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# NATIONAL ADVISORY COMMISSION ON HEALTH SCIENCE AND SOCIETY, 1971

GOVERNMENT  
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UMENTS



77 JOINT HEARING  
BEFORE THE  
SUBCOMMITTEE ON HEALTH  
AND THE  
AL SUBCOMMITTEE ON NATIONAL  
SCIENCE FOUNDATION  
OF THE  
COMMITTEE ON  
LABOR AND PUBLIC WELFARE  
UNITED STATES SENATE  
NINETY-SECOND CONGRESS

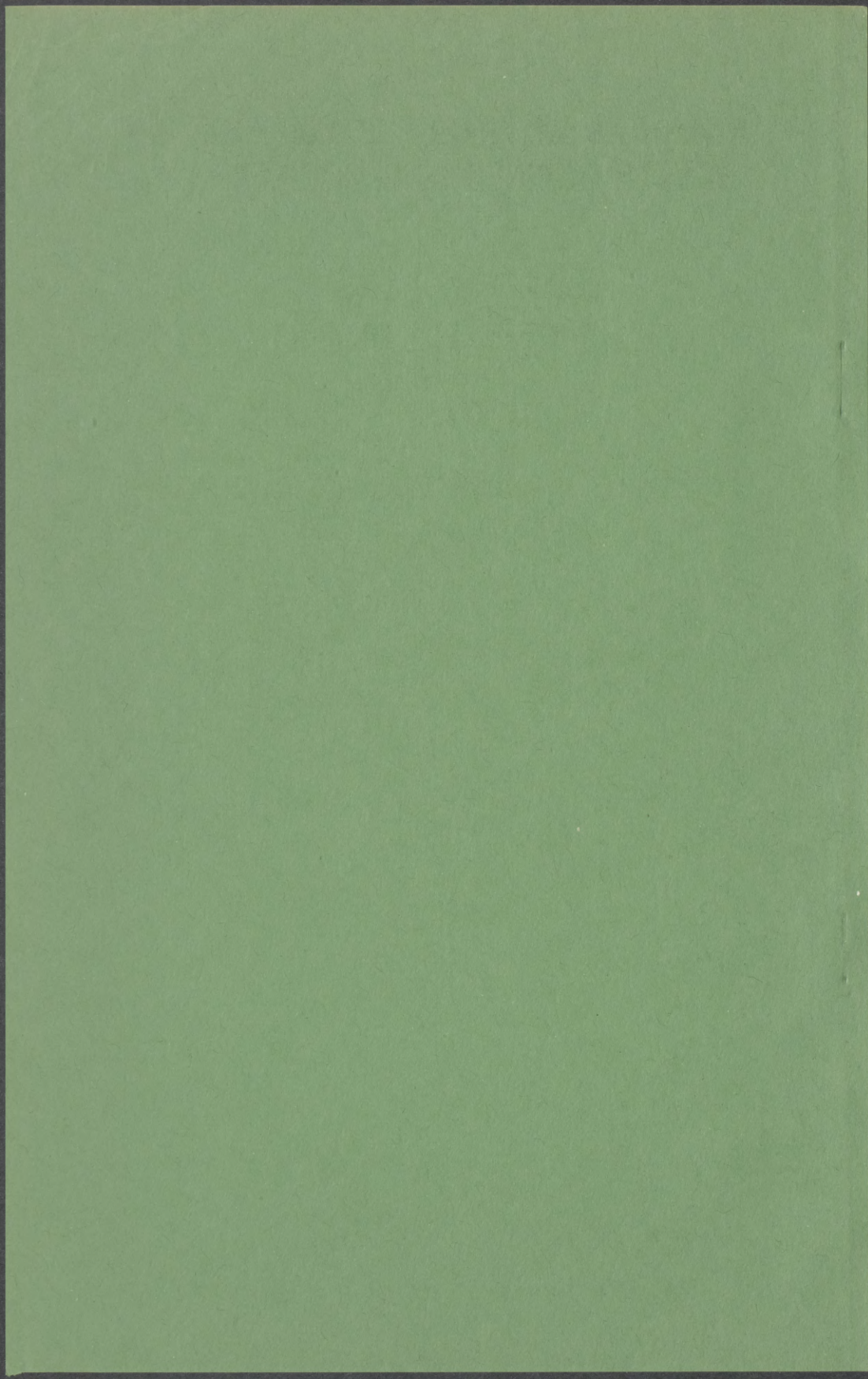
FIRST SESSION  
ON

## S. J. Res. 75

TO PROVIDE FOR A STUDY AND EVALUATION OF THE ETHICAL,  
SOCIAL, AND LEGAL IMPLICATIONS OF ADVANCES IN  
BIOMEDICAL RESEARCH AND TECHNOLOGY

NOVEMBER 9, 1971





# NATIONAL ADVISORY COMMISSION ON HEALTH SCIENCE AND SOCIETY, 1971

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NOVEMBER 9, 1971



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

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# NATIONAL ADVISORY COMMISSION ON HEALTH SCIENCE AND SOCIETY, 1971

TUESDAY, NOVEMBER 9, 1971

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U.S. SENATE,  
THE SUBCOMMITTEE ON HEALTH  
WITH THE SPECIAL  
SUBCOMMITTEE ON NATIONAL SCIENCE FOUNDATION  
OF THE COMMITTEE ON LABOR AND PUBLIC WELFARE,  
*Washington, D.C.*

The subcommittees met at 9:15 a.m., pursuant to notice, in room 4232, New Senate Office Building, Senator Edward M. Kennedy (chairman) presiding.

Present: Senators Kennedy, Mondale, Javits, and Dominick.

Committee staff present: Elilis R. Mottur, scientific adviser; Roy H. Millenson, minority professional staff member, and Jay B. Cuttler, minority counsel, Health Subcommittee.

Senator KENNEDY. The subcommittees will come to order.

The hearing today is part of a series of studies which we are conducting on the problems of health, science, and human rights.

Advances in modern medical science have lengthened the span and changed the quality and very meaning of human life. At the same time, these advances have opened a Pandora's box of ethical, social, and legal issues. The hearings will focus on these problems in areas such as heart transplants, artificial kidneys, test tube babies, genetic intervention, and experiments on humans.

For example, just last week a hospital in Virginia was sued for allegedly allowing a black laborer to die so that his heart could be used in a transplant operation. It would not be appropriate to comment on the merits of that particular case, but it illustrates the range of difficult questions which must be faced: When heart beat and other vital signs can be maintained by artificial means, how is death to be defined? Under what circumstances may the organs of the deceased be used for transplants? Who should give permission for such transplants? Did racial considerations affect the decision to use this heart, as alleged in the suit?

Another example occurred last month when the press reported that the Defense Department was sponsoring research on radiation effects on human beings, without adequately informing the individuals concerned of the military purpose of their irradiation. The news story charged further that the subjects of these experiments were charity cases with little education and low IQ's, implying that these factors limited their understanding of the purpose of the experiments.

I do not wish to comment on the validity of these charges until we complete our investigation of the case, but it illustrates the dangers involved in human experimentation. Does the whole body radiation

used in this project shorten the patients' life span? Does it increase their suffering or discomfort? How should answers to such questions be determined? And by whom? What information and guidance should be provided to the potential subjects of the experiment? How should their consent be obtained? And how should their rights be safeguarded?

Other difficult ethical and social questions arise:

Should carriers of hereditary diseases be allowed to have children?

Should retarded persons be segregated from members of the opposite sex? Should they be sterilized?

What are the ethical implications of test tube babies? What will happen to society when men and women are free to determine the sex of their children?

Which individuals should receive the benefits of artificial kidney facilities? How should we choose among those who need this help?

How should society regulate the use of behavior modification drugs and other techniques to control human behavior? How can we control the controllers?

How should the Nation allocate scarce medical resources between organ transplants for a few individuals versus research and services which help many?

The solutions to these problems cannot be found within science alone. Dr. Jerome Wiesner put it simply when he said: "Science is no substitute for thought." These issues cannot be resolved by complex mathematical formulas or high-speed computers.

They fundamentally involve questions of ethics and social responsibility. To come to grips with them, we must focus the full range of human talent and imagination—from the natural and social sciences, the arts and humanities, religion and philosophy, and the professions of law, medicine, and public service.

We must draw on all the resources mankind has to offer; for, after all, it is man's fate which is at stake.

Last month the Joseph P. Kennedy, Jr., Foundation sponsored an international symposium on these questions in Washington. The symposium drew together 1,200 outstanding scientists, scholars, and social activists from all over the world, from all disciplines and professions, to explore these problems and stimulate research and action on these issues.

Following the symposium 84 of the leading participants urged the establishment of programs that "improve the quality of our thinking and acting in matters so laden with potential for human welfare or woe, for human decency or human callousness."

These hearings are intended to carry forward the important work begun at the symposium, and to determine specific policies and legislative proposals which are needed to cope with these problems.

The hearing today will focus on the joint resolution to establish a National Advisory Commission on Health Science and Society, Senate Joint Resolution 75. This resolution was introduced last March by Senator Mondale who has provided leadership in this whole area.

I cosponsored it along with Senator Mondale and 16 other Senators. Since its introduction, Senators Cranston, Eagleton, Stevens, and Stevenson have been added as cosponsors.

At this point in the record we will enter a copy of the resolution.

(A copy of S.J. Res. 75 follows:)



## MEMBERSHIP

1

2       SEC. 3. (a) The Commission shall be composed of fifteen  
3 members to be appointed by the President from among the  
4 fields of medicine, law, theology, biological science, physical  
5 science, social science, philosophy, humanities, health ad-  
6 ministration, government, and public affairs.

7       (b) Any vacancy in the Commission shall not affect its  
8 powers.

9       (c) The President shall designate one of the members  
10 to serve as Chairman and one to serve as Vice Chairman  
11 of the Commission.

12       (d) Eight members of the Commission shall constitute a  
13 quorum.

14

## DUTIES OF THE COMMISSION

15       SEC. 4. (a) The Commission shall undertake a com-  
16 prehensive investigation and study of the ethical, social, and  
17 legal implications of advances in biomedical research and  
18 technology, which shall include, without being limited to—

19           (1) analysis and evaluation of scientific and techno-  
20 logical advances in the biomedical sciences, current and  
21 projected;

22           (2) analysis and evaluation of the implications of  
23 such advances, both for individuals and for society;

24           (3) analysis and evaluation through the use of  
25 seminars and public hearings and other appropriate

1 means, of public understanding of and attitudes toward  
2 such implications;

3 (4) analysis and evaluation of implications for pub-  
4 lic policy of such findings as are made with respect to  
5 the biomedical advances and public attitudes.

6 (b) The Commission shall make maximum feasible use  
7 of related investigations and studies conducted by public and  
8 private agencies.

9 (c) The Commission shall transmit to the President  
10 and to the Congress one or more interim reports and, not  
11 later than two years after the first meeting of the Commis-  
12 sion, one final report, containing detailed statements of the  
13 findings and conclusions of the Commission, together with  
14 its recommendations, including such recommendations for  
15 action by public and private bodies and individuals as it  
16 deems advisable.

17 POWERS OF THE COMMISSION

18 SEC. 5. (a) The Commission or, on the authorization  
19 of the Commission, any subcommittee or members thereof,  
20 may, for the purpose of carrying out the provisions of this  
21 joint resolution, hold such hearings, take such testimony,  
22 and sit and act at such times and places as the Commission  
23 deems advisable. Any member authorized by the Commis-  
24 sion may administer oaths or affirmations to witnesses ap-

1 pearing before the Commission or any subcommittee or  
2 members thereof.

3 (b) Each department, agency, and instrumentality of  
4 the executive branch of the Government, including independ-  
5 ent agencies, is authorized and directed, to the extent per-  
6 mitted by law, to furnish to the Commission, upon request  
7 made by the Chairman or Vice Chairman, such information  
8 as the Commission deems necessary to carry out its functions  
9 under this joint resolution.

10 (c) Subject to such rules and regulations as may be  
11 adopted by the Commission, the Chairman shall have the  
12 power to—

13 (1) appoint and fix the compensation of an execu-  
14 tive director, and such additional staff personnel as he  
15 deems necessary, without regard to the provisions of  
16 title 5, United States Code, governing appointments in  
17 the competitive service, and without regard to the pro-  
18 visions of chapter 51 and subchapter III of chapter 53  
19 of such title relating to classification and General Sched-  
20 ule pay rates, but at rates not in excess of the maximum  
21 rate for GS-18 of the General Schedule under section  
22 5332 of such title, and

23 (2) procure temporary and intermittent services  
24 to the same extent as is authorized by section 3109 of

1 title 5, United States Code, but at rates not to exceed  
2 \$100 a day for individuals.

3 (d) The Commission is authorized to enter into con-  
4 tracts with Federal or State agencies, private firms, institu-  
5 tions, and individuals for the conduct of research or surveys,  
6 the preparation of reports, and other activities necessary to  
7 the discharge of its duties.

8 COMPENSATION OF MEMBERS

9 SEC. 6. Members of the Commission shall receive com-  
10 pensation at the rate of \$175 per day for each day they  
11 are engaged in the performance of their duties as members  
12 of the Commission and shall be entitled to reimbursement  
13 for travel, subsistence, and other necessary expenses incurred  
14 by them in the performance of their duties as members of  
15 the Commission.

16 APPROPRIATIONS AUTHORIZED

17 SEC. 7. There is hereby authorized to be appropriated  
18 the sum of \$1,000,000 for the fiscal year beginning July 1,  
19 1971; and \$1,000,000 for the fiscal year beginning July 1,  
20 1972.

21 TERMINATION

22 SEC. 8. On the ninetieth day after the date of submis-  
23 sion of its final report to the President and the Congress,  
24 the Commission shall cease to exist.

Senator KENNEDY. I would like to ask Senator Mondale if he wishes to make any comments at this time.

Senator MONDALE. First, Mr. Chairman, I wish to express my appreciation to you for holding these hearings, and I have a full statement which I think I will just put in the record rather than read.

This is, I think, the fourth year now that we have tried to make some progress on this question. We held substantial hearings on this proposal 3 years ago in the Subcommittee on Government Research, chaired by Senator Fred Harris. It seems to me that the need for this kind of Commission on Health Science and Society is becoming more obvious every day. I sense that many who once opposed it are now for it, or at least have dropped their opposition.

Because many of the things that we predicted 4 years ago, such as the heart transplant lawsuit, are now coming true, and increasingly we see examples of where people are being experimented upon and don't know it. We are coming closer to breakthroughs in such areas as genetic engineering, by which it might be possible for one generation to more or less define what it wants in the next.

In no sense do I wish to interfere with science. Yet, I think science must serve society, and society has a right to know what science has in mind, because it, after all, has a right to say something about its own future.

I think this has to be a public process. I think there is a fear and a reluctance in the scientific community to let the public in on the act, as though the public is always irresponsible or dangerous or too rigid, or doesn't understand.

But I think, in a free society, the public must be a part of it. We obviously are. The Congress appropriates fantastic quantities of money for American medicine, which produces many of these technological breakthroughs. I don't see how we can be neutral on the matter.

For all these reasons, and the reasons I set out more fully in my statement, I am very appreciative we are having these hearings and I am hopeful we might finally adopt this resolution.

Senator KENNEDY. Your statement will be printed in its entirety in the record.

#### **STATEMENT OF HON. WALTER F. MONDALE, A U.S. SENATOR FROM THE STATE OF MINNESOTA**

Senator MONDALE. Mr. Chairman, I am very pleased that the Health Subcommittee is initiating today a series of hearings on health, science, and human rights. I think that such hearings will be very helpful to the health professions as well as to the Congress and the executive branch.

I am especially gratified that the hearings are opening with consideration of a resolution which I initially proposed in the Congress almost 4 years ago. There were extensive hearings on that proposal (S.J. Res. 145) in the 90th Congress before the Subcommittee on Government Research of the Senate Committee on Government Operations, chaired by Senator Fred Harris. We had an opportunity then to go into some of the details of developments in health sciences.

The resolution has wide bipartisan cosponsorship, including that of the Health Subcommittee chairman and the ranking minority members

of the full committee and of the Health Subcommittee. A companion measure in the House, introduced by Congressman Tom Foley, of Washington, has similar bipartisan cosponsorship. This reflects a welcome consensus on the need for action which has developed since 1968.

And it should not be otherwise. Medical science, whose wonders are known to us all, also has mysterious and far-reaching implications which need to be recognized and planned for. As I said in the Senate upon introducing this proposal last March:

We can ill afford to wait until the crush of events forces us to make hasty and often ill-considered decisions.

The advent of artificial organs and organ transplants has presented us with decisions about the definition of death and the power to determine who shall live and who shall not. In the field of chemical modification of behavior, we have already seen serious abuses, as in the sedation of schoolchildren and in the tranquilizing of nursing home residents.

Behavior modification through electrical means and through conditioning approaches has also captured our attention. But how many of us have fully faced the implications for our society of placing power in the hands of a few to modify the behavior of large groups of people?

With fertilization of human egg cells in the laboratory, with the possibility of successful implantation of such eggs in human beings, and with the potential for developing so-called duplicate people, we may be facing fundamental changes in the status of the individual, the role of the family and in the very character of our society.

These are possibilities which can no longer be left to health science professionals to grapple with alone. Scientists and laymen, ethicists and lawyers, philosophers and administrators, medical practitioners and humanists, all have something to contribute to and to learn from each other.

This cannot be—and should not be—a private process. The public's stake is too great. And the need for consensus as to how society should deal with these profound problems is too clear. We cannot depend entirely on studies by academics, health professionals, and learned societies.

I do welcome the greatly increased interest in the form of new institutes to study these issues, one of which was just established at Georgetown University with the assistance of a grant from the Kennedy Foundation. We will have witnesses from two of these institutes this afternoon. But I think we need something far more official and far more public if we are to reach agreement on the ways in which society is to organize itself to handle these unprecedented problems. I hope that the advisory commission, which would be established under Senate Joint Resolution 75, would serve that need.

May I say one further thing?

I think perhaps among the most important recent events are the symposium sponsored by the Kennedy Foundation and the development of a Center on Bioethics at Georgetown University.

I think this has moved the issue along faster than anything else. Senator KENNEDY. We appreciate that, Senator Mondale. Your views were very ably presented at the conference by Herbert Jasper of the committee staff.

So we appreciate your remarks.  
Our first witness is Dr. Duval.

**STATEMENT OF MERLIN K. DUVAL, M.D., ASSISTANT SECRETARY  
FOR HEALTH AND SCIENTIFIC AFFAIRS, DEPARTMENT OF  
HEALTH, EDUCATION, AND WELFARE, ACCOMPANIED BY ROBERT  
MARSTON, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH,  
AND PROFESSIONAL STAFF MEMBERS**

Dr. DUVAL. Thank you, Mr. Chairman. I have at the table with me Dr. Robert Marston.

Senator KENNEDY. Promise not to mention cancer this morning.  
[Laughter.]

Dr. DUVAL. Mr. Chairman, and members of the Subcommittee on Health, I am pleased to appear before you today to participate in your consideration of Senate Joint Resolution 75, which would provide for a study and evaluation of the ethical, social, and legal implications of advances in biomedical research and technology.

As proposed, the resolution would establish a National Advisory Commission on Health Science and Society, which would analyze and evaluate current and projected scientific and technological advances in the biomedical sciences, the implications of such advances for individuals and society, public understanding and attitudes toward these implications, and related public policy aspects.

The Commission would be composed of 15 representatives of medicine, law, theology, biological science, physical science, social science, philosophy, humanities, health administration, government, and public affairs; and its members would be appointed by the President.

The Commission would utilize the many already completed studies in the field made by public and private agencies and any future studies that become available. It would have the power to hold hearings, take sworn testimony, receive information from Government agencies, and enter into contracts for the conduct of research or surveys, the preparation of reports, or other necessary activities.

The Commission would make one or more interim reports and a final report to the President and Congress not later than 2 years after their initial meeting. Such reports would contain detailed statements of the Commission's findings and conclusions, together with its recommendations, including any recommendations for action by public and private bodies and individuals.

Funding authorizations would be \$1 million for fiscal year 1972 and a like amount for 1973. Ninety days after it makes its final report, the Commission would cease to exist.

Mr. Chairman, in considering this proposed legislation, the first question to ask ourselves is: Does this bill deal with matters significant enough to warrant national attention and concern? This century, beyond question, has witnessed a revolution in the biological and medical sciences—a revolution that raises a whole spectrum of critical problems, which at least in some instances appear to transcend the inherent capabilities of science and scientists alone to deal with them, and present acute challenges to both existing law and conventional wisdom. Some

of the more important and provocative of these problems might be mentioned:

Population growth, accelerated by advances in medicine and socio-economic conditions, has brought the world in just a short time to within sight of what most experts believe to be the maximum population density that this finite globe can sustain.

A host of ethical and legal problems have emerged in connection with control of birth rates through contraceptives and abortion.

What, for instance, is the measure of safety for contraceptive drugs that have a potential market of many hundreds of millions of normal women—and soon, perhaps, men—in the prime of life? Can society rely on the voluntary behavior of individuals to prevent absolute overpopulation? If not, what are the alternatives, and what implications would their adoption carry for the governance of society?

New techniques for obtaining cells from the fetus, amniocentesis, almost from the start of pregnancy, and for determining many of the characteristics of that fetus from a study of these cells, give a physician and a parent unequivocal answers to questions such as the sex of the unborn child or its freedom from any genetically determined diseases.

The potential availability of such knowledge coupled with rapidly changing societal attitudes toward abortion raise interesting problems. Will the interests of individuals and of society always be congruent? What would be the impact on the human race if the preferences of a generation were to affect significantly the normal balance between male and female births? Should society countenance the birth of defective individuals when this could be avoided by timely intervention?

The extraordinary advances in genetics have illuminated to a remarkable degree the mechanisms through which biological information is transmitted from generation to generation. Parallel advances in virology have provided at least one lead to a method for replacing the genetic material of a cell with different information.

Thus, the very real possibility of "genetic engineering" is on the horizon. What, if any, ethical limits are appropriate in this area? What unique or special considerations come into play when the experimental species is man? How rigid should be the criteria for determining that an induced genetic alteration is not, in the longrun, compatible with species survival? What attitude should we take on the question of cloning—possible asexual replication of individuals in the form of genetically identical products?

