery for introduction into interstate commerce of the drug diethylstilbestrol (DES) for purposes of administering the drug to any animal intended for use as food, and for other purposes."

Calendar No. 256

94TH CONGRESS }
1st Session }

SENATE

{

REPORT
No. 94-264

FOOD, DRUG, AND COSMETIC ACT AMENDMENTS OF 1975

JULY 3, 1975.—Ordered to be printed

(Filed under authority of the order of the Senate of June 26, 1975)

Mr. KENNEDY, from the Committee on Labor and Public Welfare,
submitted the following

REPORT

[To accompany S. 963]

The Committee on Labor and Public Welfare, to which was referred the bill (S. 963) To amend the Federal Food, Drug, and Cosmetic Act to prohibit the administration of the drug diethylstilbestrol (DES) to any animal intended for use as food, and for other purposes having considered the same, reports favorably thereon with an amendment and recommends that the bill as amended do pass.

COMMITTEE REPORT ON DES

I. TITLE I—DES

A. HISTORY OF THE REGULATION OF DES

1. *Animal feed supplement*

In 1941, the Food and Drug Administration of the Department of Health, Education, and Welfare permitted 11 pharmaceutical firms to begin to market DES for clinical use.

In May 1945, the Food and Drug Administration received the first application for the use of DES pellets in poultry (pellets were to be implanted under the skin at the base of the skull of poultry). In January 1947, that application was permitted to become effective. It was known at the time that DES had been shown to produce cancer in test animals, but it was believed that no significant residues of the drug would remain in the edible tissues of the treated birds.

In 1954, an application was permitted to become effective for marketing of DES through addition to the feed of beef cattle. Since that

time, many similar applications have been made effective—all of them were based on the absence of detectable residues in meat from the treated animals.

In 1955, an application was made effective for the implantation of DES pellets in the ears of beef cattle. This was also based on the absence of detectable residues in the edible tissues. Subsequently, a similar use was permitted for lambs.

In 1957, a reliable method of assay for DES in animal tissues had been developed. Tests showed no residues in beef, but confirmed the presence of 20–30 parts per billion in the skin fat of treated poultry. The Commissioner of FDA concluded that any drug applications involving DES could not be suspended at that time.

In 1957, FDA permitted the marketing of DES for addition to the feed of sheep.

In September 1958, Congress enacted the Food Additives Amendment, including the Delaney provision. (The Delaney amendment prohibits the appearance of any known carcinogen in food.) In May 1959, FDA published a statement of policy in the Federal Register in which it interpreted the Delaney provision as prohibiting FDA from making effective any further applications for the addition to animal feed or any use which leaves residues in human food of any drugs which produce cancer in man or animal when ingested. On December 10, 1959, the Secretary of HEW took the following steps:

- a. He requested all authorized manufacturers of DES for use in poultry immediately to suspend the sale of the product.

- b. He requested representatives of the poultry industry and the retail food industry to arrange for the immediate discontinuance of the sale of treated birds to consumers.

- c. He requested FDA to initiate actions suspending all effective new drug applications for the use of DES in poultry.

The 1962 Drug Amendments sponsored by Senators Kefauver and Harris added to the original Delaney amendment (the original Delaney clause read as follows: "No additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found after tests which are appropriate for the evaluation of the safety of food additives to induce cancer in man or animal.") the following language: "... except that this proviso shall not apply with respect to the use of a substance as an ingredient to feed for animals which are raised for food production. If the Secretary of HEW finds that under the conditions of the use in feeding specified in proposed labeling and reasonably certain to be followed in practice, such additive shall not adversely affect the animals for which such feed is intended, and (2) that no residue of the additive will be found by methods of examination prescribed or approved by the Secretary by regulations in any edible portion of such animal after slaughter or in any food yielded by or derived from the living animal."

On July 13, 1968, Congress enacted the animal drug amendments which created the section of the law dealing exclusively with animal drugs and medicated feeds containing such drugs. Prior to the effective date of the Animal Drug Amendments in 1969, such drugs and feed were handled under law and regulations as both new drug and food additives. The animal drug amendments retained the Delaney clause and the other requirements to apply to such drugs and feeds

under the food additive law, but permitted the Secretary of HEW to allow the use of a known carcinogen if he were "reasonably certain" that no residues of the carcinogen would appear in food.

In December 1971, the Commissioner of the FDA conceded that administrative procedures for the control of DES residues in food were not working, and he changed them. The change required a seven-day withdrawal for all cattle fed with DES as opposed to the earlier regulation requiring 48-hour withdrawal. (Withdrawal means that the drug administration is stopped early enough so as to assure no residue of the drug in the tissue of the slaughtered animal.) In the six months following the institution of the new regulations, the incidence of DES residues, as detected by the Department of Agriculture, quadrupled.

In July 1972, the Commissioner of the FDA testified at the Health Subcommittee hearings on DES that the rising incidence of use was due to faulty compliance with the administrative procedures. Two weeks later, the Commissioner of FDA cited new scientific evidence explaining that DES residues appear in cattle even after the seven-day withdrawal period had been carefully observed. Because of that, he announced an immediate ban on the production of DES and a phased withdrawal—over a five-month period—of existing DES supplies from the market.

In the fall of 1972, the Senate passed legislation to prohibit the use of DES as a cattle feed additive. The Senate acted even after the FDA action because it felt the action was incomplete—implants, for example, were covered by the legislation but not by FDA's action. The legislation died in the House of Representatives.

FDA's administrative ban succeeded in removing most DES from American meat. But the Commissioner's actions were challenged by the pharmaceutical industry on the grounds that they had been denied a fair hearing on the matter. The Commissioner had chosen not to declare DES an imminent health hazard, and yet he also failed to provide for a full administrative hearing. The courts upheld the petition of the pharmaceutical industry and the ban on DES was overturned. No subsequent effort has been made by the Food and Drug Administration to begin proceedings to administratively remove the drug from the market in an appropriate way. The Department of Agriculture now reports that the residues of DES have returned at levels equal to their peak in 1972.

2. DES as a Morning-After Contraceptive

In the 1950s, Diethylstilbestrol was widely used throughout the country for the approved purpose of preventing miscarriages in women who had had difficulty carrying their pregnancies through to term. In 1968, Dr. Arthur Herbst, a gynecologist at the Massachusetts General Hospital in Boston, began to see patients with a form of vaginal cancer virtually unknown in the United States. After seeing nine of these cases, Dr. Herbst discovered that they had one common antecedent: The mothers of the women who had developed the cancer had all taken DES during the first trimester of pregnancy in order to prevent a possible miscarriage. Additional confirmatory evidence was developed by Dr. Peter Greenwald, the Director of the Cancer Control Bureau in New York State. The information was transmitted to the Food and Drug Administration. The demonstrated

cause-and-effect nature of the relationship between DES and the development of two new forms of cancer—vaginal and cervical cancer—caused the Food and Drug Administration to act. It issued a letter to all physicians in 1971 warning that DES should not be used in the treatment of impending miscarriages. DES could still be used, however, for its other approved indications.

At the same time, laboratory work was going on, directed at the development of a safe and effective morning-after contraceptive agent. Diethylstilbestrol was a prime candidate to fulfill that function. In 1973, the Food and Drug Administration's Advisory Committee on Obstetrics and Gynecology began reviewing an application to approve DES as a morning-after pill. In 1974, the Eli Lilly Company, a major manufacturer of the dosage form of DES required for its use as a morning-after pill, informed all doctors in the country that it would cease manufacturing the product in that dosage form. The company expressed the opinion that the product was not up to Lilly's standards of safety.

In March 1973, the Food and Drug Administration sent a letter to all physicians informing them that DES had been approved as a morning-after pill, but only for emergency situations. The definition of "emergency" was left up to the individual physicians. In testimony before the Health Subcommittee in 1973, however, the Commissioner of the Food and Drug Administration defined "emergency" as rape, incest, or a comparable medical emergency.

In fact, the FDA letter to all physicians was in error as the drug had not been approved. The Food and Drug Administration never corrected the error. In March 1975, two years after the error was committed, the Food and Drug Administration officially approved DES as a morning-after pill, once again stressing that its use should be limited to emergency situations. The Food and Drug Administration also announced that it would require a patient package insert to accompany the use of the drug. Only one manufacturer, Tablicaps Inc., of New Jersey, applied to market the drug.

In the course of its deliberations, Dr. David P. Rall made the Committee aware of research ongoing at the National Institute of Environmental Health Sciences on DES. The Committee notes that in a report prepared by John A. McLachlen of the Institute, there may be effects from DES on males (see Appendix).

B. HEARINGS

The Committee has conducted three hearings on DES since it began following FDA's regulation of the drug in July 1972. These hearings have fully explored the issues raised by the continuing use of DES in cattle feed and the use of DES as a morning-after contraceptive. Witnesses in these three hearings have included Senator William Proxmire of Wisconsin, two successive Commissioners of the Food and Drug Administration, Dr. Charles C. Edwards and Dr. Alexander McKay Schmidt; Dr. Frank J. Rauscher, Jr., Director of the National Cancer Institute; Dr. Peter Greenwald, Director of the Cancer Control Bureau of New York State; Dr. Arthur L. Herbst, gynecologist at Massachusetts General Hospital in Boston; Dr. Duane Flack,

President of the Montfort Feed Lots in Greeley, Colorado, and Chairman of the Task Force on DES for the American National Cattle-men's Association; Mr. Sidney Wolfe and Ms. Anita Johnson of the Health Research Group; the Eli Lilly Company; Tablicaps Inc.; Dr. Robert Pantell, pediatrician at Stanford University Hospital; Dr. Marvin Seif of the Food and Drug Administration; Janice Luder of Los Angeles, California, a woman who has had DES-caused vaginal cancer; Mrs. John Malloy and Mrs. Albert Green, mothers of daughters who have died of DES-caused vaginal cancer; and Belita Cowan from the University of Michigan.

The Summer 1972 hearing focused on the use of DES in cattle feed. A summary of that hearing appeared in the Committee Report on S. 2818 as follows:

The Committee conducted hearings on July 20, 1972, on S. 2818, a bill to prohibit the administration of the drug Diethylstilbestrol (DES) to any animal intended for use as food. Witnesses included Senator William Proxmire of Wisconsin; Dr. Charles C. Edwards, Commissioner of the FDA; Dr. Frank L. Rauscher, Jr., Director, National Cancer Institute; Dr. Peter Greenwald, Director, Cancer Control Bureau of New York State; Dr. Arthur Herbst, gynecologist at Massachusetts General Hospital in Boston; and Mr. Duane Flack, President, Monfort Feed Lots in Greeley, Colo., and chairman of the task force on DES for the American National Cattlemen's Association. The Pharmaceutical Manufacturers Association and the Animal Health Institute were invited to testify, but declined.