Thus, a whole series of problems that can perhaps be adumbrated under the title "Human Experimentation" arises. What ethical limits, based on what logical argument, should govern? Again, are the needs of society and the rights of individuals always congruent? When they are not, on what grounds should resolution take place? What legal and ethical ambience should surround the use of prisoners, terminal patients, normal volunteers, and so forth, in experimental medicine?

The increasing technical feasibility of organ transplantation has raised a unique set of moral, ethical, and legal question concerning the rights of the donor, the rights of the dying who might be saved by transplantation at the opportune time, and the use of organs from normal volunteers when lasting results are improbable.

Modern medical technology has made possible unprecedented experiences that society has yet to integrate into its traditions. These

include: The prolongation of dying without hope of recovery, a particularly poignant situation when the patient is in unremitting coma. The classic question of euthanasia takes on specific dimensions here.

The prolongation of life through extremely drastic and deforming operations or artificial means entailing permanent disability.

The extension of life, with an ever larger proportion of individuals reaching older ages, has provided a serious challenge to the adequacy of the existing social structures.

The treatment of few patients at extremely high cost, through new knowledge and technology that cannot be readily extended, such as intensive-care procedures, organ transplants, and renal dialysis; and

Selective life saving by means of scarce artificial kidney machines, repeated blood transfusion, and so forth. Such modern innovations make it both possible and necessary for individuals or groups to literally decide who shall live and who shall die.

With the recent emergence of drugs that produce remarkable effects on human behavior, and the refinement of techniques for stimulating selected regions of the brain with similar effects on behavior, society must ponder deeply how such potent agents and instrumentalities shall be used.

The range of ethical, social, and legal problems raised by the advances enumerated above has generated a great deal of interest and activity in both the public and private sectors. This Department, particularly the National Institutes of Health, which supports the major portion of clinical research in this country, has engaged in a continuing discussion and examination of the questions posed by clinical investigation in research conducted or funded by the NIH.

In 1952, with the onset of research activities at the clinical center in Bethesda, the NIH established what is still regarded as model guidelines for the review and conduct of clinical research. This policy has been extended three times in the past 20 years:

In 1965, NIH required its grantee institutions to provide assurances that similar care would be taken in the conduct of research projects.

In 1966, the Public Health Service began to require that grantee institutions conduct initial and continuing review of all PHS-funded clinical investigations.

And in 1971, this Department again extended these guidelines to all DHEW grantees and contractors.

Senator KENNEDY. Would you give us a copy of the guidelines?

Dr. DUVAL. I certainly will.

(The information subsequently supplied follows:)

CHAPTER 1-40  
 PROTECTION OF HUMAN SUBJECTS

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1-40-00	Purpose
10	Definitions
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1-40-00 PURPOSE

To provide for the protection of human subjects involved in activities supported by DHEW grants or contracts, procedures are prescribed for the initial review and approval of proposals for such support and for the continuing review of all supported activities.

1-40-10 DEFINITIONS

A. Subject

This term describes any individual who may be at risk as a consequence of participation as a subject in research, development, demonstration, or other activities supported by DHEW funds.

B. At Risk

An individual is considered to be "at risk" if he may be exposed to the possibility of harm--physical, psychological, sociological, or other--as a consequence of any activity which goes beyond the application of those established and accepted methods necessary to meet his needs. The determination of when an individual is at risk is a matter of the application of common sense and sound professional judgment to the circumstances of the activity in question. Responsibility for this determination resides at all levels of institutional and Departmental review. Definitive determination will be made by the operating agency.

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(1-40-10 continued)

C. Informed Consent

Informed consent is the agreement obtained from a subject, or from his authorized representative, to the subject's participation in an activity.

The basic elements of informed consent are:

1. A fair explanation of the procedures to be followed, including an identification of those which are experimental;
2. A description of the attendant discomforts and risks;
3. A description of the benefits to be expected;
4. A disclosure of appropriate alternative procedures that would be advantageous for the subject;
5. An offer to answer any inquiries concerning the procedures;
6. An instruction that the subject is free to withdraw his consent and to discontinue participation in the project or activity at any time.

In addition, the agreement, written or oral, entered into by the subject, should include no exculpatory language through which the subject is made to waive, or to appear to waive, any of his legal rights, or to release the institution or its agents from liability for negligence.

Informed consent must be documented. (See Documentation, Section 1-40-40 G.4.)

D. Institution

Any corporation, institution, organization, agency, or other legally accountable person, other than an individual.

1-40-20 POLICY

- A. Safeguarding the rights and welfare of human subjects involved in activities supported by grants or contracts from the Department of Health, Education, and Welfare is the responsibility of the institution which receives or is accountable to the DHEW for the funds awarded for the support of the activity.

In order to provide for the adequate discharge of this institutional responsibility, it is the policy of the Department that no grant or contract for an activity involving human subjects shall be made unless the application for such support has been reviewed and approved by an appropriate institutional committee.

This review shall determine that the rights and welfare of the subjects involved are adequately protected, that the risks to an individual are outweighed by the potential benefits to him or by the importance of the knowledge to be gained, and that informed consent is to be obtained by methods that are adequate and appropriate. 1/

In addition the committee must establish a basis for continuing review of the activity in keeping with these determinations.

The institution must submit to the DHEW, for its review, approval, and official acceptance, an assurance of its compliance with this policy. The institution must also provide with each proposal involving human subjects a certification that it has been or will be reviewed in accordance with the institution's assurance.

No grant or contract involving human subjects at risk will be made to an individual unless he is affiliated with or sponsored by an institution which can and does assume responsibility for the protection of the subjects involved.

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1/ In the United States, adherence to the regulations of the Food and Drug Administration (21 CFR 130.37) governing consent in projects involving investigative new drugs (IND) is required by law.

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(1-40-20 continued)

- B. Since the welfare of subjects is a matter of concern to the Department of Health, Education, and Welfare as well as to the institution, no grant or contract involving human subjects shall be made unless the proposal for such support has been reviewed and approved by an appropriate professional committee within the responsible component of the Department. This review must establish that the activity, as described in the proposal, will not interfere with or impair the rights and welfare of the subjects, nor involve risks that outweigh either potential benefits to the subjects or the expected value of the knowledge sought, nor deny the rights of the subject to adequate and appropriate informed consent. The committee may recommend to the operating agency, and the operating agency may require, the imposition of specific grant or contract terms providing for the protection of human subjects, including requirements for informed consent.

1-40-30 APPLICABILITY

This policy applies to all grants and contracts which support activities in which subjects may be at risk. Since the identification of such programs requires the application of sound professional judgment, such determination should involve professional staff within the component agencies of the Department.

The Assistant Secretary for Administration, the Assistant Secretary for Health and Scientific Affairs, the Commissioner of Education, the Administrator of the Social and Rehabilitation Service, and the Commissioner of Social Security shall report annually to the Secretary, DHEW, the identity of those programs within their respective agencies which shall be subject to the provisions of this policy. The agency involved should be prepared to document its purpose and objectives in including or excluding a program from the list.

DHEW staff and consultants serving programs included in the list shall be responsible for identifying those specific projects or activities which require application of the policy. Nothing shall prevent DHEW staff and consultants, however, from identifying individual projects in excluded programs which, in their opinion, also require the application of this policy. The Division of Research Grants, NIH, PHS, will be responsible for implementation and enforcement of this policy.

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1-40-40 GRANTEE IMPLEMENTATIONA. Negotiation of Assurances

An institution applying to the DHEW for a grant or contract involving human subjects must provide written assurance that it will abide by DHEW policy. The assurance shall embody a statement of compliance with DHEW requirements for initial and continuing committee review of the supported activities; a set of implementing guidelines, including identification of the committee; and a description of its review procedures or, in the case of special assurances concerned with single projects or activities, a report of initial findings and proposed continuing review procedures. Institutions that have not previously filed assurances should request instructions for the preparation of an assurance from the Division of Research Grants, NIH.

Negotiation of assurances is the responsibility of the DRG, NIH. Negotiation will be initiated on receipt of a copy of a grant application, a contract proposal, or other documentation identifying the project and the offeror or sponsoring institution.

Assurances will not be accepted from institutions or institutional components which do not have control over the expenditure of DHEW grant or contract funds unless they are an active part of a cooperative project or activity.

An assurance will be accepted only after review and approval by the DRG, NIH.

B. Types of Assurance

Assurances may be one of two types:

1. General Assurance.

A general assurance describes the review and implementation procedures applicable to all DHEW-supported activities within an institution, regardless of the number, location, or types of its components. (See Exhibit XI-40-1.) General assurances will be required from institutions having a significant number of concurrent DHEW projects or activities involving human subjects.

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(1-40-40 continued)

2. Special Assurance.

A special assurance will, as a rule, describe those review and implementation procedures applicable to a single project or activity. (See Exhibit X1-40-2.) Special assurances may also be approved in modified forms to meet unusual requirements either of the operating agency or of the institution receiving a grant or contract. Special assurances are not to be solicited from institutions which have accepted general assurances on file.

C. Minimum Requirements for General Assurances

1. Statement of Compliance.

A formal statement of compliance with DHEW policy must be executed by an appropriate institutional official.

2. Implementing Guidelines.

The institution must include as part of its assurance implementing guidelines that specifically provide for:

- a. The statement of principles that will assist the institution in the discharge of its responsibilities for protecting the rights and welfare of subjects. This may be an appropriate existing code or declaration or one formulated by the institution itself. It is to be understood that no such principles supersede DHEW policy or applicable law.
- b. A committee or committee structure which will conduct initial and continuing reviews. Committee members shall be identified by name, occupation or position, and by other pertinent indications of experience and competence in areas pertinent to the areas of review such as earned degrees, board certifications, licensures, memberships, etc.

## PROTECTION OF HUMAN SUBJECTS

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1-20-60C.1.e

The committee must be composed of sufficient members with varying backgrounds to assure complete and adequate review of projects and activities commonly conducted by the institution. The committee's membership, maturity, experience, and expertise should be such as to justify respect for its advice and counsel. No member of an institutional committee shall be involved in either the initial or continuing review of an activity in which he has a professional responsibility, except to provide information requested by the committee. In addition to possessing the professional competence to review specific activities, the committee should be able to determine acceptability of the proposal in terms of institutional commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. The committee may therefore need to include persons whose primary concerns lie in these areas rather than in the conduct of research, development, and service programs of the types supported by the DHEW.

- c. The procedures which the institution will follow in carrying out its initial and continuing review of proposals and activities.
- d. The procedures which the committee will follow to provide advice and counsel to project and program directors with regard to the committee's actions as well as the requirements for reporting to the committee any emergent problems or proposed procedural changes.
- e. The procedures which the institution will follow to maintain an active and effective committee and to implement its recommendations.

(1-40-40 continued)

D. Minimum Requirements for Special Assurances

An acceptable special assurance covering a single activity consists of a properly completed statement of compliance, similar to that illustrated by Exhibit X1-40-2. This assurance shall identify the specific grant or contract involved by its number, if known; by its full title; and by the name of the project or program director, principal investigator, fellow, or other person immediately responsible for the conduct of the activity. The assurance shall be signed by a committee of not fewer than three members and executed by an appropriate institutional official. The committee shall describe in general terms those risks to the subject that it recognizes as inherent in the activity. Consent procedures to be used are to be described. Any consent statement to be signed, heard, or read by the subject or responsible third parties should be attached. The assurance should outline the circumstances under which the director or investigator will be required to inform the committee of proposed changes in the activity, or of emergent problems, involving human subjects. The assurance should also indicate whether the director or investigator will be required to submit written reports, appear for interview, or be visited by the committee or committees to provide for continuing review. It should also indicate the intervals at which such reviews will take place.

E. Timing and Certification of Institutional Review1. General Assurancesa. Timely review.

All proposals involving human subjects submitted by institutions with accepted general assurances should, whenever possible, be given institutional review and approval prior to submission to the DHEW. The proposal or application should be appropriately marked in the spaces provided on forms, or the following statement should be typed on the lower or right hand margin of the page bearing the name of the institutional official authorized to sign or execute applications or proposals for the institution:

"HUMAN SUBJECTS -- REVIEWED AND APPROVED  
ON \_\_\_\_\_ (date) \_\_\_\_\_."

(This date should be no more than 90 days prior to the submission date, and must not be more than 12 months prior to the proposed starting date.)

b. Pending review.

If it will be necessary to delay the review, the proposal is to be appropriately marked in the spaces provided on forms, or the following statement is to be typed in the lower or right hand margin of the page bearing the name of the institutional official authorized to sign or execute applications or proposals for the institution:

"HUMAN SUBJECTS -- REVIEW PENDING ON  
(date) \_\_\_\_\_."

(This date should be at least one month earlier than the proposed starting date of the project to avoid possible conflict with the award date.)

c. Completion of pending review.

Review should be initiated as soon as possible after the submission of the proposal so that final action can be completed prior to the pending review date. If this final action is disapproval, or is approval contingent on substantive changes in the proposal, the operating agency is to be notified promptly by telegam; an immediate confirmatory letter; and, where appropriate, by withdrawal of the application from further consideration by the agency.

d. Institutional review of proposals lacking definite plans or specifications for the involvement of human subjects.

Certain types of proposals are submitted with the knowledge that human subjects are to be involved within the project period, but definite plans for this involvement cannot properly be included in the proposal. These include (1) certain training grants where trainee projects remain to be selected, and (2) research, pilot, or developmental studies in which involvement depends upon such things as the completion of instruments, or of prior animal studies, or upon the purification of compounds.

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(1-40-40 continued)

Such proposals should be reviewed and certified in the same manner as more complete proposals. The initial certification indicates institutional approval of the application as submitted, and commits the institution to later review of the plans when completed. Such later review should be completed prior to the beginning of the budget period during which actual involvement of human subjects is to begin.

- e. Institutional review of proposals not submitted with the intent of involving human subjects.

If a proposal, at the time it is submitted to the DHEW, does not anticipate involving or intend to involve human subjects, no certification should be submitted. In those instances, however, where funds are awarded in response to the proposal and it later becomes appropriate to use all or parts of these funds for activities which will involve human subjects, such use must be reviewed and approved in accordance with the institutional assurance prior to the use of subjects:

- (1) Where support is provided by project grants or contracts, review and approval of such changes must be certified to the awarding agency or contracting agency, together with a description of the proposed change in the project plan or contract workscope. Subjects should not be used prior to receipt of approval from agency staff and in the case of contracts prior to receipt of an amended contract description of work.
- (2) Where support is provided by a mandatory grant or institutional grant, in which cases the institution determines within broad guidelines the project or activities supported, including the use of human subjects (i.e., general research support grants, clinical research center projects), review must be carried out in accordance with the institutional assurance. Certification for individual projects need not be forwarded to the awarding agency.

Whenever the committee is uncertain as to whether a change should or should not be reported, the question should be referred to the operating agency concerned.

All certifications are subject to verification by DHEW representatives authorized to examine institutional and committee records.

## 2. Special Assurances

When a special assurance is submitted, it provides certification for the initial grant or contract period concerned. No additional documentation is required. If the terms of the grant or contract provide for additional years of support, with annual obligation of funds, the noncompeting renewal application or proposal shall be certified in the manner described in the preceding section (1-40-40 E.1.).

## F. Cooperative Activities

Cooperative activities are those which involve other than the grantee or prime contractor (such as a contractor under a grantee or a subcontractor under a prime contractor). In such instances the grantee or prime contractor may obtain access to all or some of the human subjects involved through the cooperating institution. Regardless of the distances involved and the nature of the cooperative arrangement, the basic DHEW policy applies and the grantee or prime contractor remains responsible for safeguarding the rights and welfare of the subjects. The manner in which this responsibility can be discharged depends on whether the grantee or contractor holds an institutional general assurance or an institutional special assurance.

### 1. Institutions with General Assurances

Initial and continuing institutional review may be carried out by one or a combination of procedures:

- By the grantee's or contractor's committee;
- By committee reviews conducted at both institutions; or
- Through cooperation of appropriate individuals or committees representing the cooperating institution.

(1-40-40 continued)

The procedures to be followed must be made a matter of record in the institutional files for the grant or contract before funds are released by the grantee or contractor for the cooperative project. There are three relationships that may govern in reference to the cooperating institution:

- a. Cooperating institutions with accepted general assurances.

When the cooperating institution has on file with the DHEW an accepted general assurance, the grantee or contractor may request the cooperator to conduct its own independent review and to report to the grantee's or contractor's committee the cooperating committee's recommendations on those aspects of the activity that concern individuals for whom the cooperating institution has responsibility in accordance with its own assurance. The grantee or contractor may, at its discretion, concur with or further restrict the recommendations of the cooperating institution. It is the responsibility of the grantee or contractor to maintain communication with the cooperating institutional committees. The cooperating institution should promptly notify the grantee or contracting institution whenever the cooperating institution finds the conduct of the project or activity within its purview unsatisfactory.

- b. Cooperating institution with no accepted general assurance.

When the cooperating institution does not have an accepted assurance on file with the DHEW, the awarding agency concerned may request the DRG, NIH, to negotiate an assurance.

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c. Interinstitutional Joint Reviews.

The grantee or contracting institution may wish to develop an agreement with cooperating institutions to provide for a review committee with representatives from cooperating institutions. Representatives of cooperating institutions may be appointed as ad hoc members of the grantee or contracting institution's existing review committee or, if cooperation is on a frequent or continuing basis as between a medical school and a group of affiliated hospitals, appointments may be made permanent. Under some circumstances component subcommittees may be established within cooperating institutions. All such cooperative arrangements must be accepted by the Department as part of a general assurance, or as an amendment to a general assurance, or in unusual situations as determined by the DRG, NIH, as a special assurance.

2. Institutions with Special Assurances

While responsibility for initial and continuing review necessarily lies with the contractor, the DHEW will also require acceptable assurances from those cooperating institutions having immediate responsibility for subjects.

If the cooperating institution has on file with the DHEW an accepted general assurance, the contractor shall request the cooperator to conduct its own independent review of those aspects of the project or activity which will involve human subjects for which it has immediate responsibility. Such a request shall be in writing and should provide for direct notification of the contractor's committee in the event that the cooperator's committee finds the conduct of the activity unsatisfactory.

If the cooperating institution does not have an accepted general assurance on file with the DHEW, the operating agency concerned must request the DRG, NIH, to negotiate an assurance.

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(1-40-40 continued)

G. Institutional Administration of Assurances

1. Institutional Responsibility

The grantee or contracting institution's administration is accountable to the Department for effectively carrying out the provisions of the institutional assurance for the protection of human subjects as accepted and recognized by the Department. Revisions in the institutional assurance, including the implementing procedures, are to be reported to the Department prior to the date such revisions become effective. Revision without prior notification may result in withdrawal of Departmental recognition of the institution's assurance.

2. Executive Functions

Specific executive functions to be conducted by the institutional administration include institutional policy formulation, development, promulgation, and continuing indoctrination of personnel. Appropriate administrative assistance and support must be provided for the committee's functions. Implementation of the committee's recommendations through appropriate administrative action and follow-up is a condition of acceptance of an assurance. Committee approvals and recommendations are, of course, subject to review and to disapproval or further restriction by institutional officials. Committee disapprovals, restrictions, or conditions cannot be rescinded or removed except by action of the committee or another appropriate review group as described and accepted in the assurance filed with the Department.

3. Assurance Implementation

Under no circumstances shall proposed activity plans, not approved by the committee, be implemented with Department funds. The principal investigator, program or project director, or other responsible staff must be notified as promptly as possible of committee actions, including any restrictive recommendations made by the institutional committee or the administration. They must also be informed and reminded of their continuing responsibility to bring to the attention of the committee any proposed significant changes in project or activity plans or any emergent problems that will affect human subjects. Where continuing review of projects involves the channels of administrative authority in the institution, notification of committee actions should be sent through these channels. Establishment of mechanisms for consultation and appeal by investigators and subjects may be an important condition of acceptance of an assurance by the Department.

4. Documentation

a. General

Development of appropriate documentation and reporting procedures is an essential administrative function. The files must include copies of all documents presented or required for initial and continuing review by the institutional review committee and transmittals on actions, instructions, and conditions resulting from review committee deliberations addressed to the activity director are to be made part of the official organizational files for the supported activity. Committee meeting minutes including records of discussions of substantive issues and their resolution are to be retained by the institution and be made available upon request to representatives of the DHEW.

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(1-40-40 Continued)

b. Informed Consent

An institution proposing to place any individual at risk is obligated to obtain and document his informed consent; the terms "at risk" and "informed consent" will apply as defined in Section 1-40-10.

The actual procedure in obtaining informed consent and the basis for committee determinations that the procedures are adequate and appropriate are to be fully documented. The documentation will follow one of the following three forms:

- (1) Provision of a written consent document embodying all of the basic elements of informed consent. This form is to be signed by the subject or his authorized representative. A sample of the form as approved by the committee is to be retained in its records. Completed forms are to be handled in accordance with institutional practice.
- (2) Provision of a "short" form written consent document indicating that the basic elements of informed consent have been presented orally to the subject or his authorized representative. Written summaries of what is to be said to the patient are to be approved by the committee. The "short" form is to be signed by the subject or his authorized representative and an auditor-witness to the oral presentation and to the subject's signature. A copy of the approved summary, annotated to show any additions, is to be signed by the persons obtaining the consent on behalf of the institution and by the auditor-witness. Sample copies of the consent form and of the summaries as approved by the committee are to be retained in its records. Completed forms are to be handled in accordance with institutional practice.

- (3) Modification of either of the above two primary procedures. All such modifications must be approved by the committee in the minutes signed by the committee chairman. Granting of permission to use modified procedures imposes additional responsibility upon the review committee and the institution to establish that the risk to any subject is minimum, that use of either of the primary procedures for obtaining informed consent would surely invalidate objectives of considerable immediate importance, and that any reasonable alternative means for attaining these objectives would be less advantageous to the subject.

The committee's reasons for permitting modification or elimination of any of the six basic elements of informed consent, or for altering requirements for a subject's signature, or for signature of an auditor-witness, or for substitution (e.g., debriefing), or other modification of full, complete, written prior consent, must be individually and specifically documented in the minutes and in reports of committee actions to the institutional files. Approval of any such modifications should be regularly reconsidered as a function of continuing review and as required for annual review, with documentation of reaffirmation, revision, or discontinuation as appropriate.

- (4) Reporting to DHEW.

No routine reports to DHEW are required. Significant changes in policy, procedure, or committee structure shall, however, be promptly reported to the DRG, NIH, for review and acceptance. Review of these changes, or of institutional and other records of performance under the terms and conditions of DHEW policy, may require renegotiation of the assurance or such other action as may be appropriate.

(1-40-50)

1-40-50 DEPARTMENTAL IMPLEMENTATIONA. Departmental Review of Assurances

All assurances submitted for approval are to be forwarded to the DRG, NIH, for review and acceptance on behalf of the Department. Review will be principally concerned with the adequacy of the proposed committee in the light of the probable scope of the applicant institution's activities, and with the appropriateness of the proposed initial and continuing review in the light of the probable risks to be encountered, the types of subject populations involved, and the size and complexity of the institution's administration. Institutions submitting inadequate assurances will be informed of deficiencies. The appropriate operating agency will be kept informed, on request, of the status and acceptance of an assurance.

Special assurances will be reviewed in close cooperation with the operating agency concerned, either along guidelines provided by the agency, or on an assurance-by-assurance basis.

All forms or other general means intended in whole or in part for instruction of, or for obtaining information from, institutional sources that pertain to implementation of this policy, or related procedure, require prior approval by the DRG, NIH.

The DRG, NIH, will periodically issue a cumulative list of institutions which have filed acceptable general assurances. If an institution has filed such an assurance but has had no active grants or contracts involving human subjects for a period of 3 years, the assurance may be inactivated and administratively deleted from the cumulative listing.

B. Review of Proposals Involving Human Subjects1. Review Procedures

Because of the wide variety and scope of DHEW programs involving human subjects, no review standards are established beyond those provided in Section 1-40-20. The Assistant Secretary for Administration, the Assistant Secretary for Health and Scientific Affairs, the Commissioner of Education, the Administrator of the Social and Rehabilitation Service, and the Commissioner of Social Security

shall establish appropriate review procedures within their respective agencies applicable to programs identified in accordance with the provisions of Section 1-40-30. These procedures shall be reported to the Secretary, DHEW, for review by the Office of the General Counsel and the Office of Grant Administration Policy.

In the course of review of proposals, DHEW review groups should apply review standards uniformly regardless of the status of the proposal, or of its state or country of origin. Review groups may (a) recommend disapproval if the hazards are so grave as to be unacceptable; (b) recommend approval without restrictions when the subject's rights and welfare are not infringed; (c) recommend approval but record expressions of concern to be communicated to the institution sponsoring the project or activity; or (d) recommend approval contingent on limitation of the scope of the work proposed, or the imposition of restrictions, or on the elimination of objectionable procedures involving human subjects.

When DHEW review of an application indicates that it involves questionable procedures, DHEW staff should ask the institution to provide the substance of the rationale which led to the approval of these procedures. Inquiries should be directed to an appropriate official of the institution and should emphasize the initial review group's need to benefit from the institutional review committee's opinions.

The DRG, NIH, will provide information as to the identity of the institutional officials concerned and, if requested, will assist in making inquiries.

2. Informing Institutions of Concern for Use of Human Subjects

When the action on an unsolicited proposal results in (a) approval, but indicates concern for activities involving human subjects, or (b) contingent approval with imposition of grant or contract restrictions affecting or eliminating the scope of activities involving human subjects, or (c) disapproval, and the recommendation by the HEW reviewers indicates that the proposal involves undue hazards to subject, this information should be conveyed in writing by operating agency staff to both the official signing the proposal and to the principal investigator concerned.

[-40-50 continued)

3. Documentation for Information of the Division of Research Grants

Copies of summary statements, memoranda, correspondence with investigators and other institutional personnel, and other documents identifying concern for the welfare of subjects of specific proposals, whether the final recommendation is for approval or disapproval, should be forwarded to the DRG, NIH.

C. Award of Grants and Contracts Involving Human Subjects

1. Assuming all other requirements are met, routine awards for grants or contracts involving human subjects received from institutions with accepted assurances may be issued without further requirements within the year following the date of review and approval certified on the proposal. On the other hand, an agency may withhold funding and request institutional re-review and re-consideration before funding an activity involving human subjects when in the considered judgment of the professional staff of the agency:
  - a. Significant change in the circumstances has occurred or new knowledge or information has developed that may affect the rights or welfare of subjects or require the reevaluation of risks to subjects.
  - b. The risks inherent in the proposed activity are of such magnitude or concern that continuing review on a short-term basis is considered essential.
2. Agencies wishing to make an award prior to the institutional review and approval date certified on the proposal have the option of:
  - a. Asking the institution to arrange for earlier review and certification.
  - b. Making the award contingent on the nonuse of grant or contract funds for any activity involving human subjects.

D. Management of Grants and Contracts Involving Human Subjects

Staff of Department of Health, Education, and Welfare operating agencies having program or project responsibility for grants or contracts, should alert responsible officials of proposing institutions to the necessity for institutional review of research involving human subjects, particularly in the case of proposals for the development of cooperative research programs involving work to be conducted by a number of institutions.

Staff should call to the attention of the operating agency and of the DRG, NIH, instances of possible non-compliance with established assurances or evidence of procedural deficiencies which should have been corrected by the institution's review committee.

E. Enforcement

The DRG, NIH, will follow up reports by reviewers, evaluators, consultants, and staff of the DHEW indicating concern for the welfare of subjects involved in approved and funded grants or contracts and of subjects potentially involved in activities approved but not funded, and in disapproved proposals. On the basis of these reports and of other sources of information, the DRG, NIH, may, in collaboration with the operating agency concerned, correspond with or visit institutions to discuss correction of any apparent deficiencies in its implementation of the procedures described in its institutional assurance.

If, in the judgment of the Secretary, an institution has failed in a material manner to comply with the terms of this policy with respect to a particular DHEW grant or contract, he may require that it be terminated in the manner provided for in applicable grant or procurement regulations. The institution shall be promptly notified of such finding and of the reason therefor.

(1-40-50 continued)

If, in the judgment of the Secretary, an institution fails to discharge its responsibilities for the protection of the rights and welfare of the individuals in its care, whether or not DHEW funds are involved, he may question whether the institution and the individuals concerned should remain eligible to receive future DHEW funds for activities involving human subjects. The institution and individuals concerned shall be promptly notified of this finding and of the reasons therefor.

F. Implementation Procedures

Operating agencies shall implement this policy within 60 days of its publication in accordance with the general guidelines of Chapter 1-20. The initial report required by Section 1-40-30 of this policy should be forwarded to the Office of Grant Administration Policy within 90 days of publication and in following years by July 30. Procedures for the internal review of proposals involving human subjects as required by Section 1-40-50 B.1. shall be submitted to the Office of Grant Administration Policy within 6 months of publication.

General assurances previously accepted by the DRG, NIH, for the PHS and listed in its current "Cumulative List..." will be considered acceptable for the purposes of this policy. Application of the policy to ongoing grants and contracts shall be made at the start of the first budget period following operating agency implementation, but no later than July 1, 1972.

PART ONE OF A GENERAL INSTITUTIONAL ASSURANCE

The (name of institution) will comply with the policy for the protection of human subjects participating in activities supported directly or indirectly by grants or contracts from the Department of Health, Education, and Welfare. In fulfillment of its assurance:

This institution will establish and maintain a committee competent to review projects and activities that involve human subjects. The committee will be assigned responsibility to determine for each activity as planned and conducted that:

The rights and welfare of subjects are adequately protected.

The risks to subjects are outweighed by potential benefits.

The informed consent of subjects will be obtained by methods that are adequate and appropriate.

This institution will provide for committee reviews to be conducted with objectivity and in a manner to ensure the exercise of independent judgment of the members. Members will be excluded from reviews of projects or activities in which they have an active role or a conflict of interest.

This institution will encourage continuing constructive communication between the committee and the project directors as a means of safeguarding the rights and welfare of subjects.

This institution will provide for the facilities and professional attention required for subjects who may suffer physical, psychological, or other injury as a result of participation in an activity.

This institution will maintain appropriate and informative records of committee reviews of applications and active projects, of documentation of informed consent, and of other documentation that may pertain to the selection, participation, and protection of subjects and to reviews of circumstances that adversely affect the rights or welfare of individual subjects.

This institution will periodically reassure itself through appropriate administrative overview that the practices and procedures designed for the protection of the rights and welfare of subjects are being effectively applied and are consistent with its assurance as accepted by the Department of Health, Education, and Welfare.

Official signing for the Institution

Signature \_\_\_\_\_

Title \_\_\_\_\_

Date \_\_\_\_\_

Enclosure: Implementing Guidelines, Part Two of a General Institutional Assurance

SPECIAL INSTITUTIONAL ASSURANCE IN CONNECTION WITH  
SINGLE PROJECTS INVOLVING HUMAN SUBJECTS

- (0) The (name of institution) will comply with the policy for the protection of human subjects participating in projects or activities supported by grants and contracts made by the Department of Health, Education, and Welfare. This policy requires a review independent of the investigator or director to safeguard the rights and welfare of those subjects. An initial review of the application for a grant or contract identified as \_\_\_\_\_ submitted by this institution on behalf of \_\_\_\_\_ indicates that:
- (1) In the opinion of this committee the risks to the rights and welfare of the subjects in this project or activity are:
- The committee states that adequate safeguards against these risks have been provided.
- (2) In the opinion of the committee the potential benefits of this activity to the subjects outweigh any probable risks. This opinion is justified by the following reasons:
- (3) In the opinion of the committee the following informed consent procedures will be adequate and appropriate. Documentation is attached.
- (4) The committee agrees to arrange for a continuing exchange of information and advice between itself and the investigator or director, particularly to deal with proposed changes in project or activity design, or with emergent problems which may alter the investigational situation with regard to the criteria cited above. This exchange will be implemented through:

This institution will provide whatever professional attention or facilities are required to safeguard the rights and welfare of human subjects.

- (5) The signatures, names, occupations, or titles of the members of the committee are listed below.

\_\_\_\_\_  
Name Occupation or Title

\_\_\_\_\_  
Name Occupation or Title

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Name Occupation or Title

- (6) Official signing for Institution

\_\_\_\_\_  
Name

\_\_\_\_\_  
Title

\_\_\_\_\_  
Date

(see instructions)

Dr. DUVAL. This policy required that, prior to the beginning of any research project involving the use of human subjects, there must be review of each proposed course of study that would be carried out by a committee of institutional associates, to include consideration of (1) the protection of the rights and welfare of the individuals; (2) the relative weights of the risks and potential benefits of the investigations; and (3) the adequacy and appropriateness of the methods to be used to secure informed consent.

Senator KENNEDY. Of course, I haven't had an opportunity to review your written testimony, since you just brought it to us this morning. Perhaps you are going to get into how those three requirements are balanced against your earlier very elaborate expression of the kinds of opportunities and problems that exist within the whole range of human behavior.

You illustrated, I thought, marvelously well the whole range of questions and legitimate areas of inquiry. Then you give us the three kinds of institutional requirements for the protection of the rights and welfare of the individual, the relative weights of the risk, and potential benefits of the investigations, and the adequacy and appropriateness of the methods to be used to secure informed consent.

Those seem limited in scope, when measured against the wide range of opportunities. Later in your testimony, will you get to that?

Dr. DUVAL. To the extent the testimony treats that, the testimony will speak for itself. If you want to bring that up in the questioning, I would be glad to speak to it.

Senator KENNEDY. Fine.

Dr. DUVAL. This policy required the establishment of procedures in over 500 major U.S. institutions for a review of the ethical, legal, and moral questions raised by specific and immediate situations. On a day-to-day basis, these groups must confront such thorny and difficult present-day issues as research involving minors and the mentally retarded, the use of prisoner and student volunteers, the research use of diagnostic procedures such as biopsy and catheterization, and the legal problems associated with research on the effects of narcotics.

The NIH has also been concerned with the value questions, most broadly construed, which are raised by clinical investigation involving human beings. In 1963, the National Institute of General Medical Sciences awarded a grant to Boston University for a study of the place of clinical investigation in modern society, and the report of this study, "Clinical Investigation in Medicine," by Irving Ladimer and Roger W. Newman, is considered a classic reference in its field. In the spring of 1966, the National Heart Institute awarded a grant to the American Academy of Arts and Sciences to study the general problems posed by the use of human beings in biomedical research, the special problems of voluntary, informed consent, the need for new criteria of death, and other vital questions. An issue of *Daedalus*, in the spring of 1969, resulted from that study, "Ethical Aspects of Experimentation With Human Subjects."

Most recently, the John E. Fogarty International Center for Advanced Study in the Health Sciences of the NIH cosponsored with the Institute for Society, Ethics, and the Life Sciences, a 4-day conference on "Ethical Issues in Genetic Counseling and the Use of Genetic Knowledge," the second of a pair of conferences devoted to ethical issues in human genetics.

The first, held in May 1970, was devoted to the scientific aspects of prenatal diagnosis by amniocentesis and cytological or biochemical analysis of the amniotic fluid and amniotic fluid cells. The proceeding of that conference are about to be published.

The National Science Foundation recently awarded a \$68,000 grant to the National Academy of Sciences to conduct a 1-year technology assessment in biological and medical science developments. A \$1.5 million grant has been awarded by the NSF to the Center for Advanced Studies in the Behavioral Sciences to establish an integrated program of technology assessment, which will take into account the societal impacts of current and future developments in medicine and biology. The NSF expects that, as a result of these studies, there will be a more active concern within the academic community for the value questions associated with science research, and additional studies in the sciences and humanities.

It is also anticipated that within the next 1 to 2 years NSF-supported research will yield a major conceptual assessment and significant research plans for further work in societal impacts of biological and medical technology.

In the private sector, several distinguished groups already in existence have broad responsibilities in the areas outlined for the proposed Commission on Health Science and Society. These include the National Academy of Sciences, with its newly established Institute of Medicine, and its National Research Council; the American College of Surgeons, the National Academy of Engineering, the American Academy of Arts and Sciences, and the American Philosophical Society.

These prestigious organizations have taken very seriously the legal, social, and ethical implications of advances in the health sciences. Also in the private sector, the IBM Co. has funded a program on technology and society at Harvard University, which has produced a research review of the literature on the implications of biomedical technology, and the World Council of Churches has recently completed a conference on "Technology and the Future of Man and Society."

Finally, Mr. Chairman, a contribution to the public discussion of these questions has also been made by the Joseph P. Kennedy, Jr., Foundation at its recent symposium on human rights, research, and retardation, and by its funding of an institute at Georgetown University to consider the ethical and moral aspects of medical research.

This brings us to the critical decision points with respect to the proposed legislation. In the light of relevant activities already underway, and the number of existing institutions concerned on a continuing basis with issues raised by health research advances, is there a need for the National Commission proposed in Senate Joint Resolution 75?

The issues are so complex and the underlying currents of change moving so swiftly that in our view no attempt to describe this particular healthscape at what would have to be a given moment of time could be definitive for long.

In other words, society might be better served by lower keyed but continuing efforts by the present variety of private and semipublic organizations and entities attempting to assess, rationalize, and explain.

One cannot help but be impressed by the variety and quality of work already underway in this area, and the seriousness with which individuals and institutions are attempting to deal with these matters.

Additional Federal support—apart from that already afforded through various means by such agencies as the National Institutes of Health and the National Science Foundation—does not appear to be an urgent need.

I am persuaded, too, of the appropriateness of a minimum overt role for the Federal Government in the debates and discussions taking place on these very fundamental issues. For these reasons, I cannot recommend enactment of Senate Joint Resolution 75.

Thank you, Mr. Chairman. I will be happy to answer any further questions you may have.

Senator KENNEDY. Thank you very much, Dr. Duval. As always, your testimony is extremely helpful.

I understand in 1968 the then Acting Secretary Cohen, Assistant Budget Director Cary, Surgeon General Steward, and NIH Director Shannon all looked favorably on such a Commission, and I understand your Department also reported favorably on the bill during the last Congress.

What has happened to change your mind on it?

Dr. DUVAL. I think, Senator, we can see that superb examples of advances have been made in the sectors that I referred to in the statement, and we believe that a single-shot approach by a commission with a 2-year life may not be as effective as the machinery that has already been established.

Senator KENNEDY. Of course, as I understand it, the commission is supposed to make recommendations to establish the institutional guidelines by which there would be an ongoing study and review of these problems. So rather than take a one-shot, 2-year approach as you have suggested, it would establish procedures by which there would be ongoing continuity, responsibility and information available.

It seems to me that all the things you have listed here have been pretty scatter-shot, haven't they? I mean, you have one group like IBM doing a study here, another group doing a study there, all of them on their own.

I don't yet see from what you have said this morning, that there is anything in your Department that is consolidating this, coordinating it, and able to give reliable information from time to time on what is happening.

You list various studies which are being done, all of which, I think, are extremely worthwhile, but you haven't told us what institutional apparatus has been set up so that there would be an ongoing, continuing setup—either within NIH or some place in your Department—that would be responsible in this area.

Dr. DUVAL. The guidelines under which we operate through the research grant procedures at the NIH have to date, in our judgment, been very trustworthy.

We have had very few abuses under those guidelines when it comes to the use of public funds to support work in this area.

I would and in response to your opening comment, that the fact that the Commission may exist for 2 years, but lay down guidelines that will have a duration presumably greater than that—

Senator KENNEDY. Of course, I don't understand that to be the necessary result of such a study. They might say that what we ought to do is establish a group made up of different scientists, engineers,

theologians, ethicists, and various groups that would have an ongoing responsibility, and it might periodically report to the Congress as well as to the President; but at least, it would be an ongoing-type of existing institution. That might be the result.

They might have, as the special group suggested, a separate institution in terms of cancer. As I see it, they are wide open regarding the kinds of things that can be recommended, and I fail to see why you think the present situation—with all the uncoordinated studies that have been done—why that is a more satisfactory way of proceeding.

Dr. MARSTON. Senator Kennedy, I read the very, very valuable hearings of now almost 4 years ago, and I would only say that if the commission had been set up at that time and had completed its work 2 years ago, I think some of the points that you brought out in your opening statement would have been missed.

So, whatever the Congress eventually decides in this area, I think the point that I would like to emphasize along with Dr. Duval, and I gather with you, is that this is a dynamic field and that the most important thing is to have some mechanism periodically to bring before the American people and before the scientific community and the public, some of these very important questions.

Some of these, I think—

Senator KENNEDY. How often? You mentioned “periodically.” It seems to me it is being handled on a rather ad hoc basis now, isn’t it?

What group do you have within the Department which is thinking about this type of question all the time?

Dr. MARSTON. Could I go back—

Senator KENNEDY. And you feel that it is of sufficient importance that you have people whose primary responsibility is to come in every day and think and work on these kinds of problems?

Dr. MARSTON. Yes, I think it is very important, and I think a question you raised during Dr. Duval’s testimony deserves a little more exploration, and clarification of the problem. Could I take a couple of minutes to respond to that question?

Senator KENNEDY. All right.

Dr. MARSTON. Since the hearings of this committee last, I think the major change in the NIH position in the area of human experimentation has been to require greater evidence of institutional competence.

As we started working in the area of protection of patients from adverse effects of human experimentation, it was first on the individual investigator, first on the peer review system, itself, and then the development of local committees to look at individual projects.

Now, as questions arise, we are looking at total institutions, universities, or teaching hosts, and their competence to cope with the question in the broader aspects of human experimentation, and here, I think, one can never be completely comfortable that we do have mechanisms that work on a day-by-day basis that call attention with every grant and every institution that receives a grant in this country.

Now, the areas in which we are far less comfortable are some that we are just beginning to go into at present, and this is where there is a true mixture of the problems of society and the problems of science. They extend to the question of the allocation of scarce resources, whether one is talking about the distribution of physicians on the one

hand or the allocation of expensive equipment, such as renal dialysis on the other.

They also cover areas such as our recent conference and the questions raised by new knowledge in genetics and also the one that the Kennedy Foundation covered.

Here, I think there is no answer, but there have been a significant number of serious attempts in a reasonably organized fashion. The Fogarty Center has set up a series of conferences on this. Others in the country have focused on it.

The more difficult problem, as I see it over time, is the changes that will result from advances in biomedical science and, if you will, man's image of himself. It makes a major difference in the whole area of how many children people plan for when the prospect is that few children will die of infectious diseases.

There is a great difference when an individual recovering from a previously fatal disease, whether it be cancer or a myocardial infarction, looked forward to an active life for a number of years.

And, of course, the whole question of prevention of illness through smoking being one that we know at present, the whole problem of diets, the large-scale clinical trials, and very difficult areas.

I think that this set of hearings of 4 years ago did a very good job in laying out the problems in the first two areas. I think we have made progress in a clearer understanding in this country at least that the boundaries and conditions of human experimentation. I think in the other two areas, we have fairly far to go, and need to seek a variety of mechanisms, not to find an answer, but to make progress in these life and death questions.

Senator KENNEDY. Say with respect to renal dialysis, do you have grants now directed at experimentation on that? Do you make such grants now?

Dr. MARSTON. Yes. We have a major target program to try to bring down the cost and try to improve the effectiveness of the machines themselves, the technology; and in addition, we have major programs to try to prevent the occurrence of renal dialysis.

Senator KENNEDY. What are your guidelines, say, as to who should get those machines?

Dr. MARSTON. As far as the question of the grants and accounts to work on the machines, it is a matter of who has the best ideas and what are the national needs for the development of the artificial process. We have at NIH no service programs that provide instruments to individuals for the treatment of patients.

Senator KENNEDY. When you OK a grant for experimenting with these machines, do you have any guidelines as to the kinds of people who ought to be benefiting from them? Or is that up to the local people?

Dr. MARSTON. In the award of our grants for the support of renal dialysis centers, which tend to be different than some of the others, the first assessment is the likelihood that the proposal will give new knowledge which will improve the efficiency of the treatment of patients.

Beyond that, there is a requirement that there be an adequate selection process which focuses from the standpoint of the experiment largely on the protection of the patient and his suitability to meet the needs of the specific research protocol.