Both Drs. Greenwald and Herbst presented studies they have completed which indicated that children of women who had taken therapeutic doses of DES during pregnancy ran a significant risk of developing vaginal cancer in their early 20s. Both pointed out that there was an absence of vaginal cancer in girls of this age group born before the time of common use of DES. Both witnesses agreed that although there are many causes for any given cancer, DES was probably a significant factor in the appearance of all the cases of vaginal cancers that their two studies had uncovered.

Greenwald pointed out that there was more evidence of the linkage between the therapeutic use of DES and vaginal cancer than there had been between cyclamates or pesticides and any known human cancer. Said Dr. Greenwald, "It is clear that with DES we have direct evidence of a cancer-producing effect in humans, while with the other compounds, we do not." He felt that the prudent course would be to ban the use of DES.

Dr. Frank L. Rauscher, Jr., Director of the National Cancer Institute, agreed that there was evidence linking DES to cancer in humans. He agreed that the prudent course would be to try to remove all possible carcinogenic stimuli from the environment and to limit man's carcinogenic burden as much as is possible. Dr. Rauscher also raised the question of a possible occupational health hazard to workers involved in the

production and administration of DES. He recommended that a survey of occupational sources of exposures be conducted as well as an epidemiologic study of the exposed populations. He pointed out that it is currently impossible to determine whether very low doses of a known carcinogen will have a carcinogenic effect in man if he is exposed to it over a long period of time. In the absence of such knowledge, he felt that the prudent course would be to reduce the carcinogenic burden to man.

Commissioner Charles C. Edwards of the Food and Drug Administration testified that FDA had commenced appropriate proceedings to withdraw the approval for the use of DES because of persistent and increased violations of FDA restrictions on the use of the drug.

Edwards stated that an immediate ban would require the declaration that DES was an imminent hazard to health. He was not prepared to make that recommendation. He testified that the doses of DES appearing in meat residues were of such small magnitude that its carcinogenicity to man in that dose was unproven and unlikely. The Commissioner admitted, however, that he could not define a known maximum safe dose of DES for humans.

Commissioner Edwards further testified that in the past, administrative procedures designed to remove a product from the market had taken up to 15 months to complete. He gave assurance to the Committee that action on DES would be prompt and that if there were no protests against his notice to withdraw approval for DES, he would ban it. Commissioner Edwards also testified that manpower shortages prevented him from administering the regulations in the most desirable fashion. The administration opposed the enactment of S. 2818 on the grounds that DES would not be the only substance to generate these issues. The administration stated that piecemeal legislation directed at any given substance would not be appropriate.

Mr. Duane Flack testified on behalf of the American National Cattlemen's Association that the appearance of DES in animal tissues could be prevented because the fault lay in the implementation of FDA regulations and not in the regulations themselves. He also testified that the carcinogenicity of DES was of significant economic importance.

The 1973 and 1975 hearings focused on the use of DES as a morning-after pill. At the 1973 hearings, Sidney Wolfe and Anita Johnson testified that based on a national study which they conducted, the drug was in widespread inappropriate use on college campuses across the nation. Dr. Peter Greenwald confirmed that this was true for New York State, and testified in 1975 that over 220 cases of DES-caused cancer were now recorded in the national registry being kept on this matter by Dr. Herbst. Each of these cases developed in the daughters of mothers who had taken DES to prevent miscarriage. Dr. Greenwald pointed out that the dosage required to cause the cancer was, in one instance, smaller than the dosage required for DES to work as

a morning-after pill. Dr. Greenwald urged that DES be banned in cattle feed and that if it was to be used at all as a morning-after contraceptive, it should be made a fully controlled substance.

Dr. Robert Pantell testified that in his experience in the State of Idaho, DES was still being used to prevent miscarriages, an indicated use of the drug which was thoroughly discredited by the FDA in 1971.

Belita Cowan reported on the results of the study she had conducted at the University of Michigan, indicating the misuse of the drug. She pointed out that this misuse continued and increased even after the FDA approval letter went out to all doctors in 1973. Although the letter was in error, it did say that DES should be used only in emergency situations. And Ms. Cowan and Dr. Greenwald both confirmed that misuse of the drug actually increased after the FDA letter went out. Ms. Cowan testified that many women stopped taking DES in the middle of a course of treatment, thus exposing them to potential risks without the possibility of effective birth control. The use of the drug did not appear to be curtailed by the fact that the University of Michigan did provide patient package inserts to all coeds requesting the drug, according to Ms. Cowan.

Mrs. Malloy and Mrs. Green testified about their experiences during the time their daughters discovered they had vaginal cancer. They urged all mothers to try to recall if they had taken DES during pregnancy so that their daughters could be carefully followed in order to catch the cancer early if it developed. Janice Luder testified as to her experience as a DES daughter who developed vaginal cancer. She told of the heavy burden of guilt borne by her mother for having taken DES during the first trimester of her pregnancy.

Eli Lilly testified that it would no longer make the dosage of DES required for the morning-after pill, because DES did not meet Eli Lilly's standards of safety. Lilly pointed out that the drug was being approved by FDA on the basis of an abbreviated new drug application, rather than a full new drug application. Lilly stated that they felt that this was a bad policy. Tablicaps Inc. testified that they would market the drug in ways consistent with the FDA's order that the drug only be used in limited emergency situations.

Dr. Frank Rauscher of the National Cancer Institute testified that he was in favor of an immediate ban on DES in cattle feed, and that he thought that FDA's approach to limited approval of DES as a morning-after pill deserved a one-year trial. Dr. Rauscher stated that "... I recommend and the National Cancer Institute recommends very strongly that DES not be used in animal feed, that DES not be used routinely as a post-coital drug. That its use be confined to victims of rape, incest, to other illnesses, or illnesses which could be life-threatening following pregnancy." Dr. Rauscher added that, "If the FDA cannot set up adequate means for repeated and effective monitoring, then we have not controlled the situation, it can be presumed. And under those circumstances, again, I would recommend that its use be withdrawn."

Dr. Schmidt testified that he would support legislation to ban DES in cattle feed. He testified that the limited FDA approval of DES as a morning-after pill, coupled with a strongly worded patient package insert, would assure the appropriate use of drug. He admitted that

FDA mistakenly wrote all physicians, telling them that the drug had been approved two years earlier. He agreed that that approval also was limited only to emergency situations, and that FDA's admonitions had been ignored. He stated it would be different this time because of the inclusion of a strongly worded patient package insert.

C. NEED FOR THE LEGISLATION AND COMMITTEE VIEWS

The Committee remains committed to an all-out attack on cancer, as originally outlined in the National Cancer Act of 1971—P.L. 92-218, and recognizes that such an effort is extremely complex and must be carried forth in many ways simultaneously: By support for basic biomedical research; by support for clinical research; by support by the training of needed professional manpower; by epidemiological investigations, by providing prompt treatment for those who need it; by control of environmental hazards; and by the elimination of carcinogenic agents wherever possible.

1. DES and Cattle Feed

The Committee very much regrets that it must once again consider Senate-passed legislation in the 93rd Congress designed to remove DES from cattle feed. The need for such legislation was outlined in the 1972 Committee Report. The Director of the National Cancer Institute, the Director of the National Cancer Control Bureau in New York State, and Dr. Arthur Herbst, Massachusetts gynecologist who first connected DES to human vaginal cancer, all strongly supported the ban of DES in cattle feed.

The Committee is very distressed to learn that DES residues are now appearing in beef livers, at levels equal to or higher than those which first prompted Senate action. The Committee is impressed by the fact that Dr. Rauscher, Director of the Cancer Institute, has reaffirmed his support for the ban of DES from cattle feed; so has Dr. Greenwald, head of the Cancer Control Bureau of New York State; and so has Dr. Arthur Herbst in a new letter to the Committee. Commissioner Schmidt of the FDA also said that he would support the concept of such legislation, although not on the basis of an imminent health hazard.

The Committee was deeply concerned by Dr. Rauscher's warning to all American women not to eat beef livers during the first trimester of their pregnancies. This startling policy, pronounced from the nation's director of the war on cancer, should convince all concerned of the immediate need to remove DES once and for all from the nation's food supply.

When the FDA first took administrative action on this matter in 1972, DES was a known animal carcinogen, and a suspected human carcinogen. It has now been conclusively proven to be a human carcinogen in certain cases.

The Committee believes that the burden of proof in matters such as this should always rest with those who say that a known cancer-causing substance is not a health hazard to man. The Committee believes that if a substance is hazardous enough to be banned, it is hazardous enough to be banned immediately. If the Food and Drug Administration felt strongly enough to ban the product in 1973, then it should be moving expeditiously to ban it again now.

In short, the Committee reaffirms all of the views expressed in the 1972 Committee Report, and believes that the new evidence of the significant human carcinogenicity of DES adds a sense of great urgency to this legislation. Over 20 countries have banned the importation of United States meat raised with DES. The United States has always adhered to the highest safety standards for its population. The Committee believes that nothing short of a complete ban on DES in cattle feed will enable the United States to live up to its own standards of safety.

2. The Use of DES as a Morning-After Pill

When the Committee first began hearings on the use of DES in cattle feed in 1972, Dr. Arthur Herbst testified about nine cases of human vaginal cancer in the daughters of mothers who had taken DES to prevent miscarriages during their pregnancy. In 1973, the Committee learned from Dr. Greenwald that not one, but two, separate kinds of cancer were caused by DES—vaginal and cervical cancer—both in the daughters of mothers who had taken DES during pregnancy to prevent miscarriages. By 1975, the Committee had learned that the number of reported cases of DES-caused cancer had risen from nine to 220. The Committee is aware of the grave nature of these two cancers. It is indeed tragic that many of these women have died.

The Committee was profoundly moved by the testimony of Janice Luder, Mrs. Malloy, and Mrs. Green on their personal tragic experiences as a result of DES-induced cancer.

The Committee is now convinced beyond a doubt that DES is a potent, lethal human carcinogen in certain cases. The Committee takes note of Dr. Greenwald's testimony that the annual incidence of DES-caused cancer among the exposed population is 44 times higher than the annual incidence of leukemia in the United States. The Committee also notes with great alarm that new data published by Dr. Herbst indicates a potentially pre-cancerous condition, called abnosis, is developing in a very large percentage of women whose mothers have taken DES during pregnancy. The Committee is concerned at estimates that the incidence of abnosis in this population may be as high as ninety percent. The Committee understands that no one can predict what will happen to the women who have abnosis. The Committee acknowledges that many respected researchers throughout the United States consider abnosis to be a potentially pre-cancerous condition.

The Committee is worried about the vast population of DES daughters in the United States who are still not aware that their mothers took DES during pregnancy and who, therefore, are not seeking the appropriate prophylactic medical care. The Committee is alarmed because no one knows the magnitude of the health problem and because no one knows how many women are at risk. The Committee notes that the April issue of the prestigious *Pediatrics Journal* warns all pediatricians in an editorial to begin to look for new DES daughters. The Committee is aware that thousands more may be found, and hopes that they will be found in time for effective treatment, and that they will not develop either form of the deadly cancer.

The Committee is aware that the use of DES as a morning-after pill has not been associated with the development of a single human cancer. But the Committee also knows that DES as a morning-after pill has

only been used for a few years, and that DES-caused cancer has heretofore only been acquired in the daughters of mothers who have taken the drug during pregnancy, and in those cases, 16 to 20 years later. The Committee is greatly disturbed that the doses required in morning-after pill treatment exceed dosages that have caused cancer in young women in the past several years.

The Committee recognizes that there is a need for a safe morning-after contraceptive agent for emergency situations like rape or incest. The Committee notes that the Food and Drug Administration has approved DES only for such emergency situations. However, the Committee is concerned that the FDA has left the definition of "emergency" to the discretion of the nation's practicing physicians, and has not established firm guidelines for what an emergency is. The Committee believes that this will lead to continued overuse and misuse of DES beyond the limited indications that the FDA believes are appropriate.

The Committee notes that the majority of witnesses testified to the effect that DES is widely misused as a morning-after pill in the United States. This view is shared by the Commissioner of the FDA. Where the Committee differs with the FDA is that the Committee does not believe that the measures outlined by the FDA will assure appropriate use of DES in emergency situations. Although the Committee regrets FDA's error in announcing approval of DES for emergency situations two years before it was actually approved, the Committee believes much can be learned from that experience. The Committee is persuaded that in spite of FDA's warning in 1973, the use of DES continued to be widespread and inappropriate during the last two years. The Committee points out that the Commissioner of the Food and Drug Administration acknowledged this fact in testimony. The Committee does not believe, as the Commissioner of the Food and Drug Administration does, that a simple addition of a package insert will immediately assure appropriate use of a widely misused drug. The Committee agrees with the Director of the National Cancer Institute that if the drug can be absolutely controlled, then it should be allowed on the market for emergency situations. The Committee is concerned that the experiences of the last two years strongly indicate that the drug cannot be controlled under the Commissioner's regulatory procedures at the present time.

The Committee notes that the Eli Lilly Company has withdrawn its own 25 mg. product from the market for reasons of safety. The Committee notes that the Food and Drug Administration has used DES as the first case in which an abbreviated new drug application (ANDA) has been used when a new use is to be approved for a drug which is already on the market. This ANDA waives the requirement that the drug company which is to market the drug prove that the drug is safe and effective. The proof in this case is based on outside, independent research.

The Committee also notes that although DES-caused cancer has, up to now, been limited to the female offspring of mothers who took the drug during pregnancy, that that does not mean that the mothers themselves or the male population are not at risk in the future. On the other hand, the Committee believes that it should be pointed out that there is no evidence that mothers or the male population are at risk

at the present time. However, the Committee agrees with Dr. Rauscher that these situations must also be monitored closely in the years ahead.

Thus, the Committee is concerned the drug DES is being widely misused in the United States today as a morning-after contraceptive agent; that it causes cancer in human beings in doses lower than those required in treatment as a morning-after pill; that the measures proposed by the Food and Drug Administration to control the use of the drug have not been effective; and that until the full extent of DES carcinogenicity in human beings is known, the American people must have the benefit of that doubt. Therefore, the Committee has adopted several measures which it believes will effectively make DES a controlled substance, thereby minimizing the possibility of inappropriate use of the drug, and maximizing the possibility of appropriate use. The Committee recognizes that bona fide medical emergencies, such as rape or incest, are tragic situations in which there is a role for the use of a morning-after contraceptive agent. The Committee intends this legislation to ensure appropriate usage and curtail its inappropriate usage.

In general, the Committee does not believe that the general problem of misprescribing and overprescribing of drugs in the United States can be properly corrected on an individual drug basis. The Committee finds this an unusual situation which should not be considered a routine precedent, i.e., legislating on individual substances that are the regulatory purview of a Federal agency (in this case, the Food and Drug Administration) under existing statute. The Committee is taking this unusual action because it believes that the FDA has not responded adequately under existing law to protect the public health and safety with respect to regulation of DES, either as a feed additive or a drug. The Committee believes there is larger need indicated by the DES problem, a need to reevaluate the Food, Drug and Cosmetic Act relative to the FDA's authority to deal with similar complex problems.

Inherent in the DES issue are the overriding problems of providing for limited use of some substances under unique circumstances, based on benefit to risk, and controlling use of substances in such circumstances.

In this regard, the Committee intends to consider whether legislative changes in the law are necessary in order to provide for more effective regulation by the Federal agency in future such circumstances.

The Committee believes that the required labelling for DES, as provided in the reported bill, will serve to alert all consumers to the potential dangers of the drug. It will also alert the consumers that they should discuss the risks and benefits of taking DES with their physicians. And that a written informed consent statement is required for each use of the drug. The Committee strongly believes that the principle of an informed consent has an appropriate place in practice of medicine, particularly when that involves the use of highly dangerous or potentially dangerous drugs.

The Committee believes that unit packaging as provided in the reported bill will significantly curtail the misuse of DES as a morning-after pill.

The Committee believes it is essential to know exactly how the drug DES is being used in the United States. Complete knowledge about its use would enable instances of misuse to be reviewed and corrected. It would enable patients potentially put at grave risk because of misuse to be found at an early time when prophylactic medical care could minimize that risk. Thus, the Committee believes it is essential that a copy of each informed consent form and each prescription be reported by the physician to the Food and Drug Administration.

The Committee also believes that a copy of each prescription filled by a pharmacist should be reported to the FDA. In this way, the FDA can truly learn the extent of DES use in this country, and will have the opportunity to help improve the appropriateness of that use. It will also enable the FDA and the Congress to discover whether appropriate use is possible at all. If it is not, then the Committee agrees with Dr. Frank Rauscher, Director of the National Cancer Institute, that the drug would have to be banned entirely. The Committee believes that this approach of controlling the usage of the drug through consumer information and tight reporting of its use will allow the drug to be continually available for those situations where its use is truly medically justified, and will minimize the grave hazards presented by the casual misuse and overuse of the drug. The Committee wishes to make it clear that in doing all this, the name of the patient receiving the drug will never be reported to the Food and Drug Administration, so that the confidentiality of the doctor/patient relationship will be retained. In those instances where overuse or misuse of the drug is determined through the reporting system, or after following up upon the reporting system, it will be up to the individual physician to contact any patient who might be at risk because of inappropriate prescribing.

II. TITLE II—FOOD AND DRUG ADMINISTRATION

A. NEED

Title II seeks to improve national health law by providing for a statutory Food and Drug Administration, prescribing its powers, and establishing terms, Presidential appointment, and Senate confirmation of its top officials, and to strengthen the public health agency responsible for consumer safety by giving it and its top officials a basic statutory mandate.

Title II, which was added to S. 963 by the Committee, would establish within the Department of Health, Education, and Welfare a statutory Food and Drug Administration (FDA). Section 200 would add a new Section 903 to the Federal Food, Drug and Cosmetic Act which would, in effect, give a charter to the FDA. The Committee believes this is necessary in view of the unique status of the FDA as a regulatory agency within one of the largest executive departments.

The Committee believes that FDA derives benefits from being within HEW, since it may thus have better access to the research capabilities of the National Institutes of Health and to related programs in such other agencies as the Alcoholism, Drug Abuse and Mental Health Administration. However, the Committee also believes that, as a regulatory agency, FDA must have a clear statutory base to be able to vigorously prosecute violations of the law, and that this result is best ensured by providing the agency with a charter so that FDA may not be administratively reshuffled elsewhere in the HEW struc-

ture, submerged under layers of bureaucracy, or renamed. The prospect of such alterations in FDA's stature is not merely hypothetical. For a year-and-a-half FDA was submerged in an entity known as the Consumer Protection and Environmental Health Service. This change was made without Congressional approval, by mere publication of notice in the Federal Register.

Other guarantees of a strong FDA are provided by the bill. The President would appoint the Commissioner of Food and Drugs by and with the advice and consent of the Senate for a term of five years. The Commissioner is made responsible for the effective administration of all laws subject to his jurisdiction. The two other top FDA officials, the Deputy Commissioner and the General Counsel for the Administration, would also be appointed by the President for five-year terms and would also be subject to Senate confirmation. The Commissioner of Food and Drugs is one of the most powerful officials in Washington, making decisions every day which affect our daily lives since they involve food, drugs, and other common consumer products. Yet he is appointed by and serves the pleasure of the Secretary of HEW, and Congress has no voice in his appointment. The Committee believes that Congress needs to be involved in the appointment of the Commissioner of Food and Drugs and the other two most powerful FDA officials. By providing for Presidential appointment of the Commissioner of Food and Drugs, by and with the advice and consent of the Senate, the Committee has given effect to the view long held by many members of Congress that the stature and responsibility of these positions merit this form of appointment.

The five-year term of appointment for the Commissioner, Deputy Commissioner, and the General Counsel is needed to provide these officials with an important measure of other political appointees who come into and leave HEW. In establishing independent regulatory commissions, Congress has commonly provided for fixed terms for the commissioners as a means of insulating them from political pressures. We believe that the same justification applies in the case of the three top officials of FDA.

The Committee is not persuaded by arguments that vesting authority at subordinate levels of an executive department will undermine the accountability of the Secretary of HEW in administering and coordinating HEW programs. The Committee intends to hold the Commissioner fully accountable for his performance at the helm of the FDA, and believes that any possible losses in HEW's ability to coordinate programs are very much outweighed by potential gains in FDA's regulatory vigor. Both Congress and the President have in the past found it necessary to meld features of the two traditional models of "independent agency" and "executive department" in order to achieve a measure of independence while at the same time facilitating coordination with related programs. This was true, for instance, of the organizational structure adopted for the National Cancer Institute pursuant to the National Cancer Act of 1971. FDA's unique status as a regulatory agency within HEW and its power to make decisions having a massive economic impact on our society are ample reasons for developing an alternative to traditional public administration theories.