Senator KENNEDY. How do you define an adequate selection process and the patient's suitability?

Dr. MARSTON. If the purpose of the grant were to develop, for instance, a small unit that could be used perhaps at home, then one of the criteria would be to select an individual who could use it.

Senator KENNEDY. What do you recommend as to how they ought to select? Say there are four or five applications for that? Do you make any judgment about how to select them?

Dr. MARSTON. Again, for the purpose of our grants, it would be those situations that would generate the greatest scientific knowledge and the selection of those patients which would give the most useful information for the research protocol. This is quite different from the support of dialysis units for service purposes.

Senator KENNEDY. Say the city of Boston comes down to NIH, and we have, say, 25 machines and 100 different applications, and 75 people, 75 of those people, are going to die if they don't get the machines.

We would like to know how we ought to select those people. What can you tell us about that?

Dr. DUVAL. Senator, I think Dr. Marston's point——

Senator KENNEDY. No, I got his earlier point.

Dr. DUVAL. We understand this is different. This is not a function that we undertake at the National Institutes of Health.

Senator KENNEDY. What kind of help and assistance can you give the city of Boston on this?

Dr. DUVAL. In terms of guidelines?

Senator KENNEDY. Yes.

Dr. DUVAL. None.

Senator KENNEDY. What do you think you ought to do? Take a smaller community. Take Milford, Mass. They might have one or two. How are they going to be able to bring together the various different kinds of disciplines to make some kind of decision in terms of what they ought to do with that machine? I think one thing that we are seeing is that people in these communities who are trying to do it are throwing up their arms. They just don't want that responsibility. They set up some kind of ad hoc group at a hospital, which makes decisions that amount to playing God, and they don't want any part of it.

They want some kind of help and assistance. They want to talk to people at the school of theology or the school of medicine or some other place, where they can get some guidance.

Dr. DUVAL. Yes, sir.

Senator KENNEDY. What they want is some place or someone who can help them. Not necessarily by saying "Here it is," or "This is it"; but at least some central place that can give them a range of alternatives, or a framework for their decisions.

I am just wondering. I don't know whether this study will lead to the recommendation that we should establish one place to resolve these questions, but at least the Commission could identify the kinds of alternatives which must be considered.

What are the people in those communities supposed to do? Where are they supposed to go; and if they come to HEW, what kind of answer or help can you give them?

Dr. DUVAL. May I say that you have expressed this dilemma extremely well, and we are all familiar with it.

We interpret our role as being that to provide such counsel and advice we can to persons who come forward with this kind of situa-

tion. We do not tell the community which guidelines to use in making their judgments. The small community group to which you may have had specific reference in mentioning a town in Massachusetts, may come up with a different set of circumstances than, say, a group into Seattle.

Senator KENNEDY. Where do they go? Who within HEW is spending his time just thinking about that kind of question?

Dr. DUVAL. I think that in terms of how to make the moral decision in the community about who will or will not benefit from the procedure, I would have to say there is no focal point inside the Department that attempts to make that decision.

Senator KENNEDY. It's not a question of trying to make the decision. But who is saying that we need more time to work on this particular kind of problem, and therefore, we ought to fund this study here; that there is more of a demand for medical science in this area, and therefore, we need more kinds of studies here; and here are three or four different kinds of alternatives, and these are some of the things that we have found successful under these circumstances—who is there to counsel us along these lines?

Or are you saying that there is some one in the Department who can say, "Here are 15 studies, and I hear there is something that is going to be done at the University of Chicago, and when that comes in, I will send you up a copy."

Dr. DUVAL. I believe your question is directed toward the situation in which Federal funds are involved in supporting an effort in the community, usually supporting research and involving equipment, where a person might or might not be the beneficiary of an esoteric system.

We have a peer review procedure to decide whether or not the investment should be made.

Once this has passed out of the frame of reference in which pure research is involved and it becomes a service that professional people in the community decide to make available, we do not thereafter have a focal point that serves as advice and counsel to that community as to how they should resolve that professional and moral question.

Senator KENNEDY. Where does that community of Milford go? If they call up my office, who am I supposed to send them to over in HEW? Where do they go?

Dr. MARSTON. Well, Senator, I think as you know, the attempt would be to put them in touch with those individuals with the greatest information about the specific area that they were interested in.

Senator KENNEDY. In other words, a specific area like renal dialysis?

Dr. MARSTON. Yes.

Senator KENNEDY. There is some specialized unit in HEW that can respond to specific technical questions in its particular area; but that can't address the broader questions and issues which are involved.

Should he just go to somebody in NIH who is an expert in terms of kidney disease? You have the best in the world on it—I don't think anyone is questioning that—but is that all that we need? Do we need somebody who is an expert on that, or rather some kind of agency that isn't specialized on kidney disease, but also has other kinds of inputs in terms of the wide range of ethical questions involved?

I think that is what we need to address ourselves to.

Dr. MARSTON. The question you raise is one that is going—

Senator KENNEDY. Where does he get it?

Dr. MARSTON. I don't know that there is any place that one can go, to answer this question, or to get very much help on a question where you have a gross disparity between resources and the need for resources, this is the question whether it is a question of a physician or a physician assistant, a renal dialysis machine, or something of that type.

It is one of the major problems that faces us. I think one needs contact with a specialist, if there is a particular interest, as there is in many communities, and also a need for working at the broader question of allocation of scarce resources.

There is no place in NIH, or HEW that I know of that people can come to ask how to handle the health resources in the community and get at one place a single answer.

Dr. DUVAL. We might add that we don't think there is a single answer.

Senator KENNEDY. That is right, but we need to try, I feel, to raise some of these questions in order to provide help to those who have to make decisions. I think this is all. Maybe this commission would never recommend that there be that one place. Maybe they would.

At least, they would be able to guide the community in terms of some of these areas.

Senator Mondale?

Senator MONDALE. I don't know of any issue that fascinates me more than this one, because there is generally some proportionate relationship between an action and a reaction. But in this case, the reaction is grossly disproportionate to the action.

All we are proposing here, and have been proposing for some years, is to create a measly little study commission to look at some very profound technological breakthroughs which could revolutionize human society, including such issues as behavior control, genetic engineering, vital organ transplants, kidney dialysis, experimentation on human beings, or any number of other things.

All we have said is, "Let's have a public study commission to look at it."

That is all we have asked for. But the reaction has been fantastic.

In 1968, they bootlegged Christiaan Barnard in here to tell us why this would put South Africa ahead of the United States in medical science. He said, "You will have a politician in every surgical room."

The major portion of the American public bought what he said. He said they didn't have any problems in South Africa on the vital organ transplant issue.

I know that a widow in South Africa recently complained that her husband's heart was taken away without consultation. She took that personally.

But they have no problems, he said, and to do anything about it would be terrible. They got Dr. Kornberg in here, who is a great scientist, and what did he say?

In 1968, he said the biochemist who deals with molecules cannot afford any time away from them. "Today, I am not in the laboratory. I do not know what is going on at the bench. Tomorrow, I will be less able to cope with the identity and the behavior of molecules. The more

I am estranged from the laboratory, the less competent I am to advise you regarding special problems in this field."

In other words, he asked us, "Why are you wasting my time here?"

Today, your position apparently is that if we have a little study commission, it would freeze American technology. That is apparently the position taken here.

Why do we assume that if the public understands this that their reaction will be necessarily anti-science? Might it not be more supportive and, in the long run, doesn't medical science require public support, public understanding and, above all, public confidence?

My point is that we are asking to do so little, and the resistance seems to be entirely disproportionate. Everybody is getting studies these days. What is wrong with a little bit of study here?

Dr. DUVAL. Senator, my response to that would be to reiterate that we are in full accord with the objective for which these hearings are held now and as a consequence of the submission of your resolution, and that the objective you are trying to achieve is eminently desirable.

I would submit that as a consequence of the very rapid technological advance that has been made in the last 3 or 4 years in science that society, itself, has responded rather well to the number of abuses considering the extreme work that is going on in this field.

It has been very small, and I am very impressed that at the moment society has indeed responded in the way in which you have hoped and expected that they would.

I want to throw in with that argument the possibility that by setting up some form of central or national commission, you will be somewhat inclined to relieve local communities and local groups of some element of local responsibility.

Senator MONDALE. Just tell me why that is true?

Dr. DUVAL. I believe there is probably a natural inclination to say, "I can do this as long as group A has not told me that it isn't OK."

We think the system of defending everything you do locally—which is what we do now—is working rather well.

Senator MONDALE. Do you have some study groups on science and ethics and so on?

Dr. DUVAL. Yes.

Senator MONDALE. Does that paralyze local initiative?

Dr. DUVAL. No, sir, it doesn't.

Senator MONDALE. In other words, if you do it on your own, it is fine, if we ask you to do it, it is not?

Dr. DUVAL. No, sir, I didn't mean to imply that.

We have a group that must examine everything that is done in this general area before it can be funded. So, among his own peers and associates and colleagues, every person involved in this work locally must present his case before a court, so to speak, that includes the same type of representatives that you have already described in your Commission.

We would not like to see that decompressed or relieved of responsibility by guidelines established by central governmental authorities.

Senator MONDALE. I have great respect for what you are doing, great respect for the medical profession. In Minnesota, we have a great medical apparatus.

But I sense an almost psychopathic objection to the public process, a fear that if the public gets involved, it is going to be anti-science, going to be hostile and unsupportive.

I think, in fact, the public very much wants a healthy, growing medical science. Trying to keep the public out is, actually, a greater risk than opening up the process and letting the public participate.

This sort of bias shows up in several ways. I have asked several medical witnesses about how many medical schools, for example, teach these issues, regarding science and its implications for society. I think very little is being done.

How many medical schools try to train their doctors to be broadly understanding of the economic and social implications of the field? Far too little is being done. I think there is more than was true a few years ago, but it is too often considered a waste of time.

I think the medical profession suffers from trying to keep all their functions private. I think the more they would let the public in, I think the more surprised they would be of how understanding and supportive the public would be.

I think resistance to this modest little proposal underscores the inflated fear that the medical profession has.

Dr. DUVAL. Senator, I would like to respond by saying that to the extent that my colleagues are guilty of giving you the impression of privatizing in this area, I would apologize, because I firmly believe there is a very real feeling in the scientific community that the public interest with regard to this field at this time has never been more appropriate and more warmly received.

I have no explanation for such interpretations as you may have put on it in the past.

With regard to your point about instruction in this type of activity in the medical schools, it is my impression that there is a great deal going on now in the United States. In the school I started at the University of Arizona, we have a complete course which takes on the entire field.

Senator MONDALE. When was that course set up?

Dr. DUVAL. 1967.

Senator MONDALE. As I mentioned, I think there is some progress in this area, but I think it is slow and late, and that you are a leader in the field.

Dr. DUVAL. It is because you held hearings and directed our attention to this that there has been an adequate response.

Senator MONDALE. At one medical school.

How many medical schools have courses like the one you have set up?

Dr. DUVAL. More than half.

Senator MONDALE. That is quite a change.

Dr. DUVAL. There may have been less than 10 percent in 1967, Senator.

Dr. MARSTON. Senator Mondale, may I respond to your comment on behalf of NIH?

I was Associate Director at the time that Dr. Shannon made his statement in your longer hearings. I have reread those, and I think they are very positive and I agree with a statement that was made 4 years ago.

I think it is important that the position of NIH is precisely yours, that this is a question of great importance and one that must be shared

with the public. It cannot be held within the scientific community, and I would want no misunderstanding on my personal feelings on reviewing last night the statements made 4 years ago before your committee.

Senator MONDALE. Thank you very much.

Senator KENNEDY. Senator Dominick?

Senator DOMINICK. Dr. Duval, I want to start out by saying that I think that Senator Mondale and Senator Kennedy have introduced a resolution which by drawing attention to the problems here which have not been drawn attention to before in Congress, have performed a very useful service, and I really think that.

I had the opportunity of having lunch with Dr. Barnaard a couple of years ago right after his spectacular heart transplants, and raised some of these questions at that time at lunch.

As Senator Mondale said, any effort to question what he was doing in terms of legal or ethical positions were greeted as though you were attacking him personally on his skill as a doctor, and this I found a little frustrating.

I noticed in your statement here on page 9, Doctor, that you refer to the private sector and the groups who are actively investigating some of these problems now, including the National Academy of Sciences, the American College of Surgeons, the National Academy of Engineering, the American Academy of Arts and Sciences, the American Philosophical Society, IBM, and the Kennedy Foundation, amongst others.

About when did they start becoming involved in this?

Was it really after the heart transplant operations started drawing attention to these problems in a rather massive way?

Dr. DUVAL. Senator Dominick, the first entry of this kind into the field coincided with the NIH Clinical Research Center in 1952. The great impetus in the area did occur subsequent to the first heart transplant.

I might add that it has gotten a great deal of stimulation by hearings on this type of issue.

Senator DOMINICK. I am having trouble hearing you.

Dr. DUVAL. It has had further progress and impetus as a result of the focus provided by hearings in this room.

In other words, I would make the same comment, Senator Dominick, that you have already made, that these have served a great purpose in bringing these to our attention in this way.

Senator DOMINICK. In what particular fields are these people and groups you are talking about now working?

Dr. DUVAL. In the broad fields of medicine, biology, theology, but the purpose of their undertaking investigations or explorations in these broad areas is to specifically treat the issue of the local regional management of problem situations involving genetic counseling, genetic manipulation, organ transplantation, time and cause of death, et cetera.

Senator DOMINICK. There used to be in several States, at least, and I would presume pretty much nationwide, an experimental, a human experimental scientific situation where, if a prisoner legally convicted was on death row or something, and he wanted to go through with a

medical experiment, he would be given remission from his sins, let's put it that way, in the event he survived.

This, as far as I know, was the only voluntary human method of experimentation that I know, except on a minority, maybe antibiotics or something like this where they wanted to experiment with a new one.

Is that still going on?

Dr. DUVAL. So far as I know, it is not, Senator, but I must say I do not have the answer to the question.

Dr. MARSTON. The guidelines in any experiment that involve human subjects are the same as far as we are concerned with, I think, a special emphasis on any circumstances in which those that are unable to make decisions of their own—for example prisoners, particularly the younger ones. There is a special sense of protection of the rights of the individual under those circumstances.

Senator DOMINICK. Well, if the man is on death row, he doesn't have much choice anywhere.

Dr. MARSTON. And the statement has been made that he can't make a rational choice if he is in those circumstances.

Senator DOMINICK. Take a normal human being, and he has been advised by as many people as he can reach that his case is hopeless in one form or another. What does he have to do now in order to get the right to have someone experiment on him, or her?

Dr. DUVAL. I don't believe, stated that way, it is likely to happen. I don't think one could come forward and identify a particular experiment in which he might be a subject. With professional help, I suppose he might be able to determine what work is being done where, and he might go to that particular point. It would be a very unstructured arrangement.

Senator DOMINICK. This is one of the things that was concerning me, frankly, in terms of being able to make use of what may be new advances in one area that hasn't been heard up in another area.

The question is, where do you get that type of information and how do you make yourself available as a voluntary experimenter in it as the guinea pig, so to say?

Dr. DUVAL. The movement of the information of the type to which you refer having to do with useful progress now occurs so rapidly, that it is difficult to believe that someone could be left out of a treatment that might be available.

Senator DOMINICK. Well, with all due respect, Doctor, I am not quite sure that is true. If you have got a lot of money and have the ability to go around to the various places, treatment centers and clinics, you might by chance happen on someone who has particular skill in a particular operation, or something of this kind.

Just for an example, I suppose our hospital at the University of Colorado Medical Center has done more liver transplants than most hospitals have. I doubt very much if that is known around the country.

Similarly, if you didn't have any money, there is no way of your getting information.

Now, is there any kind of an informational source through the NIH or any other group?

Dr. DUVAL. Senator, I will ask Dr. Marston to respond, but I would submit that the reputation of the University of Colorado Medical Center and specifically the work done there in liver transplantation is known by virtually every physician in the United States.

Senator DOMINICK. It is possibly true on that one, but I would say to you that any one living in Chicago or New York on a typical income wouldn't have the foggiest idea of where Colorado was, let alone what they were doing there.

Is there a source of information on this at NIH, or anybody else?

Dr. MARSTON. Senator Dominick, I think in a sense there are two questions here. One is the exchange of information as far as research protocols are concerned, and here, there are regular advertisements throughout the country of types of research that are being carried on at the Clinical Center at NIH.

There are similar types of information exchange from a place such as the work of Dr. Stanzal at Colorado, the types of work he is doing and the types of patients who fit into his research.

Now, these are investigative techniques, though, in which one is seeking individuals who uniquely might give information of benefit to many people by participating in some type of exercise.

When a technique has gone beyond the experimental stage, I would agree completely with Dr. Duval that one does know throughout the medical community at least where the dozen, 50, 100 experts in areas such as renal transplantation are, and this is not, once these have become established techniques, then an information exchange problem.

There are reasons that one might not want, in the experimental cases, to have wide publicity and false hopes raised when one is trying to work out the actual procedures.

Senator DOMINICK. Well, it was only 10 years ago that a friend of mine in New York, a very close friend, had an aneurism problem, which was known about. The doctor there said to his relatives, "Don't worry about having him operated on, because there is no chance of his recovery."

Yet, at that very time, they were doing those operations in Texas and doing them well.

Where do you find information like that? How would you find it? This person wasn't poor. They could have gone there very easily and he could have been operated on, but there was no information available.

Now, how do you find the informational source? This, I think, is important.

Dr. DUVAL. Senator, the only reasonable answer to that under the circumstances of the timing of that kind of work, is that as soon as it was known, for example, in Texas, that aneurisms of the type that perhaps your friend had were in fact operable with a reasonable chance of success, the medical profession would know about it. Texas would have to have had enough experience to know that this would work.

I do not know how far they were toward building their cases at the time of your friend's case, but there will always be lag time, and there should be.

Senator DOMINICK. I have difficulty following this. If a person is said to be in terminal condition by his local physician or local clinic

or whatever it is, but there are people in other areas of the country which are doing experimental work, why shouldn't he have the right to volunteer to go there, regardless of whether the experimental work is valid or whether it isn't?

Dr. DUVAL. I think, again, the only way that I would be able to answer that at this time is that this might result in the development of a pattern that in the aggregate would be very disadvantageous to the normal moral development of the society.

If one had them mass migration around the United States of persons considered terminal who were looking for some last resort, I can see that the total amount of heartbreak, the total stimulus to even move into the area could be very undesirable. I would like only to urge that a consideration of a solution of that kind be approached very cautiously.

Senator MONDALE. Would you yield there?

Senator DOMINICK. I would be glad to.

Senator MONDALE. I think Senator Dominick's question is well taken. What it means is that if we do not have an informational source, the very wealthy are able, through their sources and contacts in the medical field and their capability to pay appropriate fees, to sort out all the possibilities from a medical standpoint and because of that advantage may migrate where their health chances are the best.

But the average American, who does not have those resources, is left with options which considerably reduce his life chances under those circumstances. It seems to me that that raises a legitimate ethical issue, whether the prospects for life and health should depend solely on money and contacts and influence.

Senator DOMINICK. It isn't even necessarily that, Senator. It is just the question of whether the medical profession or medical clinics or your informational sources, wherever they are, are sufficiently up to date so that you can find out.

In other words, is there any kind of an information bank that is what I am really trying to find out.

Dr. MARSTON. Again, there are two questions here. One is as far as the experimental programs are concerned. We circularize on a regular basis the kinds of research that we do at the National Institutes of Health, and that is also done from other research centers.

Suitable patients for such research projects are referred to the research centers by local physicians, after which referral, there is another screening of patients at the research center itself. Thus, one could say that two professional staffs select patients for experimentation.

There is another side to this, though, and that is when somebody is about to become a treatment subject, and Senator Mondale, you remember very well the problems in Minnesota with the early enthusiasm for cortisone as a cure-all of arthritis, and how much harm could have been done if there hadn't been some restraints on what looked like a miracle drug.

So, this is another aspect of the ethical side. What type of evidence do you accumulate before you raise the expectations of the people, when you may do harm by treating prematurely?

I think this is a point Dr. Duval and I have been trying to make.

There is a third point, and that is, how can we assure equal access without regard to economics and all of the rest?

I think that is one of the major problems of this country and one of the ones that I think we have to work very hard on, and it is a very real question that all of us need to put all our support behind.

But I would say again as far as the identification of research opportunities, the protocols for a large study such as the one that we just completed, a 10-year study on the use of oral antidiabetics, this was well known, well advertised by multiple clinics throughout the country, and patients had a chance to participate or not participate.

We had an ethical problem in that study, because it turned out that the treatment we thought was going to help was actually harming the patients, and this has led to a lot of discussion in and the medical area.

But the fact that there was a study was widely circulated, that it involved multiple institutions across the country. That is what raised a serious question about how individuals who were not very sick—diabetics who didn't require insulin—might benefit from a new type of therapy.

It took us 10 years to unravel that one, and we did have people from all over the country who were involved in that, Senator Dominick.

Senator DOMINICK. Well, I don't mean to be particularly difficult on this—maybe I am being that way—but there seems to be such an emphasis on security these days. I don't know whether it is that people get sued if they do something wrong, doctors, hospitals, and clinics. This is a certain part of the problem, I know. It seems to me if a person is willing to volunteer for treatment, there isn't any reason in the world why they shouldn't have the right to go there. It is their money and life and health. Why shouldn't they have the right?

Dr. DUVAL. No argument, Senator.

Senator DOMINICK. Yet, if you try and get any kind of an informational source from a hospital or from—well, I frankly have never tried the NIH, Dr. Marston, and I am sure that maybe things would be better there—but if you try to do it anywhere, they will tell you, "That is nothing but a bunch of quackery, and forget it," because it hasn't been proved in scientific journals.

Who cares? It may be nothing but psychosomatic, but it might help.

Dr. DUVAL. I am sure, Senator, we know there is no single answer to the profound observation you have just made. I would submit that, on balance, it is better to be conservative in the management of something that deals with human life.

It would be a difficult thing to answer in an area as profound as you have just raised.

Senator DOMINICK. Well, I recognize the need for some kind of discipline within all these professions, regardless of what they are in order to get some sound scientific results, but at the moment, people who tend to experiment on different theories are either not granted licenses or whatever grants they have had may have been cut off. I have two or three things of this kind that I know. Or they are forced to go to another country.

I know some in the cancer field, and I am sure both of you know what I am talking about, where they moved to another country because they weren't permitted to practice here, and yet, nobody really knows whether that is going to work or whether it isn't.

I have some real difficulty in determining why we go to this length.

Dr. MARSTON. Senator Dominick, we may have a difference of opinion. I thought for a moment that we didn't, but we may have one.

It seems to me that one does have a responsibility in 1971 to try to utilize the best judgment and the best minds in the treatment of the patient, whether they have a minor illness or whether they have a serious illness, and the major danger that has plagued people interested in cancer and the claims for cures is the frequency with which those claims, often based on quackery, have prevented access to really effective therapy. I think this is the danger when one says, "Why not go and use something because you haven't proved that it is good?"

The big danger is that you might be withholding from that patient really effective therapy.

Senator DOMINICK. I can understand that, but I don't see why you can't in light of present scientific knowledge or medical knowledge or whatever it is, put up an information bank and say, "This thing has been shown to operate. It has an  $x$  percent of chance of curing, if you go down and take sarsaparilla five times a day, we don't think it has much benefit as far as you are concerned, but here are the people who are given five doses of sarsaparilla a day."

Then, if a person wants to go and drink five doses of sarsaparilla a day, why shouldn't he? This is what I don't understand. Yet, they are not permitted to do that. I think that is pretty rugged.

In any event, getting back to the main case, and I got off on a little tangent of my own, for which I apologize to my colleagues, I will ask just one more question, again, with respect to page 9 of our statement, Dr. Duval.

Specifically, you say that several distinguished groups already in existence have broad responsibilities in the areas outlined for the proposed Commission on Health Science and Society, and then you go through that list.

Now, what are they doing, really? You say they have broad areas of responsibility.

What do you mean by that?

Dr. MARSTON. Each of the institutions and agencies mentioned in that portion of the testimony perhaps sees its own contribution to this question differently than any other, except that in the aggregate each is concerned that they deliver competent, quality advice to the efforts of its member scientists in the area of ethics and morals as it relates to biomedical research.

One of the nicest examples of this, perhaps, is the creation recently of the Institute of Medicine as a division of the National Academy of Science.

While it does exist in fact for several reasons, clearly one of its primary reasons is to oversee the advances being made in the United States in biomedical research, the manner in which the new information is deployed, and the ethics and morals that attach to the decision-making process within that arena.

I would simply submit that in response to the stimulation provided from many sources, including this committee, and consideration of this issue since 1968 that this is precisely the response in the scientific community that I assume that you would want to see develop.

Senator DOMINICK. Is it your concern, then, that if this national commission was put through as had been suggested by this resolution that the efforts in the private fields or in the semipublic fields would lessen?

Dr. DUVAL. No. I would only be concerned about the one comment I made earlier that I would hope that, were such a Commission established, it would not be created in such a way as to relieve local groups, particularly those involved with scientists who are doing the work of the obligation and responsibility to continue to oversee what they are doing.

Senator DOMINICK. I will pass on. Excuse me for taking so long.

Senator KENNEDY. Just one final question. Doctor.

On page 6, you mentioned that in 1971, the Department has again extended these guidelines to all grantees.

Can you tell us who was involved in the development of those guidelines? Did you have philosophers and theologians and ethicists?

Dr. MARSTON. Yes, Senator, we have required NIH not only at the national level—and I can give you the names of the advisers we used in setting them up—but also at the local level, that there be non-physicians, lay representatives on the human representation committees, and in most instances, all that I know of, these have included clergymen as members of those commissions.

Senator KENNEDY. I was interested, really, from the NIH point of view and how you developed your guidelines.

Could you give me a note on that?

Dr. MARSTON. Along that line, at our recent meeting on the ethical considerations in genetics, we did have about a third theologians, about a third scientists and about a third philosophers, generally.

Senator KENNEDY. Yes. I would appreciate it if you could give me a note on that: covering how you developed the guidelines and who participated in their development.

Dr. MARSTON. We will be pleased to.

(The information subsequently supplied follows:)

ORIGINS OF THE DHEW POLICY ON  
PROTECTION OF HUMAN SUBJECTS

1. The Department's policy on protection of human subjects involved in activities supported by its grants and contracts is a direct lineal descendant of three prior Public Health Service issuances:

- a. Policy and Procedure Order No. 129, February 8, 1966
- b. Policy and Procedure Order No. 129, Revised, July 1, 1966
- c. Protection of the Individual as a Research Subject, May 1, 1969.

The Department's policy appeared as:

- d. Grants Administration Manual Chapter 1-40, April 15, 1971 (included on page        of the hearings).

2. The development of the Public Health Service guidelines has been documented in considerable detail in an independent study carried out by the Program of Policy Studies in Science and Technology of the George Washington University by Mr. Mark Frankel.

3. The development of the Department of Health, Education, and Welfare policy from the Public Health Service policy is referred to only briefly in the above study and requires further description.

Shortly after the release of "Protection of the Individual as a Research Subject," Under Secretary John G. Veneman distributed copies to all non-Public Health Service operating agencies within the Department, requesting that they move immediately to bring their operations into compliance with the policy.

This request met with immediate agreement in principle from all agencies, but with substantial reservation with regard to the language and applicability of the document, which was understandably strongly medical, and rather casual in its treatment of social and behavioral studies.

A committee was set up under the chairmanship of Dr. Ernest M. Allen, Deputy Assistant Secretary for Grant Administration Policy in the office of the Assistant Secretary, Comptroller, The committee consisted largely of administrative staff who had been concerned with the administration of the Public Health Service policy, related programs in the Office of Education, or were familiar with the policy issues raised by the programs of the Social and Rehabilitation Service and the Social Security Administration.

Staff support for the committee was provided by the Institutional Relations Section, Division of Research Grants, NIH. As the committee progressed with its work, the Institutional Relations Section initiated a series of meetings with grantee institutions to discuss the existing policy, to explore the feasibility of proposed modifications, and to gather suggestions. Meetings were held in association with the University of North Carolina-Duke University, University of Maryland, University of Minnesota, Rockefeller University, and Syracuse University.

All major Public Health Service grantees in the vicinity of the meeting sites were asked to send at least two representatives; the chairman of the local institutional review committee established under the PHS policy, and at least one other institutional representative such as a responsible senior administrative officer, institutional legal counsel, or members of the institution's staff interested in the interfaces between scientific research, the law, philosophy and religion. Average attendance at each meeting was around 50-60 people. Among those contributing strongly to certain of these several meetings were:

Joseph H. Burchenal, M.D., Memorial Hospital Sloan-Kettering for  
Institute Medical Research

L. P. Covington, L.L.B., North Carolina Department of Mental  
Health

Sidney Dymond, L.L.B., Q. C., University of Toronto, Canada

Renee C. Fox, Ph.D., University of Pennsylvania  
Ward O. Griffen, M.D., University of Kentucky  
J. T. Hamill, III, M.D., University of Virginia  
Nash Herndon, Ph.D., Associate Dean, Bowman Gray School of Medicine  
Leslie Hicks, Ph.D., Howard University and American Psychological Association  
Sherman Kupfer, M.D., Associate Dean, Mount Sinai School of Medicine  
Irving Ladimer, S.J.D., Mount Sinai School of Medicine  
Mrs. Lorraine Lasker, A.B., New York Medical College  
Allen McCoyd, L.L.B., University of Minnesota School of Law  
Humphrey Osmond, M.D., New Jersey Neuropsychiatric Institute  
Samuel Polsky, L.L.B., M.D., Temple University  
David L. Segel, L.L.B., Associate Counsel, SUNY  
Claudia Sutherland, Ph.D., Vanderbilt University  
Gordon Walker, M.D., Johns Hopkins University

The predominance of medical and legal contributors is apparent. Minutes and full attendance lists for these meetings are available.

As drafting continued, Dr. Ernest M. Allen circulated copies to representatives of the Deans' Committees of the American Association of Medical Colleges. Comments were received from approximately a fourth of the nation's 83 deans.

Copies of various drafts were also made available to various private organizations including the American Civil Liberties Union, (Washington Chapter), the American Psychological Association, Committee on Responsible Government, and the Society for Health and Human Values. With the exception of the ACLU, direct response from this group was negligible.

In its final stages the policy was reviewed by the Department's Grants Administration Advisory Committee, which includes representation of all of the Department's operating agencies, and of major types of private and public agencies involved in the receipt and administration of grants and contracts.

The last review, prior to publication was provided by the Office of General Counsel, DHEW. As a result of their insistence, the informed consent requirements of the policy were substantially strengthened.

4. The "Institutional Guide to DHEW Policy on the Protection of Human Subjects" is an administrative document developed during the summer of 1971 as an interpretation of the formal policy. This document was drafted by the Institutional Relations Section, Division of Research Grants, NIH, and then discussed with grantees in a second series of area meetings following the pattern of those used to discuss the substance of Grants Administration Manual 1-40.

Major meetings were held in association with the, Massachusetts General Hospital, Boston; Emory University, Atlanta, Georgia; DHEW Regional Office, Kansas City, Missouri; University of California at Irvine; University of California Medical Center, San Francisco; University of Pittsburgh, Pennsylvania.

Among these contributing notably to this series of meetings were:

Vernon Ahmadjian, Ph.D., Clark University  
 Henry K. Beecher, M.D., Massachusetts General Hospital  
 John Bowers, L.L.B., National Legal Program of Health Problems of the Poor  
 William J. Curran, L.L.M., Harvard University  
 Bernard L. Diamond, Ph.D., University of California, Berkeley  
 Rosemary Ellis, R.N., Case Western Reserve University  
 George Harwell, Dean, Pennsylvania State University School of Medicine  
 Evelyn Hess, M.D., University of Cincinnati  
 Allen Moore, Ph.D., Case Western Reserve  
 Eli M. Nadel, M.D., St. Louis University  
 Edwin B. Newman, Ph.D., Harvard University  
 Frederick Pitman, M.D., Medical College of South Carolina  
 Robert R. Sears, Ph.D., Stanford University  
 John M. Tyler, M.D., Lemuel Shattuch Hospital  
 Lowell White, M.D., University of Florida

In contrast with the meetings on the policy, this second group involved fewer legal representatives, and an increased number of non-medical scientists.

During the same period, staff were involved in other meetings in connection with the:

Florida Department of Health and Rehabilitation, Tallahassee, Florida  
 Eunice Kennedy Schriver Foundation, Fernald State School,  
 Waltham, Massachusetts  
 State University of New York, Potsdam, New York  
 Seminar on Problems in Mental Retardation Center for  
 Continuing Education, Durham, New York



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
WASHINGTON, D.C. 20201

REFER TO:

February 8, 1966

TO : The Heads of Institutions Conducting Research with  
Public Health Service Grants

FROM : Surgeon General, Public Health Service

SUBJECT: Clinical research and investigation involving human beings

Expanding Public Health Service support of clinical research and investigation involving human beings emphasizes the need for more formal attention to the critical issues raised by such research.

In December 1965 the National Advisory Health Council, after study of these critical issues, made certain recommendations to me which I have now formulated as the following Public Health Service grant policy:

No new, renewal, or continuation research or research training grant in support of clinical research and investigation involving human beings shall be awarded by the Public Health Service unless the grantee has indicated in the application the manner in which the grantee institution will provide prior review of the judgment of the principal investigator or program director by a committee of his institutional associates. This review should assure an independent determination: (1) of the rights and welfare of the individual or individuals involved, (2) of the appropriateness of the methods used to secure informed consent, and (3) of the risks and potential medical benefits of the investigation. A description of the committee of the associates who will provide the review shall be included in the application.

Effective immediately, this policy will be included in all future statements of Public Health Service research and research training grant policy. The wisdom and sound professional judgment of you and your staff will determine what constitutes the rights and welfare of human subjects in research, what constitutes informed consent, and what constitutes the risks and potential medical benefits of a particular investigation.

I wish to define more explicitly, however, what is meant by a committee of his institutional associates to assure an independent determination because the policy requires that the application include a description of the associates who will provide the review. The committee would need to be made up of staff of, or consultants to, your institution who are at the same time acquainted with the investigator under review, free to assess his judgment without placing in jeopardy their own goals, and sufficiently mature and competent to make the necessary assessment. It is important that some of the members be drawn from different disciplines or interests that do not overlap those of the investigator under review.

The policy does not ask for the names of the members of the committee. It does ask for a description of its composition; e.g., the number of members and the professional or public interests they reflect.

I have directed all my staff who administer the initial review of applications for grants for clinical research and investigation involving human beings -- regardless of whether these applications are for new, supplemental, renewal, or continuation support -- to ascertain that each application includes the information required by this policy and to obtain this information, when necessary, in a document signed by both the principal investigator or program director and the official for the institution.

I know that you are as deeply concerned with this issue as are any of us in the Public Health Service. I urgently request that you give my staff your cooperation in making this policy an effective instrument for the good of the public and science.

*William H. Stewart*  
William H. Stewart, M.D.

U. S. Public Health Service  
 Division of Research Grants  
 Bethesda, Maryland 20014

PPO # 129  
 POLICY  
 February 8, 1966

SUBJECT : Clinical Investigations Using Human Subjects

APPLICABILITY : All PHS Research and Research Training Grants  
 in Support of Such Clinical Investigations  
 (including General Research Support Grants)

EFFECTIVE DATE: Immediately

BACKGROUND:

The National Advisory Health Council on December 3, 1965, recommended to the Surgeon General as follows:

Be it resolved that the National Advisory Health Council believes that Public Health Service support of clinical research and investigation involving human beings should be provided only if the judgment of the investigator is subject to prior review by his institutional associates to assure an independent determination of the protection of the rights and welfare of the individual or individuals involved, of the appropriateness of the methods used to secure informed consent, and of the risks and potential medical benefits of the investigation.

The Surgeon General accepted the recommendation of the Council and instructed the Grants Policy Officer to develop implementing procedures for research and research training grants.

STATEMENT OF POLICY:

No new, renewal, or continuation research or research training grant in support of clinical research and investigation involving human beings shall be awarded by the Public Health Service unless the grantee has indicated in the application the manner in which the grantee institution will provide prior review of the judgment of the principal investigator or program director by a committee of his institutional associates. This review should assure an independent determination: (1) of the rights and welfare of the individual or individuals involved, (2) of the appropriateness of the methods used to secure informed consent, and (3) of the risks, and potential medical benefits of the investigation. A description of the committee of associates who will provide the review shall be included in the application.

2

## PROCEDURE:

The above policy becomes effective immediately and will be incorporated in all PHS research and research training grant regulations and research and research training policy statements as soon as possible. In the meantime, the attached memorandum from the Surgeon General explains the policy to grantee institutions.

The PHS staff who administer the initial review of applications for clinical research and investigation involving human beings (including the administrative review for continuation applications) shall ascertain that each application includes the information required by this policy and shall obtain this information, if necessary, in a document signed by both the principal investigator or program director and the official authorized to sign for the institution.

Attachment

ORIGINATING OFFICE: The Surgeon General, Public Health Service

APPROVED BY: Grants Policy Officer, OSG

Ernest M. AllenDate: 2/8/66Index: Clinical Investigations  
Human Subjects: Clinical Investigations



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
9000 ROCKVILLE PIKE  
BETHESDA, MD. 20014

July 1, 1966

TO : Heads of Institutions Receiving Public Health Service Grants

FROM : Surgeon General, Public Health Service

SUBJECT: Revised procedure on clinical research and investigation involving human subjects

On February 8, 1966, I issued a policy statement relating to investigations involving human beings, including clinical research, pointing out the need for group review to protect the rights and welfare of the human subjects involved. The original policy involved only the support of research and research training. The application of this policy has been extended to all grants and awards of the Public Health Service in the support of research, training, or demonstration projects, including the projects supported through general research support and those of fellows and trainees. The policy is not applicable to grants in support of construction, alterations, renovations, or research resources -- it is obviously applicable to the Public Health Service projects using these facilities and resources.

Experience gained in administering this policy has led to revision and simplification of procedure. The major procedural revision is one for making agreements between each grantee institution and the Public Health Service which will obviate the necessity for providing detailed assurance with each application. Attached to this memorandum is a statement of revised policy and procedure (Policy and Procedure Order 129) which has been issued at my instruction.

The Public Health Service will continue its study of the issues of investigations involving human subjects. As experience shows the need for revised or augmented policy or procedures, these will be developed. I shall be pleased to receive suggestions and information from officials and investigators of grantee institutions to assist the Service in the conduct of its study.

I trust that these revisions, reflective of the advice I have received from many of you, will facilitate your discharge of this important obligation.

*William H. Stewart*  
William H. Stewart, M.D.

Attachment

U. S. Public Health Service  
 Division of Research Grants  
 Bethesda, Maryland 20014

PPO #129, Revised  
 POLICY  
 July 1, 1966

SUBJECT : Investigations Involving Human Subjects, including  
 Clinical Research: Requirements for Review to Insure  
 the Rights and Welfare of Individuals

APPLICABILITY : All Public Health Service Grants and Awards

EFFECTIVE DATE: Immediately

SUPERSEDES : PPO #129, February 8, 1966  
 PPO #129 Supplement, April 7, 1966

#### I. BACKGROUND:

Culminating several years of study by various Public Health Service staff and advisory groups, the National Advisory Health Council passed the following resolution on December 3, 1965:

"Be it resolved that the National Advisory Health Council believes that Public Health Service support of clinical research and investigation involving human beings should be provided only if the judgment of the investigator is subject to prior review by his institutional associates to assure an independent determination of the protection of the rights and welfare of the individual or individuals involved, of the appropriateness of the methods used to secure informed consent, and of the risks and potential medical benefits of the investigation."

#### II. POLICY:

The Surgeon General accepted the resolution of the National Advisory Health Council and promulgated the following policy statement on February 8, 1966:

"No new, renewal, or continuation research or research training grant in support of clinical research and investigation involving human beings shall be awarded by the Public Health Service unless the grantee has indicated in the application the manner in which the grantee institution will provide prior review of the judgment of the principal investigator or program director by a committee of his institutional associates. This review should assure an independent determination: (1) of the rights and welfare of the individual or individuals involved, (2) of the appropriateness of the methods used to secure informed consent, and (3) of the risks and potential medical benefits of the investigation. A description of the committee of the associates who will provide the review shall be included in the application."

### III. REVISED POLICY:

By decision of the Surgeon General, the application of this policy has been extended to all grants and awards of the Public Health Service in the support of research, training, or demonstration projects, including the projects supported through general research support and those of fellows and trainees. The policy is not applicable to grants in support of construction, alterations, renovations, or research resources -- it is obviously applicable to the PHS projects using these facilities and resources.

This policy will be included in all pertinent grant program policy and instruction statements, and will be among the conditions of award agreed upon by grantee institutions and the Public Health Service. The policy applies to all investigations involving human subjects, including clinical research.

#### A. Assignment of Responsibility

Safeguarding the rights and welfare of human subjects involved in research support by PHS grants is the responsibility of the institution to which the grant is awarded. The institution must assure the Public Health Service that in the case of investigations and activities supported directly by the PHS, it will provide group review and decision, maintain surveillance, and provide advice for investigators on safeguarding the rights and welfare of human subjects. The institution also has the responsibility to provide whatever professional attention or facilities may be required for the safety and well-being of human subjects. The institution shall be responsible for developing the administrative mechanism for review, surveillance, and advice; however, the PHS requires that, prior to inception of each course of investigation, objective decisions be made on the three points cited in the Surgeon General's policy statement (above) by an appropriate committee of associates of the investigator having no vested interest in the specific project involved. The grantee institution may utilize staff, consultants, or both to carry out the review. Any group responsible for review should possess not only specific scientific competence to comprehend the scientific content of the investigations reviewed, but also other competencies pertinent to the judgments that need to be made.

The grantee is required to make and keep written records of the group reviews and decisions on the use of human subjects and to obtain and keep documentary evidence of informed consent relating to investigations carried out with the assistance of PHS financial support.

#### B. Timing of Review

While this policy requires that review be conducted prior to the use of human beings as subjects, there are advantages to both the PHS and the grantee in having the review conducted prior to application for PHS support. The PHS encourages the institution to do so, if the review can be accomplished without causing unreasonable delay in the application process and if the application is of the type that normally contains a reviewable scientific protocol.

#### IV. PROCEDURAL REVISIONS -- ASSURANCES OF APPLICANTS AND GRANTEES:

Upon issuance of this policy statement, the PHS will require necessary assurances from the grantee institutions which sponsor investigations involving human subjects, including clinical research. These assurances will cover both the general principles of safeguarding human rights and welfare in the conduct of research and the specific points of the Surgeon General's policy. The assurance should provide explicit information on the policy and procedure it employs for review and decision on the propriety of plans of research involving human subjects. The descriptions will include the competencies represented in the committees of associates utilized for review, the sources of consultants (if used), the administrative mechanisms by which surveillance is provided for projects involving human subjects -- particularly to deal with changes in protocol or emergent problems of investigations, the means of guidance and advice provided for investigators, and the manner in which the institution will assure itself that the advice of the committee of associates will be followed. Copies of documents of institutional policies on these issues should be attached to the memorandum of assurance. An example of an acceptable assurance is attached.

Assurances can be provided which apply only to individual major components of universities or other large institutions in those instances where assurances covering the total institution are impracticable or inadvisable.

Each assurance and its attachments shall be transmitted to the Public Health Service, in care of the Chief, Division of Research Grants. When the Public Health Service has reviewed and accepted the assurance, the Chief, Division of Research Grants, shall so notify both the responsible official of the grantee institution involved and all Public Health Service extramural research program offices.

Each grantee institution shall report currently any changes in its policies, its procedures, or the competencies represented on its committee of associates.

4

For each application that includes or is likely to include investigations involving human subjects, including clinical research, the applicant institution should make reference to the certification as follows:

"The investigations encompassed by this application have been or will be approved by the committee of associates of the investigator(s) in accordance with this institution's assurance on clinical research dated \_\_\_\_\_."