Another way in which Title II would strengthen FDA's regulatory base is the provision vesting in the Commissioner the responsibility for administering the laws subject to his jurisdiction.

At present, authority in the Federal Food, Drug and Cosmetic Act and other laws FDA administers is vested in the Secretary, delegated to the Assistant Secretary for Health, and then redelegated to the Commissioner of Food and Drugs. The Committee believes there have been instances in the past where FDA's vigor as a regulatory agency may have been impaired because it is so heavily layered over by these HEW Presidential appointees. The Committee fears that so long as this situation exists, there will be risks of political interference with FDA regulatory decisions. These risks can be minimized by vesting in the Commissioner the authority to carry out those laws subject to this jurisdiction pursuant to this Act. The Committee also believes it will be useful for the Commissioner to have an explicit statutory outline of the basic administrative powers to carry out his responsibilities under the functions transferred to him under the Act. This need is met by Section 904.

B. COMMITTEE VIEWS

Section 201 establishes a new section of the Federal Food, Drug and Cosmetic Act and provides the basis for a statutory charter for the Food and Drug Administration within the Department of Health, Education, and Welfare.

By establishing five-year terms for the three top FDA officials, requiring Presidential appointment and Senate confirmation of the laws subject to his jurisdiction, the Committee intends in new Section 903(a) to put the FDA on the kind of statutory footing and with the kind of real authority now found in many of the independent regulatory agencies. The FDA would, however, remain with the Department of HEW to facilitate use by FDA of the Department's research facilities and to enable better communication with officials in related programs in the Department's other health agencies.

Under new Section 903(b), it is the Committee's intent that the Commissioner of Food and Drugs, rather than the Secretary of Health, Education, and Welfare, shall be the responsible official for carrying out the laws subject to his jurisdiction, i.e., the statutes now administered by FDA (pursuant to delegations from the Secretary and the Assistant Secretary for Health) and present FDA activities as well as any other authority which the Secretary may later delegate pursuant to proposed Section 905(b). By vesting in the Commissioner of Food and Drugs the authority to carry out the laws subject to his jurisdiction, the Committee intends that no requirement be imposed for review or clearance of any FDA actions by officials of the Department of HEW, the Office of Management and Budget, or any other Office of the executive branch. In this regard the Committee would bar requirements for review and clearance of FDA actions under statutes applicable to Federal agencies generally, such as the National Environmental Policy Act, the Freedom of Information Act, and the Federal Advisory Committee Act as well as actions under statutes administered and enforced by FDA. The Commissioner may, within his discretion, notify or consult with the Secretary or other Federal officials in regard to the agency's actions in advance or as they occur. The Committee expects that the Commissioner will engage in such consultation with and notification of the Secretary and other HEW officials to the extent necessary to reduce substantive inconsistencies

in Department policies. The Committee also believes that the Commissioner of Food and Drugs should work with the Secretary and Assistant Secretary for Health to ensure that FDA's overall plans are reflected in the Department's plans for its health programs. Furthermore, under Title II, the budget estimates and legislative proposals for the FDA will still be subject to review prior to submission to Congress by the Office of the Secretary and the Office of Management and Budget. The Committee believes, however, that officials in the Department and OMB should exercise restraint in their review of FDA's proposed budget and legislation, and will refrain from substituting their own judgments as to FDA management or regulatory matters or agency priorities, as these matters are intended to be the responsibility of the Commissioner of Food and Drugs. Duly authorized congressional committees are able to require that tables be provided showing the original agency budget request before it was reviewed by the Office of the Secretary and the Department's original request before review by OMB.

New Sections 903 (b) and (c) require Presidential appointment, by and with the advice and consent of the Senate, of the Commissioner, Deputy Commissioner, and General Counsel of FDA. The Committee expects that the Secretary of HEW and the Assistant Secretary for Health will suggest well-qualified nominees for the three posts to the President. However the President should make the selections. The five-year terms would begin when the first Commissioner appointed under Section 903(b) first takes office. If the first, or any subsequent, Commissioner should leave office prior to the expiration of the five-year term, the President may make a new appointment, subject to the advice and consent of the Senate, for the remainder of the term. New Section 903(a) provides that the Commissioner may only be reappointed once. The Committee intends that removal of a Commissioner may only be by the President and only for cause.

As with the Commissioner, the Deputy Commissioner and the General Counsel for FDA would be appointed by the President by and with the advice and consent of the Senate, each for five-year terms. These terms shall begin and end on the same dates as the five-year terms of FDA Commissioners, i.e., the first such term shall begin when the first Commissioner appointed under this Act takes office. The Committee intends that the President shall, to the extent feasible, consult with the incumbent Commissioner, or the President's intended nominee to the post of Commissioner, as to appointments of the Deputy Commissioner and General Counsel to ensure compatibility of individuals who must work closely together.

Under new Section 904(a) (1), these officials are subject to the direction and supervision of the Commissioner, and they will serve at his pleasure notwithstanding their five-year terms. The Committee has, therefore, found it unnecessary to place any limitation on the number of terms for which the Deputy Commissioner and the General Counsel may be appointed.

The Committee intends that the General Counsel for the Administration shall report to the Commissioner and not to the General Counsel for HEW. Under new Section 905(c) of the bill, the personnel, properties, records, etc., of the Food and Drug Division of HEW's General Counsel, headed by the Assistant General Counsel, Food and Drugs, shall be transferred to the Commissioner of Food and Drugs.

Furthermore, the staff of the General Counsel to the Administration shall be directed by the Commissioner pursuant to new Section 904 (a) (1) and governed by the Administration's personnel policies established under new Section 904(a) (11), subject to the civil service and classification laws. The General Counsel for the Administration shall perform all legal services for FDA now performed by the Assistant General Counsel for Food and Drugs and other functions as the Commissioner may assign. The Committee believes that in order to secure the necessary independence for the Commissioner, it is essential that his legal counsel be accountable to him and not to the General Counsel attorneys, and the agency's legal staff. In particular, the Commissioner for the Department. This is also desirable to ensure the necessary coordination between FDA investigative personnel, few of whom are should be in a position to make increases in the size of the agency's legal staff commensurate with expected increases in investigations and regulatory actions.

New Section 904 outlines the powers of the Commissioner to enable him to fulfill his duties under the laws subject to his jurisdiction. By this section the Committee does not intend to provide FDA with any new powers. In no event shall this section be read as a limitation on FDA's authority under the statutes which it administers.

Under new Section 904(a) (1) the Commissioner is given authority to direct and supervise all personnel of the Administration and, under paragraph (11), to prescribe personnel policies for the Administration. It is intended that the Commissioner—and not the Secretary or other officials in the executive branch, including the White House—shall recruit, select, appoint, direct, supervise, promote, transfer, and fire employees of the Administration, subject to the civil service and classification laws. The Committee intends that the Commissioner shall have full charge over all personnel, including those in policy positions, and intends that political, partisan, or patronage considerations shall not enter into appointments to positions in the FDA or promotions of FDA officials. The Committee is concerned about recent attempts by the Administration to require political clearance for top posts in the new independent Consumer Product Safety Commission. It is believed that the likelihood of improper political influence can be reduced by placing in the Commissioner the authority to direct and supervise all personnel.

New Section 904(a) (4) empowers the Commissioner to promulgate such regulations as may be necessary or appropriate to carry out the functions vested in him, and to efficiently enforce the laws he is charged with administering.

This paragraph is intended to complement new Section 903(b), which makes the Commissioner responsible for the effective administration of these laws, and new Section 905, which transfers functions under these laws and personnel, property, etc., to the Commissioner from the Secretary of HEW. New Section 904(a) (4) does not grant any new substantive rulemaking authority which the Committee believes is already possessed by FDA under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, and other statutes the agency now administers.

New Section 904 enumerates other powers which the Committee believes are necessary or useful for an agency to possess, e.g., authority

to employ experts, appoint advisory committees, enter contracts, etc. These powers are ones which FDA already exercises and do not represent new grants of authority. Under new Section 904(a) (12), which enables the Commissioner to undertake other activities incidental to his enforcement responsibility, the key word is incidental; the Committee does not intend by this paragraph to grant any new substantive power to FDA, including any information-gathering or enforcement power.

New Section 904(b) is intended to reinforce the Committee's intention that enactment of this Title shall not be construed as reducing FDA's present scope of activities, and that all functions of the Secretary now carried out through the FDA are intended to be transferred to the FDA.

New Section 905(a) (1) of the Federal Food, Drug and Cosmetic Act transfers to the Commissioner all functions of the Secretary of HEW now administered through the FDA. These functions, now delegated administratively to the Commissioner by the Secretary and the Assistant Secretary for Health, are listed at 21 C.F.R. 2.120 as consisting of functions of the Secretary under:

(1) the Federal Food, Drug and Cosmetic Act (21 U.S.C. 301 et seq.), the Filled Milk Act (21 U.S.C. 61-63), the Federal Import Milk Act (21 U.S.C. 141 et seq.), the Tea Importation Act (21 U.S.C. 41 et seq.), and the Federal Caustic Poison Act (44 Stat. 1406), the Fair Packaging and Labeling Act (15 U.S.C. 1451 et seq.).

(2) Sections 301 (Research and Investigations); 308 (International Cooperation); 311 (Federal-State Cooperation); 314(f) (Interchange of Personnel with States); and 315 (Health Education and Information) of the Public Health Service Act (42 U.S.C. 241, 242(f), 243, 246(f), and 247) relating to the functions of the FDA.

(3) Sections 354 through 360f of the Public Health Service Act (42 U.S.C. 263b through 263n) relating to electronic product radiation control.

(4) Section 361 of the Public Health Service Act (42 U.S.C. 264) relating to interstate travel sanitation (except interstate transportation of etiological agents under 42 C.F.R. 72.25), milk and food service sanitation and shellfish sanitation.

(5) Section 351 of the Public Health Service Act (42 U.S.C. 262) relating to regulation of biological products.

(6) Section 302(a) of the Public Health Service Act (42 U.S.C. 242(a)) relating to medicinal and scientific requirements of the United States for controlled substances.

(7) Section 303 of the Public Health Service Act (42 U.S.C. 242(a)) relating to protection of confidentiality in research on controlled substances.

(8) Section 4 of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (84 Stat. 1241) with respect to the safety and effectiveness of drugs or approval of new drugs to be used in treatment of narcotic addicts.