Until an institution-wide assurance has been accepted by the PHS, the institution can fulfill requirements of this policy for individual studies by submitting an assurance with each application for PHS financial support, stating that prior to inception of investigations, the requirements of section III. A. of this Policy and Procedure Order will be followed. The statement must also describe the composition of the group which will conduct the review.

This interim procedure will be acceptable until November 1, 1966. After that date no new, supplemental, renewal, or continuation application for a Public Health Service grant or award to support investigations involving human subjects will be accepted for review unless the PHS has approved an institution-wide assurance.

Nothing in the institution-wide assurance or in the interim policy procedure used in some cases until November 1, 1966, should inhibit PHS staff, advisory groups, or consultants (1) from identifying concern for the welfare of human subjects, and communicating this concern to the grantee institution, or (2) from recommending disapproval of the application if the gravity of the hazards and risks so indicate.

In the case of awards to U.S. citizens receiving fellowships for training abroad, special conditions or circumstances relating to the place at which the training is being provided may upon occasion justify modification of these requirements. Requests from the sponsor for approval of such modifications must be reviewed by the Office of International Research, NIH, and approved by the PHS bureau chief concerned.

Attachment

ORIGINATING OFFICE: Office of the Surgeon General, PHS

APPROVED BY: Grants Policy Officer, OSG

Ernest M. Allen

Date: July 1, 1966

Index: Clinical Research  
Human Subjects, Investigations Involving  
Individuals, Rights and Welfare of

## Example of an Acceptable Assurance

Institutional Assurance on  
Investigations Involving Human Subjects,  
Including Clinical Research

The \_\_\_\_\_ (name of institution) agrees with the principles of the Public Health Service policy (identified as Policy and Procedure Order 129 dated July 1, 1966) with regard to investigations involving human subjects, including clinical research. This institution agrees that review independent of the investigator is necessary to safeguard the rights and welfare of human subjects of research investigations and assures the Public Health Service that it will establish and maintain advisory groups competent to review plans of investigation involving human subjects, prior to initiation of investigations, to insure adequate safeguard. Group reviews and decisions will be carried out in reference to (1) the rights and welfare of the individuals involved, (2) the appropriateness of the methods used to obtain informed consent, and (3) the risks and potential medical benefits of the investigations.

The institution also agrees to exercise surveillance of PHS-supported projects using human subjects for changes in protocol which may alter the investigational situation with regard to the criteria cited above. The institution further assures the Public Health Service that it will provide advice and consultation to investigators on matters of employing human subjects in investigation, and also that it will provide whatever professional attention or facilities may be required to safeguard the rights and welfare of human subjects involved in investigation. Records of group review and decision on the use of human subjects and of informed consent will be developed and kept by the institution.

Attached as part of this statement are copies of policy and procedure of this institution with regard to use of human subjects in investigation, as well as a description of the groups utilized to review projects for enforcement of these policies and the manner in which the institution will assure itself that the advice of the committee of associates is followed.

Signature: \_\_\_\_\_

Title: \_\_\_\_\_

Date: \_\_\_\_\_

Attachments

Senator KENNEDY. I'm interested in the way you are proceeding, the kinds of people who provided an input and the range of different disciplines that have been involved in their development.

Dr. MARSTON. All right, sir.

Senator KENNEDY. And also what you envisage in the future in terms of these questions.

Dr. MARSTON. And we would hope we would have an opportunity, Senator, to continue to work with the committee along these lines.

As you have heard, my particular concern is that one have a mechanism periodically surveying these fields, because they are moving so rapidly, and we want to have our activities along these lines coincide with whatever actions the Congress may take.

Senator KENNEDY. Who takes the responsibility for deciding the role of the theologians or philosophers or ethicists in terms of developing the guidelines. How is that resolved?

Dr. MARSTON. To the extent that a given meeting is set up, and the recent ones have been in the Fogarty Center, which has worked closely with my immediate office and with me personally in looking at the importance of some of these questions, in our advisory council at NIH, which have a significant number of lay people, who are secretarial appointees, and many members of those advisory members are not chosen so much by their field as by their broad competence and experience.

On the local level, we set up the guidelines that they must include nonprofessional individuals and the choice of whether these include—

Senator KENNEDY. That is pretty broad, though.

Dr. MARSTON. Yes, it is a local decision.

Senator KENNEDY. If you would give us a chance to see how you decide that—who decides that—we would have a clearer idea of the whole matter.

Dr. MARSTON. All right.

Senator DOMINICK. Would you let me ask one more question?

I am trying to find out something, Doctor, and I am not quite sure I found it out from either of you.

Are you for, or against this bill?

Senator KENNEDY. I can tell you they are against it.

Senator DOMINICK. I mean actively, or passively?

Dr. DUVAL. Senator, we believe that the original resolution that called for the establishment of this Commission in, I believe, 1968, was well placed. We feel the purposes for which this Commission is to stand are very desirable, and we share those as objectives for the Department.

We think that as a consequence of the efforts this committee and others have put out, in terms of achieving the objectives of the Commission, they are being well served in the community, and at the moment, we are taking the position at this time that legislation isn't necessary.

Senator DOMINICK. Thank you. [Laughter.]

Senator KENNEDY. Doctor, we want to thank you. You are always very helpful to this committee, and we appreciate your and Dr. Marston's appearances here this morning and we value your comments.

Thank you very, very much.

(The prepared statement of Dr. Duval follows:)



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

TESTIMONY OF

MERLIN K. DUVAL, M.D.

ASSISTANT SECRETARY FOR HEALTH AND SCIENTIFIC AFFAIRS

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

BEFORE THE

SENATE COMMITTEE ON LABOR AND PUBLIC WELFARE

SUBCOMMITTEE ON HEALTH

TUESDAY, NOVEMBER 9, 1971

TESTIMONY BEFORE THE SUBCOMMITTEE ON HEALTH  
OF THE COMMITTEE ON LABOR AND PUBLIC WELFARE

November 9, 1971

Mr. Chairman, and members of the Subcommittee on Health, I am pleased to appear before you today to participate in your consideration of S. J. Resolution 75, which would provide for a study and evaluation of the ethical, social, and legal implications of advances in biomedical research and technology.

As proposed, the Resolution would establish a National Advisory Commission on Health Science and Society, which would analyze and evaluate current and projected scientific and technological advances in the biomedical sciences. the implications of such advances for individuals and society, public understanding and attitudes toward these implications, and related public policy aspects.

The Commission would be composed of 15 representatives of medicine, law, theology, biological science, physical science, social science, philosophy, humanities, health administration, government, and public affairs; and its members would be appointed by the President.

The Commission would utilize the many already completed studies in the field made by public and private agencies and any future studies that become available. It would have the power to hold hearings, take sworn testimony, receive information from Government agencies, and enter into contracts for the conduct of research or surveys, the preparation of reports, or other necessary activities. The Commission would make one or more interim reports and a final report to the President and Congress not later than two years after their initial meeting. Such reports would contain detailed statements of the Commission's findings and conclusions, together with its recommendations, including any recommendations for action by public and private bodies and individuals. Funding authorizations would be \$1 million for fiscal year 1972 and a like amount for 1973. Ninety days after it makes its final report, the Commission would cease to exist.

Mr. Chairman, in considering this proposed legislation, the first question to ask ourselves is, Does this bill deal with matters significant enough to warrant national attention and concern? This century, beyond question, has witnessed a revolution in the biological and medical sciences-- a revolution that raises a whole spectrum of critical problems, which at least in some instances appear to transcend the inherent capabilities of science and scientists alone to deal with them, and present acute challenges to both existing law and conventional wisdom. Some of the more important, and provocative, of these problems might be mentioned:

- Population growth, accelerated by advances in medicine and socio-economic conditions, has brought the world in just a short time to within sight of what most experts believe to be the maximum population density that this finite globe can sustain. A host of ethical and legal problems have emerged in connection with control of birth rates through contraceptives and abortion. What, for instance, is the measure of safety for contraceptive drugs that have a potential market of many hundreds of millions of normal women--and soon perhaps, men--in the prime of life? Can society rely on the voluntary behavior of individuals to prevent absolute overpopulation? If not, what are the alternatives, and what implications would their adoption carry for the governance of society.
- New techniques for obtaining cells from the fetus (amniocentesis) almost from the start of pregnancy, and for determining many of the characteristics of that fetus from a study of these cells, give a physician and a parent unequivocal answers to questions such as the sex of the unborn child or its freedom from many genetically determined diseases. The potential availability of such knowledge coupled with rapidly changing societal attitudes toward abortion raise interesting problems. Will the interests of individuals and of society always be congruent? What would be the impact on the human race if the preferences of a generation were to affect significantly

the normal balance between male and female births? Should society countenance the birth of defective individuals when this could be avoided by timely intervention?

- The extraordinary advances in genetics have illuminated to a remarkable degree the mechanisms through which biological information is transmitted from generation to generation. Parallel advances in virology have provided at least one lead to a method for replacing the genetic material of a cell with different information. Thus the very real possibility of "genetic engineering" is on the horizon. What, if any, ethical limits are appropriate in this area? What unique or special considerations come into play when the experimental species is man? How rigid should be the criteria for determining that an induced genetic alteration is not, in the long run, compatible with species survival? What attitude should we take on the question of cloning?--(possible asexual replication of individuals in the form of genetically identical products).
- Thus, a whole series of problems that can perhaps be adumbrated under the title "Human Experimentation" arises. What ethical limits, based on what logical argument, should govern? Again, are the needs of society and the rights of individuals always congruent? When they are not, on what grounds should resolution take place? What legal and ethical ambience should surround the use of prisoners, terminal patients, normal volunteers, and so forth, in experimental medicine?

- The increasing technical feasibility of organ transplantation has raised an almost unique set of moral, ethical, and legal questions concerning the rights of the donor, the rights of the dying who might be saved by transplantation at the opportune time, and the use of organs from normal volunteers when lasting results are improbable.
- Modern medical technology has made possible unprecedented experiences that society has yet to integrate into its traditions. These include:
  - The prolongation of dying without hope of recovery, a particularly poignant situation when the patient is in unremitting coma. The classic question of euthanasia takes on specific dimensions here.
  - The prolongation of life through extremely drastic and deforming operations or artificial means entailing permanent disability.
  - The extension of life, with an ever larger proportion of individuals reaching older ages, has provided a serious challenge to the adequacy of the existing social structures.
  - The treatment of few patients at extremely high cost, through new knowledge and technology that cannot be readily extended, such as intensive-care procedures, organ transplants, and renal dialysis; and
  - Selective life-saving by means of scarce artificial kidney machines, repeated blood transfusions, and so forth. Such modern innovations make it both possible and necessary for individuals or groups to literally decide who shall live and who shall die.

- With the recent emergence of drugs that produce remarkable effects on human behavior, and the refinement of techniques for stimulating selected regions of the brain with similar effects on behavior, society must ponder deeply how such potent agents and instrumentalities shall be used.

The range of ethical, social, and legal problems raised by the advances enumerated above has generated a great deal of interest and activity in both the public and private sectors. This Department, particularly the National Institutes of Health, which supports the major portion of clinical research in this country, has engaged in a continuing discussion and examination of the questions posed by clinical investigation in research conducted or funded by the NIH. In 1952, with the onset of research activities at the Clinical Center in Bethesda, the NIH established what is still regarded as model guidelines for the review and conduct of clinical research. This policy has been extended three times in the past 20 years:

- In 1965, NIH required its grantee institutions to provide assurances that similar care would be taken in the conduct of research projects.
- In 1966, the Public Health Service began to require that grantee institutions conduct initial and continuing review of all PHS-funded clinical investigations.
- And in 1971, this Department again extended these guidelines to all DHEW grantees and contractors.

This policy required that, prior to the beginning of any research project involving the use of human subjects, there must be review of each proposed course of study that would be carried out by a committee of institutional associates, to include consideration of (1) the protection of the rights and welfare of the individual; (2) the relative weights of the risks and potential benefits of the investigations; and (3) the adequacy and appropriateness of the methods to be used to secure informed consent.

This policy required the establishment of procedures in over 500 major United States institutions for a review of the ethical, legal, and moral questions raised by specific and immediate situations. On a day-to-day basis, these groups must confront such thorny and difficult present-day issues as research involving minors and the mentally retarded, the use of prisoner and student volunteers, the research use of diagnostic procedures such as biopsy and catheterization, and the legal problems associated with research on the effects of narcotics.

The NIH has also been concerned with the value questions, most broadly construed, which are raised by clinical investigation involving human beings. In 1963, the National Institute of General Medical Sciences awarded a grant to Boston University for a study of the place of clinical investigation in modern society, and the report of this study, "Clinical Investigation in Medicine," by Irving Ladimer and Roger W. Newman, is considered a classic reference in its field. In the spring of 1966, the National Heart Institute awarded a grant to the American Academy of Arts and Sciences to study the general problems posed by

the use of human beings in biomedical research, the special problems of voluntary, informed consent, the need for new criteria of death, and other vital questions. An issue of Daedalus, in the spring of 1969, resulted from that study: "Ethical Aspects of Experimentation with Human Subjects."

Most recently, the John E. Fogarty International Center for Advanced Study in the Health Sciences of the NIH cosponsored with the Institute for Society, Ethics, and the Life Sciences a four-day conference on "Ethical Issues in Genetic Counseling and the Use of Genetic Knowledge," the second of a pair of conferences devoted to ethical issues in human genetics. The first, held in May 1970, was devoted to the scientific aspects of prenatal diagnosis by amniocentesis and cytological or biochemical analysis of the amniotic fluid and amniotic fluid cells. The proceedings of that conference are about to be published.

The National Science Foundation recently awarded a \$68,000 grant to the National Academy of Sciences to conduct a one-year technology assessment in biological and medical science developments. A \$1.5 million grant has been awarded by the NSF to the Center for Advanced

Studies in the Behavioral Sciences to establish an integrated program of technology assessment, which will take into account the societal impacts of current and future developments in medicine and biology. The NSF expects that, as a result of these studies, there will be a more active concern within the academic community for the value questions associated with science research, and additional studies in the sciences and humanities.

It is also anticipated that within the next one to two years NSF-supported research will yield a major conceptual assessment and significant research plans for further work in societal impacts of biological and medical technology.

In the private sector, several distinguished groups already in existence have broad responsibilities in the areas outlined for the proposed Commission on Health Science and Society. These include the National Academy of Sciences, with its newly established Institute of Medicine, and its National Research Council; the American College of Surgeons; the National Academy of Engineering; the American Academy of Arts and Sciences; and the American Philosophical Society. These prestigious organizations have taken very seriously the legal, social, and ethical implications of advances in the health sciences. Also in the private sector, the IBM Co. has funded a program on Technology and Society at Harvard University, which has produced a research review of the literature on the implications of biomedical technology, and the World Council of Churches has recently completed a conference on Technology and the Future of Man and Society.

Finally, Mr. Chairman, a contribution to the public discussion of these questions has also been made by the Joseph P. Kennedy, Jr., Foundation at its

recent symposium on Human Rights, Research, and Retardation, and by its funding of an institute at Georgetown University to consider the ethical and moral aspects of medical research.

This brings us to the critical decision points with respect to the proposed legislation. In the light of relevant activities already underway, and the number of existing institutions concerned on a continuing basis with issues raised by health research advances, is there a need for the National Commission proposed in S.J. Res. 75? The issues are so complex and the underlying currents of change moving so swiftly that in our view no attempt to describe this particular healthscape, at what would have to be a given moment of time, could be definitive for long. In other words, society might be better served by lower-keyed but continuing efforts by the present variety of private and semi-public organizations and entities attempting to assess, rationalize, and explain.

One cannot help but be impressed by the variety and quality of work already underway in this area, and the seriousness with which individuals and institutions are attempting to deal with these matters. Additional Federal support--apart from that already afforded through various means by such agencies as the National Institutes of Health and the National Science Foundation--does not appear to be an urgent need. I am persuaded, too, of the

appropriateness of a minimum overt role for the Federal Government in the debates and discussions taking place on these very fundamental issues. For these reasons, I cannot recommend enactment of S.J. Res. 75.

Thank you, Mr. Chairman. I will be happy to answer any further questions you may have.

Senator KENNEDY. Our next witness is Dr. Henry Beecher, Professor Emeritus at Harvard Medical School. He originated the Human Studies Group at Massachusetts General Hospital. He is chairman of the Standing Committee on Ethics at Harvard Medical School, and of a committee to redefine death. He is the author of eight books and 260 articles. His pioneering article in 1966—"Research and the Clinical Investigator"—opened up the whole issue of ethics in human experimentation.

**STATEMENT OF HENRY K. BEECHER, M.D., HARVARD MEDICAL SCHOOL, CAMBRIDGE, MASS.**

Senator KENNEDY. In your paper you outlined 50 examples of outrageous acts. Perhaps you will give us the current status on outrageous acts in your testimony today.

Dr. BEECHER. Thank you. I would like to say something that goes back to what you were saying earlier about dialysis.

I think there is a need for someone to point out the fact that if we had dialysis for all those needing it it wouldn't be any more costly than the care of tuberculosis was in earlier years.

The costs of caring for tuberculosis were greater in earlier years than the costs would be for dialysis for everyone now needing it. Certainly the cost for mental disease is far greater than the cost of dialysis would ever be.

I mention these things simply because it seems to me this brings out a strong argument for the Commission: There is a need for pointing out things of this kind, and the proposed Commission could serve a useful purpose in this area.

Now, to turn to my prepared remarks, we will have progress in medicine. There is no question about that. We must recognize that progress in medicine requires experimentation, and that eventually definitive experimentation must be made in man.

Man is, so to speak, the animal of necessity when it comes to the final validation of a new procedure or agent.

I must of course, stick to my own area of competence. Hopefully, it is in the field of the ethics of human experimentation. The enormous increase in the responsibilities in this area can be illustrated by the following:

**SOME DISCRETE ETHICAL PROBLEMS OF MEDICAL RESEARCH**

The university hospitals of the land have long been recognized as fields where already discovered concepts are applied, but now it is evident that they are the only places where certain discoveries basic to the advancement of pure science are likely to occur. Such institutions are indispensable units in the advancement of some aspects of conceptual science. In short, a new role of the great teaching hospital is emerging: the advancement of conceptual science through studies of sick man.

This awareness leads to a further extension of human experimentation: having seen what fundamental ends can be achieved by experimentation in man, the investigator is led to carry on where nature leaves off. These purposes thus become deeper and more complex than

ever before and so also do the ethical problems surrounding them. What I have to say about experimentation in man has relevance to both basic and applied science.

For some years now a host of important issues have been stated, challenged, argued, debated, fought over, agreed upon, defended, until I sometimes believe I am caught up in a Kafka nightmare. There seems to be endless reiteration of the truth, but nothing new. I am not denigrating the importance of these overworked subjects. The ethical overkill has been tremendous.

I refer to these constantly examined and debated subjects:

Justification for the human trial.

Valid consent. (A goal toward which we must strive but rarely attain in any complete sense).

The engineering of consent.

The perils of using captive groups as subjects, whether ward patients, children, students, prisoners, the dying.

The sterling qualifications required of an investigator.

The doctor-patient relationship versus the doctor-subject relationship.

The ethical problems arising in the transplantation of tissues and organs.

The definition of death—and so on and on and on.

These are, to be sure, important problems and nearly everybody has had his say about them—to the extent that it is unlikely that anything fresh can soon be said. I believe there is another group of less obvious, relatively little discussed, but equally important problems relevant to experimentation in man, and I would like to take a look at them.

These inadequately faced areas are inseparable from the tight little microcosm of the investigator and his subject. What are they?

Self-experimentation (when the investigator is also his subject). There was the case of John Hunter, who inoculated himself in 1767 (Treaty on Venereal Disease, 1786) with gonorrheal pus to prove that the disease was thus transmissible. He succeeded, but from the same inoculum he also acquired syphilis and concluded that gonorrhea and syphilis were merely manifestations of the same disease.

#### THE INVASION OF PRIVACY

But now to come to some of the subtleties that impinge on the microcosm of the investigator and his subject, let us take a look at the invasion of privacy.

As ancient as the common law is, is the principle that the individual shall be protected in his person and in his property. Starting from this, Warren and Brandeis, 80 years ago, recognized that "Political, social, and economic changes entail the recognition of new rights, and the common law, in its eternal youth, grows to meet the demands of society. Later there came a recognition of man's spiritual nature, of his feelings, and his intellect. Gradually the scope of these legal rights broadened; and now the right to life has come to mean the right to enjoy life—the right to be let alone." Thus, nearly 80 years ago, there was recognition by legal scholars of the value of sensations, "feelings," enjoyment, recognition that a man had a right to his privacy, privacy so often and so casually threatened in experimentation.

Here is indeed an aspect of the investigator's activities which has had too little attention to the present: his sometimes off-hand invasion of the privacy of his subject. All signs indicate that the matter is to be widely examined in the immediate future. As a basic principle, intrusion into a human body or mind under any and all circumstances is no more permissible than casual search and seizure in a house.

Mankind is spied on, recorded, reported on, and harassed by the gamut of devices and persons ranging from the simple-minded peeping tom to the devilishly complex and effective electronic surveillance techniques. Some of this is motivated by competition in business or by domestic tangles, some of it is for criminal purposes, some of it for law enforcement, but much of this is for "research," and hence comment on it is appropriate in the present considerations.

When studies are made without the consent of the subject, they constitute an invasion of privacy that can be serious; but at the same time it must be recognized that prior discussion of the work planned can distort the results; thus, the honest investigator has a dilemma not easily resolved. In the end, most scientists in the field accept something short of the ideal; a situation where a state of mutual trust exists between scientist and subject, where the latter's dignity and anonymity are preserved.

While the individual strives always to protect his privacy, the collection of individuals and institutions called society tends always to invade the individual's privacy. Serious or not, the test of importance is this: Is the threat or the invasion by the investigator unreasonable or intolerable? (Ruebhausen and Brim, 1965).

When diagnosis or therapy for the benefit of the given individual is at stake, such invasion of his privacy or his body can be proper, for the individual has, in the act of coming to the physician for relief, already given consent to reasonable efforts to relieve him. But when such invasion takes place without the knowledge or consent of the individual involved, and not for his benefit, it evokes, when exposed, a powerful and hostile public reaction, however well motivated the perpetrators considered themselves to be. Physical transgressions are easy enough to find and to identify. The subtle invasions of the private personality are more difficult to single out. The public reaction against such acts has been and is likely to be violent, and this violence inevitably leads to harsh and arbitrary restrictions.

It would be most unfortunate if the social scientist became identified in the public mind with violations of privacy, with snooping. It is unthinkable to accept progress in medicine founded on deceit, on a subject defrauded of his privacy or his physical safety. Such runs counter to all that medicine stands for.

#### DECEPTION

Deception in human experimentation can take various forms, some of which are legitimate, if hedged about with certain restrictions and requirements, some of which are not legitimate. Worst of all is the risk of patients' or subjects' health or life without their knowledge and consent.

Now, concerning "stooges." Instead of the unpleasant term "deception," sometimes the more felicitous but tricky term, "unannounced

observations," is used. However it is put, an unfavorable picture emerges. One wonders why so little is said about it in the President's Panel on Privacy and Behavioral Research.

Margaret Mead, with characteristic eloquence and forthrightness, has taken sharp issue with the use of stooges: Is it scientifically and ethically permissible to deceive the subjects of research by disguising oneself as a 'participant observer,' or by introducing stooges into an experiment, or by making use of long-distance television or hidden microphones or other devices for concealed observation? When a human being is introduced who is consciously distorting his position, the material of the research is inevitably jeopardized, and the results always are put in question as the 'participant'—introduced as a 'psychotic' into a mental ward or as a 'fanatic' into a flying-saucer cult group—gives his subjects false clues of a nonverbal nature and produces distortions which cannot be traced in his results. Concealed instruments of observation may not distort the subjects' course of action, but the subsequent revelation of their presence—as in the jury room that was tapped for sociological purposes (University of Chicago, Ford Foundation)—damages the trust both of the original participants and of all others who come to know about it. The deception violates the conventions of privacy and human dignity and casts scientists in the role of spies, intelligence agents, peeping toms, and versions of Big Brother. Furthermore, it damages science by cutting short attempts to construct methods of research that would responsibly enhance, rather than destroy, human trust."

In a further discussion of this problem several years later, Margaret Mead points out that the " \* \* \* primary consideration is whether the human beings who are involved shall either be lied to or asked to lie to others, that is, to function as stooges."

If one fails to acquaint the experimental subject of what is happening within reasonable limits, one reduces his stature as a human being where he is not permitted to judge for himself. All problems are not solved by "debriefing" the man. He is told he has been tricked, deluded, spied upon, and lied to. Acceptance of such information requires that the subject identify himself with the lying investigator or "the decision that social science is a bunch of confidence tricks and now he also knows a few."

Deceit can have in some situations a more serious effect on the investigator than on the deceived subject.

The tricky investigator becomes accustomed to deceiving and manipulating other human being. Even though this is explained after the fact to the subject, it still carries the implication that manipulation of people is acceptable. Contempt for others grows out of this. The investigator becomes omnipotent. The end of this is a threat to the integrity of his own scientific work.

#### TRUST

As science becomes more and more significant in the modern world, it is absolutely essential that this be a trusted activity. "The image of the scientist as someone who is trustworthy and humane is impaired every time that there are accounts of research which have disregarded basic human rights of consent, as in revelations about medical experi-

ments on unconsenting patients, or scientists using lying, deceit, disguises, and spying in the collection of data, or misquoting or suppressing evident in the discussion of public policy \* \* \* Trust in the responsible use of power is essential for an ordered society. Trust in the responsible use of knowledge, which increasingly gives overweening power, is crucial today."

Any exposure of unethical procedures, submission to unnecessary hazards, deceit, jury wiretapping in experimentation not only to arouse fear, but destroy trust. Whenever advantage is taken of the helplessness or unprotected state of the subject, whenever deceit is involved, trust is impaired. This rules out the use of stooges or other disguised participants. A very important obligation is that the scientist, supported as he is by society, maintain the trust given to him.

#### SOCIETY AND THE INDIVIDUAL IN HUMAN EXPERIMENTATION

In earlier years, human experimentation proceeded with fewer hindrances than were accorded work on dogs, and from those free and easy days certain abuses emerged.

In all of the current charges and countercharges a clear issue can be seen emerging. It is above personalities; it is above legalistics; it is simply this: In experimentation in man, is the individual subject to get first consideration or does this belong to society? It is time the debate was directed to this fundamental issue.

Society certainly has rights, recognized in law and by all men of good will, for example, there is the invasion of the individual's privacy by the census, in the legal requirement of certain standards of education and of hygiene, in the required reporting of venereal disease, in vaccination, in maintenance of civil order, in the required acceptance of the military draft (in war time, possibly a life-or-death issue).

It is evident that at times society properly acts against the wishes of the individual, without his consent. Thus, while freedom of choice, of consent, must stand very high, the freedom is not total as illustrated in the examples just mentioned. At times, decision has to be made against the individual to protect society. This is a grave and central problem.

The close relationship of these matters to statistical morality is evident:

#### STATISTICAL MORALITY

At the Dartmouth conference on The Great Issues of Conscience in Modern Medicine, Warren Weaver described statistical morality as derived from the prejudice against even permitting any one known specific individual to sacrifice his life for the common good, and yet we have to, in a great many circumstances, submit a lot of individuals to a partial risk, with the result that even though the risk is only one in a million, when a million are involved, one man will be dead with our acquiescence. It is a comfort to our conscience that we don't know where it occurred or when it occurred. But that individual is just as dead as though we knew all about it. In such deep waters, we strive for balance, but sometimes emerge with little more than questions and tangled arguments.

For example, in discussing new and uncertain risk against probable benefit, Lord Adrian spoke of the rise in Britain of mass radiography

of the chest. Four and a half million X-ray examinations of the chest were made in 1957. It has been calculated that bone marrow effects of the radiation might possibly have added as many as 20 cases of leukemia in that year; yet the examinations revealed 18,000 cases of pulmonary tuberculosis needing supervision, as well as thousands of other abnormalities. The 20 deaths from leukemia were only a remote possibility, but, Lord Adrian asks, if they were a certainty would they have been too high a price to pay for the early detection of tuberculosis in 18,000 people?

#### SITUATION ETHICS

Our purpose, as I hope I have already made clear, is to examine, as well as one can, a world where there are, basically, only two inhabitants: the investigator and his human subject. In this world there are a number of imponderables not the least of which is situation ethics, so eloquently described by Prof. Joseph Fletcher. If I may be permitted an oversimplification, it is a world where circumstances alter cases, a pragmatic world where things are what their results are. I realize I can easily get myself into hot water with the philosophers. Bertrand Russell has already likened the pragmatic situation to a bath which heats up so imperceptibly you don't know when to scream. But let me give you one example from our world of experimentation, for we dare not overlook the relevance of the situation to the ethics thereof. Let me do this, and I promise hastily to leave this thin ice.

When the wonders of penicillin were new but recognized and the supply heartbreakingly meager, a shipment finally arrived in North Africa in World War II. The hospital beds were overflowing with wounded men. Many had been wounded in battle; many had also been wounded in brothels. The problem: which group would get the penicillin? By all that is just, it would go to the heroes who had risked their lives and who were still in jeopardy; some were dying. By all that is seemingly just, these would get the penicillin. They did not, nor should they have, I think. It was given to those wounded in brothels. Before indignation takes over, let us look at the situation: First, there were desperate shortages of manpower at the front. Second, those with broken bodies, broken bones, were not going to be swiftly restored to the battle line even with penicillin, whereas those with venereal disease, on being treated with penicillin, would, in a matter of days, free up the beds they were occupying and return to the front. Third, no one is going to catch osteomyelitis from his neighbor; the man with venereal disease remains, until he is cured, a reservoir of infection and a constant threat. In terms of customary morality, a great injustice was done; but I think, not so, in view of the circumstances.

A considerable number of individuals are in the unhappy and really untenable position of accepting the results of unethical experimentation while disapproving the means.

If any further examples were needed, atomic fission dramatically emphasized the inseparability of science and ethics. We can hardly separate the moral equivalents bound up in means and ends in this area; but we can, for example, take a pragmatic stand and say with Lord Russell that means are determined by science, whereas ends are set by desire. We can say with Kant that people must always be treated as ends, never as means alone.

At the end of his short life, the mathematician and philosopher Clifford had this to say nearly a hundred years ago: "If I steal money from any person, there may be no harm done by the mere transfer to possession; he may not feel the loss, or it may even prevent him from using the money badly. But I cannot help doing this great wrong towards Man, that I make myself dishonest. What hurts society is not that it should lose its property, but that it should become a den of thieves; for then it must cease to be society. This is why we ought not to do evil that good may come; for at any rate this great evil has come, that we have done evil and are made wicked thereby."

(At this point, Senator Mondale assumed the chair.)

Senator MONDALE (presiding pro tempore). Thank you, Dr. Beecher, for a most useful statement.

Almost 4 years have transpired since the last time you appeared before Congress to urge creation of a National Advisory Commission on Health Science and Society.

Could you summarize very quickly why you support this proposal, and perhaps respond to some of the fears expressed by its opponents?

Dr. BEECHER. Because for all of the fine work going on in the NIH, I don't really believe there is any group there that is working ardently on these things.

I think that in this situation there is a great need for guidance here for all of us, which could be accomplished by this Commission. In certain areas, they are not getting the attention they need, certain very important areas, and a group of this kind could bring that out with a great deal of authority behind it.

Senator MONDALE. Dr. Beecher, you have spent a great deal of your life not only in medicine, but in being concerned about the ethical ramifications of research, experimentation, and so forth.

I think you heard me say earlier that I perceive a certain reluctance on the part of the medical profession to let the public in on these questions.

Do you agree with that?

Dr. BEECHER. Senator, I think the situation is tremendously improved. I never believed that these wrongs in human experimentation were a vicious disregard of the patient's rights.

Rather, they were owing to ignorance or carelessness, and having called attention to these things, the situation is much improved.

I could give you factual data to support that.

The NIH at the time this blockbuster paper of mine came out in 1966, the NIH received about 7 percent of applications that were ethically unacceptable. Six months after this paper came out—many people have said that this paper was responsible for the change—6 months after the presentation of the paper, this percentage of ethically improper applications had fallen down to one-third of what it had been, and it has remained there ever since. So far as I have checked over the last several years.

I think this is concrete evidence to support my thesis that ignorance and carelessness were responsible for many of these errors, and this Commission could do a great deal to enlighten the public on this score.

I think, to come back to your question, I think there is a new ball game going on. Almost everybody speaks to me now. There was a time they didn't.

Senator MONDALE. Senator Dominick?

Senator DOMINICK. I have no questions.

Senator MONDALE. Thank you, Dr. Beecher, for a most helpful contribution.

Our final witness this morning is Prof. Abram Chayes, of the Harvard Law School.

He is currently cochairman of the Commission on Law, Biology, and Ethics established by the Salk Institute's Council on Biology and Human Affairs.

**STATEMENT OF PROF. ABRAM CHAYES, HARVARD LAW SCHOOL,  
CAMBRIDGE, MASS.**

Mr. CHAYES. Good morning, Senator Mondale and Senator Dominick.

Senator MONDALE. We are pleased to have you with us this morning.

Mr. CHAYES. Let me apologize for not having a duplicated prepared statement. I wasn't able to get it done in time to get it typed and mimeographed, but I have a statement here.

My name is Abram Chayes. I am a professor at the Harvard Law School, and I appear today to testify in support of Senate Joint Resolution 75. I want to thank the committee for this opportunity.

First, let me explain my interest and concern with this subject matter. I am cochairman of the Commission on Law, Biology, and Ethics established by the Council on Biology and Human Affairs of the Salk Institute.

Snator MONDALE. When was that established?

Mr. CHAYES. Well, the council has been in existence for 3 or 4 years and the commission has been in existence for a couple of years.

We aren't included on Dr. Duval's list, but we are a group that has been at work in this area, and at least from my point of view, we don't appear to be in any danger from the commission to be established under this resolution.

My cochairman is Prof. Joseph Goldstein of the Yale Law School. I should say that I don't speak on behalf of the commission. I speak personally, except to say that we would welcome any opportunity to cooperate with a body set up under this resolution, and we see important areas for cooperative work between us and such a Commission.

The Salk Institute, as you know, is one of the great biological research centers in this country. It was established with proceeds, or some of the proceeds, from the immunization for infantile paralysis discovered by Dr. Jonas Salk, after whom the institute is named.

From the beginning, Dr. Salk was determined that the institute, in addition to being a superb center for hard scientific work, should not neglect the broader concern with political and social implications of this research.

This determination led a few years ago to the creation by the institute of a semiautonomous Council on Biology and Human Affairs.

The council is under the chairmanship of Dr. Victor Brunowski, philosopher and historian of science.

Its members include a number of distinguished biologists, but there are also scientists from other fields, representatives of the social sciences, and humanistic disciplines, as well as men of affairs.

The staff director is Mr. Harry Boardman, formerly director of the Council on Foreign Relations.

The Council on Biology and Human Affairs operates by establishing commissions to work in particular subject areas. The Commission on Law, Biology and Ethics is one of these. We have worked for about 2 years now in a field that I confess is more baffling and difficult and, at the same time, is as portentous as any that I have dealt with.

We have concentrated our efforts primarily in the area of genetic development, prenatal diagnosis, genetic therapy, and so-called genetic engineering.

We have had the assistance of a number of distinguished biologists and some younger people who work in the field. We are now turning to the fields of chemical and electrical methods for control and modification of human behavior.

I must report to you that we have made very little concrete progress, apart from a certain amount of self-education about the developments in the field. Part of this is due to limitations of time, staff and resources, and one of the main reasons why I support this resolution is my sense of the need for a body with the time, staff, and resources and the concentration of energy and effort sustained over a long time to make an impact on the problems in this area.

There have been a lot of conferences, as Dr. Beecher has said, and a lot of meetings and a certain number of articles, but I am of the opinion that unless one can get sustained work over a considerable period with a critical mass of people, we are not going to make much progress. We are not going to get very much further than what Dr. Beecher described.

For, as I have said, these are extraordinarily complex and difficult problems even to define, let alone solve. How are we to characterize the novelty and complexity of problems that emerge in this area? We hear a lot of awesome pronouncements about man being able now to meddle with the very stuff of life itself. And there is something to this, but we must be more careful in trying to say just what it is.

After all, man has always intervened to change his own environment, increasingly so in the last few hundred years. One generation has always dictated to some extent the terms on which succeeding generations have had to live.

Nor have these interventions been confined to the external environment. Man has sought to improve his own nature and nurture by whatever means that lay at hand.

What is different in our present state is the power of recent biological discoveries in terms of the scale of interventions they make possible and the time frames in which these may occur. A sense of the order of magnitude can be gained if we say that biology is now crossing a threshold or maybe it has crossed it already, comparable to that on which atomic physics stood a generation or so ago.

An understanding of very fundamental relationships is opening up, and there is the added significance that these are the phenomena of life itself.

Like all such new technologies, as we are beginning to learn, the availability of new biomedical technology creates enormous tensions and problems for policy. They hold out great opportunities for improvement of life for all man, but at the same time, because of the scale and time frame of intervention to which I have already referred, the natural processes of self-correction and reversal of errors and false starts may be prohibited or wholly unavailable.

I want to point out three stages or levels at which public policy problems arise, each raising very fundamental value issues and value conflicts.

The first is at the level of research, and we have been talking about that quite a bit this morning. What kinds of research should go forward? This kind of question used to be answered by reference to the right of the investigator, to pursue truth wherever it led him. Even if we were prepared to continue to rely wholeheartedly on that principle, it does not solve our policy problem any longer. Research today is and will increasingly be publicly funded. There is no escaping the basically political questions of how much public money shall be devoted to these ends, who shall allocate it among competing projects, by what criteria and under what safeguards, both for the interests of the public and the freedom of the scientist.

The second level of importance is at the stage of treatment for disease. Once discoveries are made, there is overwhelming pressure to make them available for the relief of human suffering, although Senator Dominick suggested that it might not be as overwhelming as I state here.

Uncertainties and objections may be swept aside in a wholly understandable rush for this goal. On the other hand, as may be the case with certain new kinds of drugs, gains and benefits may be indefinitely delayed in a wholly unrealistic search for absolute safeguards.

Now methods of treatment for human disease need some testing on human beings before they can be approved for general use.

How are we to balance the burdens, risks, and benefits of such a process?

Again, our usual recourse is somewhat suspect. In the past, we have referred questions of this kind to the free consent of the individual involved. "Free consent" and I put that in quotation marks, is supposed to be based on full disclosure of the risks, and in many cases, neither the kind nor the dimensions of the risks are known even to the doctor.

Moreover, we must be concerned whether consent is truly free. Submission to treatment may be consensual in form, but in fact dictated by the doctor, or the patient's illness may deprive him of a really free choice, or the patient may be incompetent, or a child, or unborn.

I do not know how questions of this kind should be resolved, but they seem to me very, very difficult, and you will have noted that they touch on such things as the doctor-patient relationship, which I need not remind you is extraordinarily sensitive.

The third stage of potential policy problems may be called the problem of regulating genetic and other forms of intervention based on new biomedical technology.

Here, the object of the technology is not so much to cure disease as to improve the race. We cannot brush this goal aside. It has always

been a prime goal of human action, and in a sense, of course, it is the product of natural selection and evolution.

In this same sense, one way to describe the biological discoveries just over the horizon is that they will give us power to intervene in this evolutionary processes in a massive and much more controlled way than ever before.

But here arise some of the most fundamental ethical and moral questions of all. Suppose we gain the power to decide in a much more literal sense than ever before who shall be born, what kind of people, with what physical or mental characteristics, or who shall die, that is, who shall be permitted to die and who shall be preserved.

Conceptions of life and its values that underlie all moral and ethical precepts may have to be reexamined.

That is why I strongly support the Commission proposed in the resolution before you today. The more sustained, sober, and serious thought that we can bring to bear on these issues, the better.

I am glad to see that the resolution brings in many disciplines, and I hope it includes the general public as well. This is not a field in which scientists have many answers. They have a lot of information about what is going on, but the information raises questions on which the scientist qua scientist is not particularly better qualified than others to say how those questions ought to be answered.

Nor in the end is this an area where the problems are likely to yield to the ministrations of experts at all. This leads me to the one reservation I have with the resolution, and it is really not a reservation so much as a matter of emphasis.

I would not stress too heavily the objective of concrete recommendations for action at the end of the Commission's 2-year life. Obviously, to the extent that such immediate proposals for policy action can be put forward with confidence, the Commission should do so.

But I believe the biggest contribution of this Commission will be in thought and reflection and in stimulating a far-reaching and informed dialog on these matters.

In this dialog, there will be need for all the specialized knowledge that the experts can find. What is at stake is indeed a reexamination of very basic human values, and that is a process that cannot be hurried, and is one in which all parts of our society must be engaged.

Thank you.

Senator MONDALE. Thank you very much, Professor Chayes, for a very useful statement, including your final recommendation.

Senator DOMINICK. Mr. Chairman, I hate to say this, but I have to go out to your fair State in about half an hour.

Senator MONDALE. You can ask questions for about 2 hours.

Senator DOMINICK. I was very interested in your statement, which I thought was excellent. It brings out a lot of points.

One of the things that particularly struck me is that you said from your own experience that the very questions are hard to define. It is going to receive a sustained program with staff and resources to go into this in considered depth.

So you really believe the Commission can define the questions and come up with the answers in 2 years?

Mr. CHAYES. Senator, I am a little doubtful about the answers, as I said at the end. I think this is a central kind of question that our

society is going to have to be grappling with over a long period of time. I do think that this Commission, this kind of Commission, can make a very important contribution to that effort, to define the issues come up with some kinds of solutions.

Again, it is not really the kind of thing that you can push a button and say it is solved and put away. A million dollars—which in terms of our health budget is really almost trivial (I hate to say that as a law school professor, but it really doesn't look like anything in terms of the budget of HEW)—is an enormous amount in this field. Our Commission operates on a budget of a few thousand dollars a year. It is just barely enough to get us into two or three meetings a year.

The ability to get full-time people involved: there are numbers of people both in the scientific disciplines and in the related social and humanistic disciplines who are terribly interested in this, but there aren't many places that they can go to get a place to work on it.

So, I do think this can make an important impact, and the only reservation, as I say, and it is really just a change in emphasis, is that I hope we won't be too concerned about coming up with a new big program or a big new code of ethics or try to rewrite the 10 Commandments in 2 years.

Senator DOMINICK. You wouldn't object, however, if we extended the life of the Commission further after the 2-year period?

Mr. CHAYES. Well, that depends a little bit on what happens in the first 2 years. We may find that this whole problem of assessment, of not only biomedical technology, but others, takes a much more central part in our public policy process over the coming years, and we may find different ways of institutionalizing that kind of process.

But I do think we need some form of institutionalization at the present time. How far into the future that should extend will really depend on what results it gets.

Senator DOMINICK. Now, the \$64 question, as far as I am concerned is this:

The history of national commissions, whether in dealing with crime, or military preparedness, or whatever, the net result is that when the report comes out, the American people as a whole, and most Members of Congress feel that this is an authoritative report with a final answer.

Now, what do you do about that? Because obviously it is not going to be, and equally obviously, the public as a whole will consider that this is the answer.

Mr. CHAYES. In the first place, I think in some senses they think it is the final answer, but in some senses, when a commission report comes out, the other objection is raised that the only thing that happens is that it goes on the shelf and gathers dust, that nothing happens.

If you look at the whole set of commissions that you just referred to, the legislative product, if you will, from some of those has been rather less than might have been hoping.

But I think—I don't want to discount the dangers that you suggest, that this has a kind of authoritative force. It comes down with the force of the Government behind it, so to say.

I would hope the Commission would be made up of men and women who would have this kind of problem and danger in mind. Moreover, I think even as to those other commissions you talk about, although

the report is announced with a lot of fanfare as containing the answers, if you look at the Commission on Violence, or the Crime Commission, or the Kerner Commission, even the weapons commissions in the 1950's, what they really have done is to lead to debate over a much longer period of time.

The issues raised by the Crime Commission, for example, are still the subject of public and political debate.

(At this point, Senator Kennedy reassumed the chair.)