(9) Section 303(f) of the Controlled Substances Act (21 U.S.C. 823(f)) regarding qualifications of practitioners wishing to conduct research with Schedule I controlled substances and the merits of the research protocol.

(10) Provisions of the Controlled Substances Act (21 U.S.C. 801 et seq.) which relate to administration of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 301 et seq.).

(11) Section 409(b) of the Federal Meat Inspection Act (21 U.S.C. 679(b)) relating to the detention of meat products.

(12) Section 24(b) of the Poultry Products Inspection Act (21 U.S.C. 467f(b)) relating to the detention of poultry products.

(13) The Egg Products Inspection Act (21 U.S.C. 1031 et seq.).

(14) Amendments to the foregoing statutes subsequent to the Reorganization Plan No. 1 of 1953 (which established the Department).

(15) The issuance of all regulations pursuant to authorities cited in paragraphs (1) through (14).

(16) Sections of Executive Order 11490 (emergency preparedness) which relate to food, drugs, and biologicals.

(17) Authorizing and approving miscellaneous and emergency expenses of enforcement activities.

(18) The Federal Advisory Committee Act to make determinations that advisory committee meetings may be closed to the public for those committees under the administrative jurisdiction of the Commissioner of Food and Drugs.

The Committee intends that any other present functions or activities now carried out by the FDA shall also be transferred from the Secretary to the Commissioner, and the Committee does not intend that the omission of any function or activity from the foregoing list to imply that such function or activity is to be reserved to the Secretary. Section 905(b) makes it clear that the Secretary may by regulation delegate additional functions to the Commissioner as he deems appropriate.

Under new Section 905(a)(2) the Secretary's non-delegable authority under Sections 505(e), 512(e), and 512(m) to suspend the approval of a drug which presents an imminent hazard to health is transferred to the Commissioner. Such authority shall not be redelegated by the Commissioner, which is an explicit exception to the Commissioner's power under new Section 904(a)(13) to delegate any of his functions and duties to other officers of the Administration.

Section 203

The Committee does not intend by enactment of Title II to express any dissatisfaction with the officials who are now serving the FDA as Commissioner, Deputy Commissioner, or Assistant General Counsel of Food and Drugs. On the contrary, the Committee believes that each of these individuals has performed admirably in service of the public interest. The Committee believes it would be in the interest of orderly transition for the incumbents to continue in office.

Under Section 203(a) the effective date of the Act is 90 days after the Commissioner first takes office, or on such prior date after enactment of this Act as the President shall prescribe and publish in the Federal Register. In no event shall the Act take effect later than 180 days after enactment, but he may act to make this appointment at an earlier date. The Committee intends that to the extent feasible, appointments be made to the positions of Deputy Commissioner and General Counsel at the same time that the initial appointment is made to the post of Commissioner.

APPENDIX

MAY 20, 1975.

Hon. RICHARD S. SCHWEIKER,
U.S. Senate,
Washington, D.C.

DEAR SENATOR SCHWEIKER: You will recall during recent appropriation hearings we discussed research ongoing at NIEHS on diethylstilbestrol. Enclosed for your information is a copy of a short report prepared by Dr. McLachlan of my staff. Should you have any further questions regarding this problem, we would be happy to provide additional information.

Sincerely yours,

DAVID P. RALL, M.D., Ph.D.,
Director.

Enclosure.

GENITAL TRACT FUNCTION IN MICE EXPOSED PRENATALLY TO
DIETHYLSTILBESTROL

(By John A. McLachlan, Developmental Toxicology Section, Environmental Toxicology Branch, National Institute of Environmental Health Sciences)

Although many compounds are continuously introduced into our environment, few of them have been examined for their potentially toxic effect on reproduction and development. Virtually nothing is known about the effect of prenatal exposure to common drugs and chemicals on the postnatal development of the offspring. The fact that no division of oocytes occurs postnatally in man or laboratory rodents makes the process of oogenesis especially susceptible to chemical intervention during the prenatal period. However, the effects of such *in utero* drug exposure may not become evident until much later in the animal's life when sexual maturity is reached. Given the possibility of long-term genetic damage to the developing oocyte or transplacental carcinogenic changes in the reproductive tract, reduced fertility in the offspring may be only the most obvious consequence of prenatal exposure to environmental chemicals.

Research in our laboratory is concerned with the effects of prenatal exposure to common environmental chemicals on the function of the reproductive tract in the offspring. For the past two years we have been particularly interested in the synthetic estrogen, diethylstilbestrol (DES). DES is currently used as a food additive for cattle and a post-coital contraceptive for women.

In 1971, Herbst and his colleagues described the latent appearance of a previously rare genital tract tumor, vaginal adenocarcinoma, in young women whose mothers had been given DES during their gesta-

tions (N. Eng. J. Med. 284:878, 1971). These findings have since been confirmed and expended (e.g., Greenwald, *et al.*, N. Eng. J. Med. 285:390, 1971; Tsukada, *et al.*, Cancer 29:1208, 1972; Gilson *et al.*, Obst. & Gynec. 41:494, 1973; Herbst, *et al.*, Am. J. Obstet. Gynecol. 119:713, 1974).

Estrogen, in high doses, has long been known to alter the development of the fetal reproductive tract in laboratory animals (A. Reynaud, pp. 179-231 in *The Ovary*, Vol. 2, S. Zuckerman, ed., 1962). However, very little is known about the effects of such fetal exposures on the subsequent function of the genital tract in the mature offspring. In light of the current confusion regarding the mechanisms of the fetotoxic effect of DES and the uncertainty of the time course of such effects in the offspring, the importance of an animal system is obvious.

We decided to approach the DES problem on several levels simultaneously by research efforts in our laboratory and in collaboration with other scientists at the Institute. Although the extrapolation of results obtained in laboratory animals to man is always dangerous, it should be pointed out that the highest dose used in our experiments (on a μg DES/kg body weight basis) was less than or equal to the doses used therapeutically during human pregnancy.

At the recent Society of Toxicology meeting (Abstract 3), a member of our group reported on a study of the distribution and metabolism of DES in the pregnant mouse. This information is important in determining how much of the maternally administered DES, if any, reaches the fetus. It was shown that DES is very rapidly removed from the mother's body, but measurable amounts of the chemically unmodified (and therefore presumably biologically active) compound reach the fetal reproductive tract.

We then asked the question: What is the effect of DES administration during pregnancy on the function of the reproductive tract in the offspring? One of our initial findings (Abstracts 1, 4) was that the primary function of the female genital tract, the ability to produce young, was severely impaired by prenatal exposure to DES.

Prepubescent female mice derived from subcutaneously DES-treated mothers were housed throughout their reproductive lifetime with a fertile, untreated male mouse. The cumulative number and "quality" of the young produced by these prenatally DES-exposed females was determined; such data has been shown to be a sensitive index of fertility in female rodents.

As shown in the enclosed figure, the effect on female mice exposed to DES from the 9th to 16th days of their gestations ranged, in a dose related manner, from minimal subfertility ($0.1 \mu\text{g}$ DES/kg of maternal body weight/day) to sterility ($100 \mu\text{g/kg/day}$ dose).

Experiments are currently underway to elucidate the mechanisms involved in these observations. Results suggest that impaired ovarian function contributes to the reduced fertility seen in prenatally DES-exposed females. Pathologic lesions of the vagina, cervix and uterus have also been observed. It seems likely that these changes (including vaginal adenosis and cellular changes resembling adenocarcinoma) will provide a possible animal model for human exposure.

Although reproductive failure in young women exposed prenatally to DES has not been reported in the clinical literature, the apparent high incidence of anovulatory bleeding and infertility in the 15 girls examined by Pomerance (Obst. & Gynec. 42:12, 1973) suggests that this would not be an unexpected finding in humans.

An other area of current investigation is the effect of gestational exposure to DES on the reproductive tract of the male offspring; except for the pseudohermaphroditic neonate described by Kaplan (N. Eng. J. Med. 261:641, 1959), little is known concerning such exposure in humans. When male offspring from mice treated with DES (100 $\mu\text{g/kg/day}$ dose) were examined at 7-9 months of age, 60% were sterile. The reproductive tract lesions found in this group of mice are summarized in the enclosed table and Abstract 5.

Experiments focusing on fetal mice have shown that similar embryonic tissues may be involved in the DES effects in both males and females. By studying various parts of the fetal genital tract *in vitro* (Abstract 2), we hope to gain a better understanding of the direct action of DES and other common environmental agents on the development of this important organ system. These studies are coupled with collaborative biochemical research with other members of our section.

Finally, our section is presently evaluating bids on a contract which will, in part, be used to expand two aspects of ongoing DES research: (1) examination of large numbers of male and female offspring derived from mothers exposed to low levels of DES; (2) determination of dietary levels of DES necessary to produce genital tract lesions in the offspring.

[Deadline Date: Monday, May 21, 1973]

Important: These instructions must be followed completely. Read all instructions before you begin typing on this special form. See also sample abstracts on the reverse of this sheet.

SESSION TOPICS SUGGESTED FOR THIS PAPER

Topic No. and Title:

28—Developmental Pharmacology.

47—Toxicology.

Practice typing the abstract in a rectangle $5\frac{1}{4}'' \times 4\frac{1}{4}''$ on plain paper before using the special form.

FORMAT FOR ABSTRACT

1. Use a typewriter, preferably electric with ELITE type. Clean type before using. Use a carbon ribbon, if possible; otherwise, a reasonably new, good quality, BLACK ribbon. (A new ribbon may smudge; an old ribbon may be too faint.)

2. Single space all typing on this form. The text of the abstract should be a single paragraph, starting with a 3-space indentation. Leave no top or left margin within the rectangle. Use short specific titles. Use standard abbreviations such as those listed on the reverse side. Capitalize the first letter of trade names.

3. When using abbreviations for compounds, spell out in full the first mention, followed by the abbreviation in parentheses (see sample abstract on reverse side). Do not abbreviate compounds in the title of the abstract. Use of unfamiliar abbreviations may be grounds for rejection unless definitions are supplied in the abstract.

4. Any special symbols, such as Greek letters, that are not on your typewriter must be drawn by hand in BLACK ink. Tables are permitted within this space.

5. Underline names and initials of all authors. Place an asterisk (*) after the name of each author who is not a member of the Society. If no author is a member, type after name of last author. (SPON: ----- followed by name of sponsoring member). See Example 2 on reverse side.

6. DO NOT ERASE. Remember that your abstract will appear in THE PHARMACOLOGIST exactly as you submit it; any erasure smudges, errors, misspellings, poor hyphenation, and deviations from good usage will be glaringly apparent in the published abstract.

NOTE.—Any poorly prepared abstract unsuitable for direct reproduction will be retyped by the printer and the author will be charged for such.

7. Prepare 3" × 5" index cards, one for each author.

8. Complete the enclosed Abstract Identification Card, one for each abstract.

9. Chemical compounds mentioned in the abstract must be adequately identified.

10. Mailing address of first author:

J. A. McLachlan, National Institute
of Environmental Health Sciences,
P. O. Box 12233 Research Triangle Park, North Carolina, Zip 27709,
Telephone No: Area Code 919-549-8411

11. Signature of Member. Each Abstract Form A submitted MUST BE SIGNED by a member of the American Society for Pharmacology and Experiment Therapeutics.

ROBERT L. DIXON,
Signature of ASPET Member.

Mail to:

Dr. Ellsworth B. Cook, Executive Officer,
American Society for Pharmacology and Experimental Therapeutics

EFFECT OF GESTATIONAL EXPOSURE TO DDT OR DIETHYLSTILBESTROL, THE REPRODUCTIVE CAPACITY OF OFFSPRING

(J. A. McLachlan*, R. L. Dixon)

NIEHS, NIH, Research Triangle Park, N.C. 27

DDT possesses weak estrogenic activity and induces sterility in rats treated neonatally. In humans, prenatal exposure to diethylstilbestrol (DES), a synthetic estrogen, has been associated with increased incidence of vaginal carcinoma in the female offspring. We have investigated the effects of natal exposure to each of these common environmental chemicals on postnatal reproductive capacity. Pregnant mice were treated s.c. with DDT (1 mg/kg) or DES (10 or 0.01 µg/kg) on day 10–16 of gestation. At puberty, no significant differences were observed between the female control or prenatally drug-exposed offspring in their ability to respond to exogenous gonadotropins, in quantitative ovarian morphology, or in the estrous cycles. However, during 30–60 weeks of repetitive forced breeding initiated at puberty, the female offspring of DDT-treated mice produced 30% fewer young than did the corresponding controls. Those females exposed to the high or low dose of diethylstilbestrol delivered 60% and 40% fewer young respectively. Although the mechanism of action is unclear, these data suggest that prenatal exposure to selected environmental chemicals may adversely affect the subsequent reproductive capacity of the female offspring.

[Presented at Society for the Study of Reproduction, August 1975]

ORGAN CULTURE OF FETAL MOUSE OVARIES

(J. A. McLachlan* and J. W. Spalding, Environmental Toxicology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, N.C.)

Recent studies in our laboratory have dealt with the effects of prenatal exposure to common environmental chemicals on ovarian development (McLachlan, J. A. and Dixon, R. L. 1973. *Pharmacologist* 15, 199). In order to investigate the mechanisms involved and to evaluate basic problems in mammalian oogenesis, a system in which ovarian development occurs *in vitro* was established. Ovaries from the fetuses of C57B1/6 mice were explanted onto siliconized lens paper rafts at the 12th or 16th day of gestation. The organs were maintained in a modified Eagle's Basal Medium (BME) supplemented with 10% fetal calf serum. The morphological development of the explanted ovaries from 12-day fetal mice during one week in culture compared well to ovarian development occurring at corresponding intervals *in vivo*. This period included the differentiation of the female germ cells from mitotically active oogonia to oocytes in the dictyate stage of meiotic prophase. Development ceased with the formation of isolated unilaminar follicles. However, when ovaries containing oocytes in various stages of meiotic prophase were explanted from 16-day fetal mice, *in vitro* ovarian development continued to closely parallel that seen *in vivo* for two weeks. At the end of this interval the cultured ovaries contained follicles ranging in size from one to three granulosa cell layers.

[Presented at the 1975 Annual Society of Toxicology Meeting, March 1975]

THE FATE OF ^{14}C -DIETHYLSTILBESTROL IN THE PREGNANT MOUSE

(H. C. Shah, S. Gipson, and J. A. McLachlan, Sponsor: I. P. Lee, National Institute of Environmental Health Sciences, Research Triangle Park, N.C.)

Although prenatal exposure to the synthetic estrogen, diethylstilbestrol (DES), has been reported to reduce fertility (McLachlan and Dixon, *Pharmacologist* 15:199, 1973) or cause vaginal tumors (Herbst *et al.*, *N. Engl. J. Med.* 284:878, 1971) in the offspring, very little is known about the physiologic disposition of DES in the pregnant animal. Thus, we have investigated the tissue distribution, metabolism, and excretion of ^{14}C -DES during gestation. Monoethyl- ^{14}C -Diethylstilbestrol ($5.8 \mu\text{Ci/kg}$; $30 \mu\text{g/kg}$) was administered intravenously to timed pregnant CD-1 mice on the 16th day of gestation. Mice were sacrificed at appropriate times after dosing, and the radioactivity characterized in plasma, liver, muscle, placenta, and fetus; localization of ^{14}C -DES in specific fetal organs was attempted. ^{14}C -DES was

rapidly distributed in the body since its concentration in plasma obtained $\frac{1}{2}$ minute following intravenous administration was half that of the corresponding $\frac{1}{4}$ minute value. In addition, the parent compound accounted for only 50% of the total plasma radioactivity by 10 minutes after dosing. The muscle/plasma radioactivity ratio (DPM per gm tissue/DPM per ml plasma) was 1.04 at $\frac{1}{2}$ minute following treatment; muscle ^{14}C -activity paralleled that in plasma throughout the rest of the 4 hour experiment. On the other hand, radioactivity entered the fetus more slowly, the fetus/plasma radioactivity ratio being less than one until 30 minutes after administration. Persistent fetal uptake resulted in a 3-fold accumulation, relative to plasma, of ^{14}C -activity in the conceptus at 4 hours. The relationship of the distribution of DES to its fetotoxic effects is presently unclear.

[Presented at the 1975 Annual Society of Toxicology Meeting, March 1975]

EFFECT OF PRENATAL EXPOSURE TO DIETHYLSTILBESTROL ON
REPRODUCTIVE TRACT FUNCTION IN THE OFFSPRING

(J. A. McLachlan*, H. C. Shah, R. R. Newbold, and B. C. Bullock,
Sponsor: R. L. Dixon, National Institute of Environmental Health
Sciences, Research Triangle Park, N.C.)

Although much is known about the teratogenic activity of drugs and other common environmental chemicals, few studies have been done on the postnatal effects of prenatal drug exposure. Recent reports (e.g., Greenwald *et al.*, N. Engl. J. Med 285:390; 1971) of the latent appearance of vaginal carcinomas in pubescent girls whose mothers had been given the synthetic estrogen, diethylstilbestrol (DES), during their gestation suggest the importance of such investigations. To assess the effect of prenatal exposure to DES on reproductive tract function in the offspring, timed pregnant CD-1 mice were treated subcutaneously with DES on days 9 through 16 of gestation, inclusive. The fertility of the offspring was determined postnatally by repetitive breeding techniques at the appropriate times. After *in utero* treatment with DES, the reproductive capacities of the female offspring were impaired. These effects ranged in a dose-response manner from minimal subfertility (prenatal DES dose: $0.01 \mu\text{g/kg/day}$) to complete sterility (10 or $100 \mu\text{g/kg/day}$ dose). A major component of the sterility seen in the high DES dose females was ovarian, since the number of ova recovered after induced ovulation was only 30% that of controls. Sixty percent of the male offspring were found to be sterile following prenatal exposure to $100 \mu\text{g/kg}$ DES; no effect was seen at the lower doses. An unusual finding was the presence of unique reproductive tract alterations (including metaplastic and/or neoplastic tissue) in 80% of the males exposed prenatally to the high dose of DES. These results suggest that *in utero* treatment with DES results in permanent impairment of the offspring's reproductive capacities.

17TH MEETING OF THE EUROPEAN SOCIETY FOR TOXICOLOGY—
JOINT MEETING WITH THE SOCIETY OF TOXICOLOGY

Please, type your abstract below. Give title in the language in which the paper will be delivered, author's names and department. Underline name of author who will present the paper. Send abstract in duplicate before January 10, 1975 to:

Robert A. Scala, Ph.D.
Exxon Research and Engineering Company
Medical Research Division
P.O. Box 45
Linden, New Jersey 07036 (U.S.C.)

Free communications are allocated 10 minutes for presentation and 5 for discussion. The manuscript of the paper should be handed to secretariat at the beginning of the meeting for the publication of the proceedings.

Title: Lesions in the Genital Tract of Male Mice Following Prenatal Exposure to Diethylstilbestrol

Authors: J. A. McLachlan.

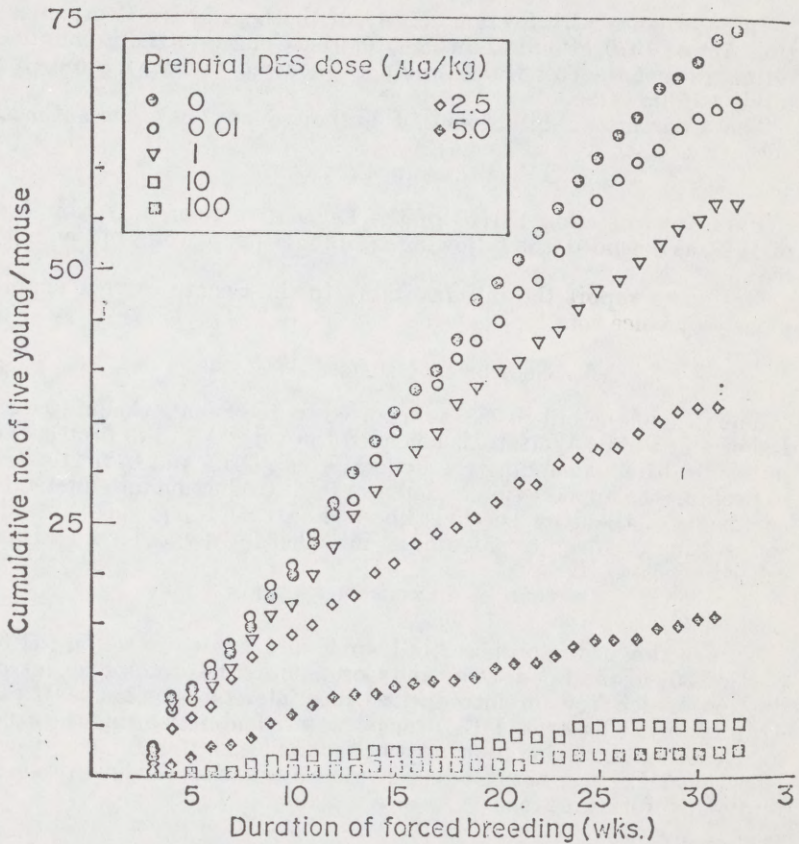
Institute, Address:

National Institute of Environmental Health Sciences,
Research Triangle, North Carolina 27709

(Please continue your abstract to space below)

Recent reports (Herbst *et. al.*, N. Eng. J. Med. 284: 878, 1971) have described the latent appearance of previously rare genital tract tumors in young women whose mothers had been given diethylstilbestrol (DES) during their gestations. On the other hand, the effects of prenatal exposure to DES on the male offspring have not been described. Thus, timed pregnant CD-1 mice were treated subcutaneously with DES (100 ug/kg) in corn oil on days 9 through 16 of gestation. Sixty percent of the prenatally drug-exposed male offspring were sterile. When these mice were sacrificed at 9-10 months of age, gonadal changes were found in 15 of 24 animals; these included intraabdominal and/or fibrotic tests. Epididymal cysts in association with fibromuscular growths were observed in one third of these young. Alterations in the accessory sex glands were observed in addition to the gonad-related lesions. Nodular enlargements associated with squamous metaplasia occurred in the amoullary region of the reproductive tract of five males. In one addition case, this enlargement appeared to be neoplastic. The fibromuscular growths and metaplastic/neoplastic nodular enlargements appeared in areas associated with Mullerian duct remnants of the male. These results raise the possibility that DES may affect the same embryonic tissue in both male and female fetuses.

Total reproductive capacity of mice exposed prenatally to DES



PATHOLOGIC LESIONS IN THE REPRODUCTIVE TRACT OF MALE MICE
EXPOSED PRENATALLY TO DES

Prenatal treatment	Incidence of lesions ¹	Location of lesions		
		Testis ²	Epididymis ³	Accessory sex glands ⁴
Corn oil.....	0/14	0	0	0
DES.....	18/24	15	10	6

Note: Males were the 9 to 10 mo. old offspring of CD-1 mice treated with DES (100 $\mu\text{g/kg}$; s.c.) on days 9 to 16 of gestation.

¹ Expressed as the ratio: number of male offspring with 1 or more reproductive tract lesion/number of male offspring examined.

² Lesions included: (1) intraabdominal retention and/or fibrosis and calcification of testes, (2) reduction in number of spermatogonia with multinucleate cells in lumina of testes.

³ Epididymal cysts.

⁴ Lesions seen in the area of the seminal colliculus, the nodular masses of 5 animals were associated with squamous metaplasia—the cellular atypia in 1 animal resembled early neoplasia.

III. COST ESTIMATES PURSUANT TO SECTION 252 OF THE LEGISLATIVE REORGANIZATION ACT OF 1970

In accordance with Section 252(a) of the Legislative Reorganization Act of 1970 (Public Law 91-510, 91st Congress) the Committee estimates that the cost which would be incurred in carrying out this bill is as follows:

The Committee's bill does not authorize any new obligational authority.

IV. VOTES IN COMMITTEE

Pursuant to section 133(b) of the Legislative Reorganization Act of 1949, as amended, the following is a tabulation of votes in Committee:

Motion to report the bill favorably to the Senate carried unanimously by voice vote.

V. SECTION-BY-SECTION ANALYSIS

The title of the bill S. 963, as reported by the Senate Committee on Labor and Public Welfare, is amended to read: "A bill to protect the public health by amending the Federal Food, Drug and Cosmetic Act to prohibit the introduction or delivery for introduction into interstate commerce of the drug Diethylstilbestrol (DES) for purposes of administering the drug to any animal intended for use as food, and for other purposes."

TITLE I—CANCER PREVENTION

Section 101

This section of the proposed bill would add a new subsection (q) to Section 301 of the Food, Drug and Cosmetic Act to prohibit the introduction or delivery for introduction into interstate commerce of the drug Diethylstilbestrol (DES) for purposes of administering the drug to any animal intended to be used as food. This section further stipulates that DES may not be administered to any animal whose product is intended for use as food.

Section 102

This section of the proposed bill would add a new subsection (q) to Section 502 of the Food, Drug and Cosmetic Act. (Section 502 of the Act lists the conditions under which a drug or device is considered to be misbranded.)

The proposed new subsection of the existing public law would consider a drug to be misbranded if it were wholly or partially composed of Diethylstilbestrol (DES), unless its labelling and packaging would adhere to a series of guidelines, which are set forth in this section of the proposed bill.

The first of these six directives require that the drug's label bear the following three statements:

- (1) Warning—This drug may cause cancer;
- (2) this drug may not be used as a contraceptive after sexual intercourse except in cases of rape or incest or a comparable medical emergency;
- (3) this drug may not be taken unless a patient or

patient's legal guardian has given his written consent after full verbal disclosure by the attending physician of the risks, benefits, and alternative methods of treatment.

The second guideline directs that each capsule or tablet be pre-packaged by the drug producer in units which contain the appropriate number of capsules or tablets for the desired course of treatment. It also requires that the three bold-faced statements mentioned above be placed conspicuously on the label next to the capsules or tablets so that the patient may have an opportunity to read them during the entire prescription period.

The third guideline directs that the bold-faced statements mentioned above must be twice as large in size as any other words and statements required by law.

The fourth item listed in this section of the proposed bill requires that a multi-copy "informed consent form" be part of the drug's label. (This form is defined later in subsection (2) (a) of the proposed bill to mean a form that will be issued by the Secretary of the Department of Health, Education, and Welfare, approved by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (*The Commission*), and fully explained by the attending physician to the patient. The form must then be completed by the attending physician and the patient or the patient's legal guardian. According to this proposed subsection (q) (2) (A) of the Act, if *The Commission* fails to take action within 60 days after the Secretary of HEW submits the proposed informed consent form, it shall be considered approved.

The fifth guideline set forth in this section of the bill requires that a copy of each completed informed consent form, along with a written record of the attending physician's prescription, be submitted by the physician to the Secretary of HEW, in whatever form and whenever the Secretary may require, but not fewer than four times a year. It further states that the completed form and prescription record are required to contain both the attending physician's license number and the name of the State which issued the license.

The sixth and final directive requires that a copy of each prescription for this drug which has been presented to a pharmacist be submitted by the pharmacist to the Secretary of HEW, in whatever form and whenever the Secretary may require, but not fewer than four times a year. It further requires that each prescription submitted contain both the attending physician's license number and the name of the State which issued the license.

Subsection (2) (A) of this section of the bill has been previously described in full.

The remainder of this section of the proposed bill is devoted to the clarification of points made in earlier statements. For example, subsection (q) (2) (B) provides that drug producers will not be held liable for misbranding. Subsection (q) (2) (C) provides that no patient names or other identifying information may appear on any informed consent form, prescription, or report submitted to the Secretary of HEW. It further states that no patient name or other identifying information may be submitted to or collected by the Secretary.

TITLE II—FOOD AND DRUG ADMINISTRATION

Section 200

This section of the proposed bill provides short title, "Food and Drug Administration Act."

Section 201

This section of the proposed bill adds new Sections 903, 904, and 905 to the Federal Food, Drug and Cosmetic Act as follows:

New Section 903—Food and Drug Administration

(a) Establishment of the Food and Drug Administration within the Department of Health, Education, and Welfare.

(b) A Commissioner appointed by the President with the advice and consent of the Senate and for a term of five years (to serve no more than two terms) would head the Food and Drug Administration. The Commissioner is responsible for the effective administration of laws subject to his jurisdiction.

(c) Provides the President shall also appoint, with the advice and consent of the Senate, a Deputy Commissioner and General Counsel for the Administration for terms of five years each.

New Section 904—Powers of the Commissioner

(a) To fulfill his duties under the laws subject to his jurisdiction, the Commissioner is empowered to:

- (1) Direct and supervise all personnel of the Administration.
- (2) Employ and compensate (not above the GS-18 level) experts and consultants.
- (3) Appoint advisory committees.
- (4) Promulgate regulations necessary under the laws subject to his jurisdiction.
- (5) Utilize facilities of other Federal, State or private agencies, with or without reimbursement.
- (6) Enter into agreements and contracts with State or appropriate private persons or corporations.
- (7) Accept gifts and uncompensated services.
- (8) Designate representatives to serve on committees to maintain effective liaison with standard-setting bodies.
- (9) Construct research or test facilities subject to authorization and funding by Congress.
- (10) Conduct public hearings anywhere in the United States.
- (11) Prescribe personnel policies for the Administration.
- (12) Undertake such other activities as are incidental to enforcement of laws subject to his jurisdiction.
- (13) Delegate any of these functions to officers of the Administration (except that the Commissioner shall not delegate power to suspend drug approvals because of imminent hazard to health).

(b) Provides that nothing in the Act prevents Commissioner from undertaking any activities previously performed by the Secretary through FDA.

New Section 905—Functions of the Commissioner

(a) (1) All functions of the Secretary of Health, Education, and Welfare administered through the Food and Drug Administration are transferred to the Commissioner of Food and Drugs.

(2) Functions of the Secretary to suspend the approval of a new drug, a new animal drug, or a medicated animal feed as an imminent hazard to health are transferred to the Commissioner and shall not be redelegated.

(b) The Secretary may delegate additional functions to the Commissioner.

(c) (1) Personnel, properties, and so forth used primarily with regard to the transferred functions are transferred to the Commissioner. For personnel so transferred, there would be no reduction in classification or compensation for one year.

(2) Transfer of Commissioned Officers in the Public Health Service Corps is authorized.

(d) The Civil Service Commission shall establish criteria in consultation with the Commissioner regarding competitive examinations for positions in the Administration.

(e) Laws so transferred will remain in effect, and cases and other actions under such statutes shall be preserved.

Section 202—Compensation: Additional Positions

(a) (1) Places Commissioner of Food and Drugs in executive level III.

(2) Places the Deputy Commissioner, FDA, and General Counsel, FDA, in executive level IV.

(b) Authorizes the Commissioner to appoint an additional 25 super-grade (GS 16-18) positions in FDA.

Section 203—Effective Date; Initial Appointment of Officers

(a) The Act will take effect 90 days after the Commissioner first takes office, or such prior date after enactment as the President may prescribe (not later than 180 days after enactment).

(b) Officers provided for under this Act may be appointed as prescribed in this Act at any time after enactment, to be compensated at the rates provided in this Act.

VI. CHANGES IN EXISTING LAW

In compliance with subsection (4) of rule XXIX of the Standing Rules of the Senate, changes in existing law made by titles I and II of the bill, as reported, are shown as follows (existing law proposed to be omitted is enclosed in black brackets; new matter printed in italic):

FEDERAL FOOD, DRUG, AND COSMETIC ACT

* * * * *

CHAPTER III—PROHIBITED ACTS AND PENALTIES

PROHIBITED ACTS

SEC. 301. * * *.

(g) *The introduction or delivery for introduction into interstate commerce of the drug diethylstilbestrol (DES) for purposes of ad-*

ministering the drug to any animal intended for use as food or to any animal the product of which is intended for use as food.

* * * * *

CHAPTER V—DRUGS AND DEVICES

MISBRANDED DRUGS AND DEVICES

SEC. 502. * * *

(q) (1) *If it is, or purports to be, or is represented as a drug composed wholly or partly of diethylstilbestrol (DES), unless—*

(A) *its label bears the following statements:*

(1) *Warning—This Drug May Cause Cancer;*

(2) *This Drug May Not Be Used as a Contraceptive After Sexual Intercourse Except in Cases of Rape or Incest or a Comparable Medical Emergency;*

(3) *This drug may not be taken unless a patient or patient's legal guardian has given his written consent after full verbal disclosure by the attending physician of the risks, benefits, and alternative methods of treatment; and*

(B) *each and every capsule or tablet is pre-packaged, by the drug producer, in units which contain the appropriate number of capsules or tablets for the desired course of treatment and the statements required by subsection (q) (1) (A) of this section are conspicuously placed on the label next to the capsules or tablets so as to permit the patient an opportunity to read the statements during the entire prescription period. The letters contained in the statements required by subsection (q) (1) (A) of this section are twice as large in size as any other words and statements required by this Act; and*

(C) *there is a multi-copy "informed consent form" which is deemed part of the label for the purpose of this Act; and*

(D) *a copy of each and every executed informed consent form and a written record of each and every attending physician's prescription for such drug is submitted by the attending physician to the Secretary at such times and in such form as the Secretary may require and not less than four times a year. Each and every executed informed consent form and prescription record submitted to the Secretary shall contain both the attending physician's license number and the name of the State which issued such license number; and*

(E) *a copy of each and every prescription for such drug which has been presented to a pharmacist is submitted by the pharmacist to the Secretary at such time and in such form as the Secretary may require and not less than four times a year. Each and every prescription submitted to the Secretary shall contain both the attending physician's license number and the name of the State which issued such license number.*

(2) (A) *For the purpose of this subsection an "informed consent form" means a form issued by the Secretary and approved by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (hereinafter in this subsection referred to as the "Commission") and is fully explained by the attending physician to the patient and is thereafter executed by the attending physician and patient or the patient's legal guardian. If the Commis-*

sion fails to take action within sixty days after the Secretary submits the proposed informed consent form, it shall be deemed approved.

(B) Drug procedures shall not be held liable for misbranding under subsections (g) (1) (D) and (E) of this section.

(C) No patient names or other identifying information shall appear on any informed consent form, prescription, or report submitted to the Secretary. No patient name or other identifying information shall be submitted to or collected by the Secretary.

* * * * *

CHAPTER IX—MISCELLANEOUS

* * * * *

FOOD AND DRUG ADMINISTRATION

Sec. 903. (a) There is hereby established within the Department of Health, Education, and Welfare an agency to be known as the Food and Drug Administration (hereinafter referred to as the "Administration").

(b) The Administration shall be headed by a Commissioner of Food and Drugs (hereinafter referred to as the "Commissioner") who shall be appointed by the President, by and with the advice and consent of the Senate, for a term of five years. A Commissioner is eligible for reappointment only once. The Commissioner shall be responsible for the effective administration of the laws subject to his jurisdiction.

(c) The President shall appoint by and with the advice and consent of the Senate a Deputy Commissioner and General Counsel for the Administration for terms of five years each.

POWERS OF THE COMMISSIONER

Sec. 904. (a) In order to fulfill his duties under the laws subject to his jurisdiction, the Commissioner is empowered to—

(1) direct and supervise all personnel of the Administration;

(2) employ experts and consultants in accordance with section 3109 of title 5, United States Code, and compensate individuals so employed for each day (including traveltime) at rates not in excess of the maximum rate of pay for grade GS-18 as provided in section 5332 of title 5, United States Code, and, while such experts and consultants are so serving away from their homes or regular place of business, to pay such employees travel expenses and per diem in lieu of subsistence at rates authorized by section 5703 of title 5, United States Code, for persons in Government service employed intermittently;

(3) appoint advisory committees composed of such private citizens and officials of the Federal, State, and local governments as he deems desirable to advise him with respect to his functions under the law subject to his jurisdiction, and to pay such members (other than those regularly employed by the Federal Government) while attending meetings of such committees, or otherwise serving at the request of the Commissioner, compensation and

travel expenses at the rate provided for in paragraph (2) of this subsection with respect to experts and consultants;

(4) promulgate such regulations as may be necessary or appropriate to carry out the functions vested in him and for the efficient enforcement of the laws subject to his jurisdiction;

(5) utilize, with their consent, the services, personnel, and facilities of other Federal agencies and of State and private agencies and instrumentalities with or without reimbursement therefor;

(6) enter into and perform such contracts, leases, cooperative agreements, or other transactions as may be necessary or appropriate in the conduct of the work of the Administration and on such terms as the Commissioner may deem appropriate, with any agency or instrumentality of the United States, or with any State, territory, or possession, or any political subdivision thereof, or with any public or private person, firm, association, corporation, independent testing laboratory, or institution;

(7) accept gifts and voluntary and uncompensated services, notwithstanding the provisions of section 665(b) of title 31, United States Code;

(8) designate representatives to serve or assist on such committees as the Commissioner may determine to be necessary or appropriate to maintain effective liaison with Federal agencies and with State and local agencies and independent standard-setting bodies carrying out programs and activities related to the protection of consumers against injury resulting from the use of products subject to his jurisdiction;

(9) construct such research or test facilities as may be necessary to carry out the purposes of the laws subject to his jurisdiction, (A) after fully utilizing the personnel, facilities, and other technical support available in other Federal agencies, (B) when authorized by the Congress to plan, design, and construct such facilities, and (C) subject to the appropriation of funds for this purpose by the Congress;

(10) conduct public hearings anywhere in the United States to further the purposes of the laws subject to his jurisdiction;

(11) prescribe personnel policies for the Administration, including selecting, appointing, fixing compensation of, hiring, firing, promoting, and transferring of employees, subject to the civil service and classification laws;

(12) undertake such other activities as are incidental to enforcement of the laws subject to his jurisdiction; and

(13) except as provided in section 905(a)(2) delegate any of his functions and duties under the laws subject to his jurisdiction to other officers or employees of the Administration.

(b) Nothing in this section shall be construed to prevent the Commissioner from undertaking any activities previously performed by the Secretary through the Food and Drug Administration.

FUNCTIONS OF THE COMMISSIONER

Sec. 905. (a)(1) All functions of the Secretary of Health, Education, and Welfare administered through the Food and Drug Administration are transferred to the Commissioner of Food and Drugs.

(2) Functions of the Secretary to suspend the approval of an application because of an imminent hazard to health, pursuant to sections 505(e), 512(e), and 512(m) are transferred to the Commissioner of Food and Drugs and shall not be delegated.

(b) The Secretary of Health, Education, and Welfare may be regulation delegate such additional functions to the Commissioner as he from time to time deems appropriate.

(c) (1) All personnel, property, records, obligations, commitments, and unexpended balances of appropriations, allocations, and other funds, which are used primarily with respect to any office, agency, bureau, or function transferred under the provisions of this section are transferred to the Commissioner of Food and Drugs. The transfer of personnel pursuant to this subsection shall be without reduction in classification or compensation for one year after such transfer, and this provision shall not be construed to impair the authority of the Commissioner to assign personnel during this period to carry out the functions of the Administration most effectively.

(2) Any commissioned officer of the Public Health Service who, upon the day before the effective date of the Food and Drug Administration Act, is serving as such officer primarily in the performance of functions transferred by that Act to the Commissioner may, if such officer so elects, acquire competitive status and be transferred to a competitive position in the Administration subject to paragraph (1) of this subsection, under the terms prescribed in section 15(b) (3)-(8) (A) of the Clean Air Amendments of 1970 (84 Stat. 1676; 42 U.S.C. 215).

(d) The Civil Service Commission shall establish criteria in consultation with the Commissioner when preparing competitive examinations for positions in the Administration.

(e) All laws relating to any office, agency, bureau, or function transferred under the Food and Drug Administration Act shall, insofar as such laws are applicable, remain in full force and effect. And orders, rules, regulations, permits, or other privileges made, issued, or granted by any office, agency, or bureau or in connection with any function transferred by that Act, and in effect at the time of the transfer, shall continue in effect to the same extent as if such transfer had not occurred until modified, superseded, or repealed. No suit, action, or other proceeding lawfully commenced by or against any office, agency, or bureau of any office of the United States acting in his official capacity shall abate by reason of any transfer made pursuant to that Act.

UNITED STATES CODE

* * * * *

TITLE 5

COMPENSATIONS: ADDITIONAL POSITIONS

* * * * *

SEC. 5314. * * *

(60) Commissioner of Food and Drugs.

SEC. 5315. * * *

(98) *Deputy Commissioner, Food and Drug Administration.*

(99) *General Counsel, Food and Drug Administration.*

* * * * *

SEC. 5108(c) * * *

(9) The Railroad Retirement Board may place 4 positions in GS-16, in GS-17, and 1 in GS-18, for the purpose of its administration of chapter 9 or 11 of title 45, or both;

(10) the Chief Judge of the United States Tax Court, without regard to this chapter (except section 5114), may place a total of 5 positions in GS-16, 17, and 18; [and]

(11) the Chairman of the Equal Employment Opportunity Commission, subject to the standards and procedures prescribed by this chapter, may place an additional ten positions in the Equal Employment Opportunity Commission in GS-16, GS-17, and GS-18 for the purposes of carrying out title VII of the Civil Rights Act of 1964 [.] ; and

(12) *The Commissioner of Food and Drugs, without regard to this chapter (except section 5114), may place twenty-five positions in the Food and Drug Administration in GS-16, GS-17, and GS-18.*