Senator DOMINICK. Would it be better to go the commission route, or would it be better to have a fund by which contract studies are authorized in a number of different areas and fields covering the same type of subject, so that you have a whole diverse group of people working on these problems?

Mr. CHAYES. The question is: Once the fund is appropriated, who decides who is going to do it?

My own view is that I would prefer a commission, because I would prefer the sense of focus, the sense of public attention, public importance that a commission of this distinction appointed under a resolution, a joint resolution of Congress, will give:

I recognize that for those assets you get the kind of dangers you are thinking about.

Senator DOMINICK. That is the very problem.

Mr. CHAYES. I would say that I would very much hope that the President, the appointing authority, would keep that in mind, and would appoint the kind of men and women who would be sensitive to this range of dangers. I think the likelihood is that they would. Once you begin work in this field, it is really quite awesome. No one is really very anxious to run out and wave the flag and say he has the answers. It is really quite the reverse. It is really an awesome field.

Senator DOMINICK. Thank you, Mr. Chairman. That is all I have.

Senator KENNEDY. Mr. Chayes, I apologize for not being here earlier. As a member of the Judiciary Committee, we were considering the Supreme Court nominees, and I had to go back and forth between the committees.

Mr. CHAYES. I have considerable concern with that activity as well.

Senator KENNEDY. I was wondering—and perhaps you have already covered this—in your role for the Salk Institute, what are the particular areas of concern that you had?

Mr. CHAYES. I said that we have devoted most of our energy so far in the field of genetics, that is, genetic diagnosis, and there are, as you know, related areas of work.

Genetic intervention, genetic therapy, and things of that kind. However, we regarded them as examples of much broader problems that could be replicated essentially in other areas of medical and biomedical advances.

Senator KENNEDY. Does the institute get any help and assistance from the Federal Government?

Mr. CHAYES. We made application to the National Science Foundation last year for the support of the work of the Council in general. The Council has a set of commissions of which this is only one. That application got mixed up in a reorganization of the National Science Foundation. We did not get a grant.

I was saying earlier to Senator Dominick that one of the significant things here is that we are working on a budget of a few thousand dol-

lars. The amount of money and resources available to the commission proposed in the resolution, even though small in relation to the Federal budget, or even the Federal health budget, is enormous in comparison to the resources being put in this area.

Senator KENNEDY. Do you know where in HEW, in NIH, you go to make applications for this kind of program?

Mr. CHAYES. One of the problems is that there was a reorganization of the National Science Foundation, and our application went properly to a branch of the Foundation that was reorganized out of existence.

But the Foundation does have now, the National Science Foundation, a very strong program in relation between law and science and technology, and our commission, itself—not some of the other things that are being done out of Salk—might have access to those new program funds.

Senator KENNEDY. Are you familiar with the application your group made?

Mr. CHAYES. Well, I was familiar with it in a general way, yes.

Senator KENNEDY. I was wondering whether the Science Foundation considered the ethical questions which are raised by genetics—whether that was part of the application requirement—or whether they left this kind of an issue up to you and made their decision solely on the basis of medical factors.

Mr. CHAYES. I don't think the decision was for medical reasons so much as reorganizational reasons. The fact is that the application did have in it a statement of what the work of these commissions would be. There was one on the international effects of biology chaired by Paul Doty.

There is one on population, there is one on environment, and then there is the one I am involved in on law, biology, and ethics.

The work program of each of those commissions was spelled out to some extent in the application. But I have to say, as I said in my statement, it is very hard to specify in concrete way what you expect to do.

All you can say is that you expect to study these problems and that you have got the people together who you think can make some impact on it, because they are very baffling.

Senator KENNEDY. As a professor of the law school at Harvard, could you tell us what the law school is doing in terms of this general area? Are they doing anything of this sort, and if so, what?

Mr. CHAYES. I think you have to say there is some work being done. Milton Katz is a chairman of the National Academy of Sciences Commission in this area, and he teaches a seminar.

Senator KENNEDY. How many students does he have?

Mr. CHAYES. I wouldn't know exactly, but it would probably be 10 or 15. There is another seminar in the general field of technology assessment by Professor Tribe who worked on the National Academy study of technological assessment. That included all technological assessments, not only the medical ones.

Again, you might have 10 or 15 people there.

Senator KENNEDY. So, it is important work, but it is still in a seminar-type of development.

Mr. CHAYES. That is true not only in the law schools, but everywhere.

Senator KENNEDY. Do you know what the medical schools are doing in this area?

Mr. CHAYES. No; but there is a great deal of reorientation of the medical school curriculum to address social problems; much more than there was 10 or even 5 years ago.

Senator KENNEDY. Could I ask Professor Beecher at this point what the medical schools are doing in terms of this?

Dr. BEECHER. I think it is doing very little indeed. There is a standing committee in ethics that I am chairman of who expects to have problems presented to us, and there are very few. "The curriculums are already crowded," is the argument we get, and that they don't have space for this.

Senator KENNEDY. In terms of courses at the medical school, is there anything related to genetics?

Dr. BEECHER. No courses that I am aware of, even voluntary courses, that deal with these problems.

Senator KENNEDY. This obviously would be an area where you personally believe there should be some.

Dr. BEECHER. Yes; Dan Callahan is going to speak this afternoon, and he is head of the institute. I hope you can get him on that.

Senator KENNEDY. There might be an area where recommendations could be made, as to whether there should be courses at the various medical schools, and these are some of the types of things that a course of that type would include?

Dr. BEECHER. I hope that would be the case.

Senator KENNEDY. Would you think so in terms of the law school as well, that it could be useful and helpful in terms of making recommendations in those areas?

Mr. CHAYES. You said a moment ago that the law school is still pretty much at the level of seminars, and I wanted to comment on something Dr. Duval said when he listed this list of people or organizations that were already in the field. There are organizations already in the field, but I think what you say, your description fits them. They are all sort of at the level of seminars, struggling to get some interconnection between them, struggling for a wider scope of action, and that, it seems to me, is one of the things that the commission can provide. Not to absorb or displace these things, but to give some helpful dialog and momentum among people in the field that is very, very seriously needed.

Senator KENNEDY. Where would you go, other than the resources of the National Science Foundation, to try and get any input in terms of some of the ethical, philosophical, theological issues raised by the work NSF is sponsoring in the field of genetics?

Mr. CHAYES. We have tried to get on our panel people who are expert in fields like philosophy, social science, psychology, psychiatry, psychoanalysis, and lawyers, of course.

I guess one of our problems is that we have got too many lawyers. But as I said earlier, I don't think the biologists or the scientists have the answers here, or believe they have the answers. They are looking for help just like we are. They can tell us what the likely technical developments are, and they can begin to identify some of the problems that those technical developments will lead to, but then

when it comes to saying what we should do about that, they are just as lost as the rest of us.

So, there needs to be an exchange between the people who are in the scientific branch of the field and others.

As I said, some members of the general public should be included as well, because I don't think the other experts that are there will have all the answers, either.

Senator KENNEDY. As one who has been active in public life and knowledgeable of how government works, Professor Chayes, what parallels do you see in this kind of recommendation to establish a commission to other situations involving national need that you have observed throughout your experience in public affairs? How do you perceive the results of such a commission benefiting the public?

I think many of us are aware of various Presidential commissions, many of which are appointed in times of a crisis, which produce recommendations that are enormously valuable and helpful, and then are usually left to gather dust. That happens usually, I find, when these commissions are appointed just in terms of a particular crisis situation.

But there are obviously some very extraordinary exceptions to that pattern: for example, the Marshall Commission on the draft, which was outside of the Defense Department and was able to bring together various approaches and ideas, including recommendations on sensitive issues like selective service and conscientious objection.

I am wondering if you, as a student of government, if you can see a similar kind of advantage for this kind of commission. The most recent issue, I suppose, that we have been considering, as the Health Committee, is the national program to combat cancer. We will enact some legislation on that, I hope.

But it seems to me that people knew a great deal about the cancer problem, at the Cancer Institute at NIH and elsewhere. Yet it took a special commission to bring together the various factors and energize these forces so that we have been able to get some result.

The Defense Department knew a lot about the draft, but the Gates Commission and the Marshall Commission were able to provide necessary focus, and led to important input in terms of national legislation.

Certainly this is true in terms of trade expansion, arms control, and a number of other public sector issues. I am wondering if you can relate this perhaps to some of the areas which you have been interested in, which I know cover a wide spectrum of issues.

Does anything strike you offhand?

Mr. CHAYES. I think you make an important distinction between crisis-originated commissions—that are supposed to come up with answers that will settle a problem that everyone thinks is urgent today, and then 2 years from now, when the Commission comes out with its report, people are thinking about something else—and commissions which are really study commissions.

Here, we have the advantage that—I think Senator Mondale and his cosponsors are really to be congratulated on this—for once, somebody is calling for study in advance of the crisis, and while there is time for the kind of wide-ranging and reflective debate that there is going to have to be on this.

Even those other commissions like the Kerner Commission, for example, the Crime Commission, where you might say the legislative output has been quite limited in terms of their recommendations, they did raise these issues to national prominence, brought them to the center of public debate and public concern.

I don't think anybody who worked on the Kerner Commission believes that this was a futile or fruitless exercise, even though one would have liked to see a lot more of the recommendations come out in legislation.

I think we feel that it was an important contribution to the development of a national policy in the area, and that the pressures and momentums developed by the Kerner Commission report are still important and positive factors on the scene today in developing public policy.

But here, as I said in my statement, I don't think this Commission can come up with a lot of recommendations for concrete legislation. The kinds of recommendations you suggested for courses or ways of getting these subjects out among the people in the relevant professions are the kinds of recommendations that are likely to come out. Or in your discussion with Dr. Duval, I recall your emphasis on the composition of review panels and so on, who gets on these review panels.

Well, that kind of recommendation one might expect from this kind of Commission, but not a lot of substantive recommendations.

I think this Commission has the potential of focusing the public concern on this area in advance of a crisis, while there is time for the political processes to take these kinds of studies and work with them.

Senator KENNEDY. Wouldn't you agree with me that considering the kind of progress that is being made with respect to the medical, scientific, biological, and genetic areas, that these questions are going to become much more acute? The ethical questions in particular, I imagine, are going to become much more acute over the next few years.

I gather from your support of this legislation, you feel that we had better start moving and gathering this kind of information and at least some ideas on how to approach these questions before we get left behind.

Mr. CHAYES. That is exactly it, and the "left behind" point is the thing. Work is going on in laboratories all over the country. Discoveries are announced in the New York Times every day. The penetration into the essence of the genetic process is what I am speaking of, and unless there is systematic attention to the implications of this thing, it is going to get out of hand.

The one thing that we really should have learned out of all the discussion over the past several years of the problems of technology, is that the time to address those problems is before the technology has spread and has become part of the way of life so that all sorts of vested interests and expectations have to be displaced in doing anything about the evils of the technology.

So that is what I think this is, a forwardlooking, timely action, one of the rare such actions.

Our usual approach is to wait for a crisis to develop before we try to do anything.

When I say there is no crisis, I don't mean that there isn't an urgency. There is an urgency. These developments are moving forward very

fast, but nothing has exploded yet. That is all I mean when I say there is no crisis.

Senator KENNEDY. All right.

I want to thank you very much, Professor, for being with us. I will look forward to reading your statement just as soon as I can.

I want to thank you very much for being with us this morning.

Mr. CHAYES. Thank you.

Senator KENNEDY. I would like to ask Professor Beecher to return. I have a couple of brief questions.

Are you familiar with the San Antonio project to study the side effects of birth control pills that involved 398 Mexican-American women?

Dr. BEECHER. Yes; I am familiar with it. I have read the paper.

Senator KENNEDY. Three groups took three types of pills. One took the experimental pill, and some took a false pill.

Dr. BEECHER. Some of the ladies got pregnant.

Senator KENNEDY. Could you tell us what you think of that?

Dr. BEECHER. I think it is outrageous. What happens if a woman dies in childbirth? What if the families are penalized economically?

Senator KENNEDY. They were under the impression that these pills were birth control pills, that they were safe.

Dr. BEECHER. That is the information I get from reading the paper.

Senator KENNEDY. One of the experimental pills was later ruled unsafe by the FDA. Is that your understanding, that the experimental pill was later ruled unsafe?

Dr. BEECHER. I didn't know that it had been ruled unsafe, but I think the whole procedure was certainly unsafe to the 10 ladies, or whatever number it was, that got pregnant.

Senator KENNEDY. So you had a situation where all of the people thought they were taking birth control pills. In one group, the pills themselves had absolutely no effect in terms of contraception, and the other one that was the experimental pill was subsequently found to be unsafe.

To my knowledge, these women had absolutely no idea as to the dangers which they were being subjected to, or to the fact that some of the pills themselves were fake.

Dr. BEECHER. I think some of the people got something which may have had some contraceptive effects. The paper is a little bit ambiguous on this.

Senator KENNEDY. It is my understanding that one group took a placebo.

Dr. BEECHER. That is right.

Senator KENNEDY. So that isn't any prevention at all. Do you know whether there are other instances like this?

Dr. BEECHER. There was that very bad thing at one of the Air Force bases where 525 young airmen had strep sore throats. The authors of this study knew this rheumatic fever as a consequence of strep throat could be prevented by penicillin. Their work had shown this to be true. Yet they wished to withhold penicillin in that group of 525 young airmen, and they did so. They admitted 25 of their subjects got rheumatic fever.

A Medical Corps officer who was there said it was 70, and these individuals didn't know they were being experimented on. There was

no discussion of this at all, and they were simply victims, and this was supported by the Surgeons General of the Air Force and the Army, and Western Research University.

Senator KENNEDY. Why was that done?

Dr. BEECHER. They wanted to study some of the nonulcerating effects of strep infection. I am not sure of that reason, but I think that is what was in their minds.

Senator KENNEDY. In other words, the servicemen were being used as experimental guinea pigs?

Dr. BEECHER. They were indeed. This wasn't discussed with them, either.

Senator KENNEDY. This wasn't voluntary?

Dr. BEECHER. No; they even didn't know they were being subjects at all.

Senator KENNEDY. Is it your understanding that there are similar types of experiments taking place in other parts of the country?

Dr. BEECHER. Yes; under the very best auspices, one might say. Of course, there was the thing in Brooklyn, the elderly Jewish people who had live cancer cells injected into them. They weren't told they were getting live cancer cells.

There are other examples I have, scores of them, in my files.

Senator KENNEDY. What procedures are in existence to control this? Who is concerned with this?

Dr. BEECHER. Dissemination of information that some things are wrong has had a good deal to do with it. I think you were out of the room when I mentioned that the NIH, at the time this paper came out, were receiving about 7 percent of ethically unacceptable applications.

Six months later, this had fallen to a third of that number, and it has remained at that. I haven't checked recently, but I checked it for several years. It is an indication to me that information and knowledge will reduce these outrages and these dangers.

Senator KENNEDY. But you don't know of any kind of group that is in Government today that is charged with the responsibility of seeing to this?

Dr. BEECHER. I was surprised at Dr. Duval's testimony. I couldn't hear it very well, however.

Senator KENNEDY. From your knowledge, and your experience in this field, you don't think it is adequate, whatever is being done; is that correct?

Dr. BEECHER. That is correct.

Senator KENNEDY. And the Commission which has been suggested by Senator Mondale might be able to make some recommendations on how to best address this particular problem?

Dr. BEECHER. I think calling attention to these things is extremely valuable.

Senator JAVITS. Mr. Chairman, could I have just 1 minute to make an observation?

In the law which we have passed related to the authority for permitting various drugs to be used, we had quite a struggle over the necessity for consent from the patient by whom these new experimental drugs were taken. Do I gather that you feel as an ethical man that any time you administer something to a person, it must not only be

with their consent, but with some assurance that they know what they are consenting to?

Dr. BEECHER. There are two problems here; two areas. A man who is ill and is in need of a physician, gives his consent in coming to the physician to reasonable efforts to cure him. There are no great problems here, except that what is reasonable might be arguable.

There are these other things where no consent is given, and one thing that I objected to in the NIH statement, not those read this morning, but having read their material, which I was part author of, I think, indirectly, or at least some of the phraseology I think I recognized as my own—there is a bland assumption on the part of the NIH that consent is ours for the asking, and that isn't the case. Consent is a goal toward which to strive. We must face that fact.

We go through the efforts of trying to get consent, the subjects themselves then know they are going to be participants in an experiment, and that has not been the case in other areas in all too many cases.

I don't mean to make this too difficult, but we simply don't know how to get informed consent when nobody knows the risks involved in many cases.

Senator JAVITS. Thank you, Doctor, and I would thank our chairman. I would like to state to the Chair, since I wasn't here much of this morning, that I think it is splendid that he is undertaking those hearings.

I was the author of this amendment to solve some of the ethical problems, and I think the idea of trying to get a Commission, which our chairman has helped so enormously, is a good one. You gentlemen are going to decide who will live and who will die. You will decide who will get the heart, who will get the kidney, who will get the blood, and there may not be a sufficient supply for all in need. There probably isn't now.

I think our chairman is rendering a fine service by concentrating attention on this problem and moving this bill forward.

Senator KENNEDY. Just one final question, are you familiar with the recently reported case of the black laborer's heart that was used in a transplant allegedly without consent of his family, which charged that in the hospital they allowed him to die prematurely?

Dr. BEECHER. That is the one in Richmond, I believe. I just read the papers on it. There is another case where there is a suit for \$4½ million.

Senator KENNEDY. What happened in this case?

Dr. BEECHER. There was a question that the donor was not dead. All I know about that is what I have seen in the newspapers.

Senator KENNEDY. From your years of study, is this type of thing happening in research as well as hospitals in this country?

Dr. BEECHER. Well, it has been, but I think the situation is very much improved over what it was even in 1966. I am very encouraged.

Senator KENNEDY. What kind of safeguards do we need in this type of situation?

Dr. BEECHER. We need the commission. I think that can help. I think it can focus attention on areas that are being neglected. You spoke movingly about dialysis. It is ridiculous to say that we cannot provide dialysis for anybody who needs it in this country. We are expending greater sums, or were in earlier years, on tuberculosis, and at the present time on mental health.

I just can't accept the fact that this country can't provide all the dialysis needed.

Senator KENNEDY. The fact remains that there are people in this country today who are dying because they are not getting the machines; is that not so?

Dr. BEECHER. It is unquestionably true.

Senator KENNEDY. Really, the only question is the question of finances; isn't it? I mean it isn't so much a question of experimentation somewhere down the road.

Dr. BEECHER. It is a lack of awareness of the problem, Senator. People haven't faced up to this. This commission could help people face up to some of these shortcomings in our society. Don't you think it is absurd for people to die of kidney disease for lack of a dialytic machine?

Senator KENNEDY. And that is happening in this country?

Dr. BEECHER. Yes.

Senator KENNEDY. We have the know-how and techniques to provide the machines; don't we?

Dr. BEECHER. Oh, yes.

Senator KENNEDY. And all that is needed is the money and the availability of the machines?

Dr. BEECHER. And awareness of the need.

Senator KENNEDY. And that could be a legitimate area of inquiry by this commission; could it not?

Dr. BEECHER. Yes; to emphasize the need here.

Compared to the cost of the care of tuberculosis in an earlier time, it is not great. These are not insuperable things. We have accomplished much greater things than this.

Senator KENNEDY. I want to thank you very much for your fine statement, Dr. Beecher. It was very informative and we appreciate it very much.

The subcommittee will stand in recess until 1.

(Whereupon, at 12 noon, the subcommittee recessed, to reconvene at 1 p.m., the same day.)

#### AFTERNOON SESSION

(The subcommittee reconvened at 1:10 p.m., Senator Walter F. Mondale presiding.)

Senator MONDALE (presiding pro tempore). The subcommittee will come to order.

Our first witness this afternoon is Dr. John Najarian, chairman, Department of Surgery, University of Minnesota School of Medicine, Minneapolis, Minn.

We are very pleased to have you back again with us. You appeared in the earlier hearings in 1968, and we hope we can do better by this proposal this time.

I understand you do not have a prepared statement, but you heard some of the testimony this morning. Proceed as you wish, and then we will ask questions.

**STATEMENT OF DR. JOHN NAJARIAN, CHAIRMAN, DEPARTMENT  
OF SURGERY, UNIVERSITY OF MINNESOTA MEDICAL SCHOOL**

Dr. NAJARIAN. That is correct. I was called last week and I was not able to prepare a statement. I would like to testify in support of this resolution. I had the privilege of testifying on this very same joint resolution in 1968, almost identical to the one that is currently proposed in Senate Joint Resolution 75, at that time Senate Joint Resolution 145, and I feel the need for such a commission even more urgently today than I did at that time, and I would like to give you some of my reflections on what has happened during that interval.

In the 3 years that have passed, I think the impact on society of the dramatic breakthroughs in biomedical research that lead to the first human heart transplant in Capetown in 1967 and the possibility of genetic engineering through synthesis of the genetic material of the cell, have raised justifiable concern regarding potential medical ethics. These advances in biomedical science have been extraordinary and continue in geometrical progression.

There are men now walking around who are walking around with someone else's heart. Even though an issue of Life magazine appeared not many weeks ago on tragedy of heart transplants, it is well to remember of 176 heart transplants that have been done, there are 28 of those patients still alive. Some have survived over 3 years.

In other words, success has been achieved, even though the article in Life magazine would make it difficult for any of us to do heart transplants in the present setting of public misinformation. The interest of the news media in creating dramatic occurrences, specifically the pictures on the cover of Life showing eight men who at one time were alive with their transplants and who are now dead.

Genetic defects are now recognizable in utero and has been stated before this morning, we can recognize genetic defects in the fetus and the recognition of these defects can lead to changes in our thinking with respect to abortion or with respect to population explosion, and so forth.

Cellular engineering is going on at the present time. There are at least half a dozen children today in the United States whose entire immune system with respect to those cells that are responsible for the immune mechanism of the individual are alive because those cells have been replaced by cells received from a sibling, a brother or sister, who was closely matched to that individual recipient. So cellular engineering has progressed remarkably in the last 33 years.

We are now transplanting organs that will provide enzymes, that will correct birth defects for a variety of diseases that have eluded us in the past and are now being treated with organ transplants, and this, again, is a breakthrough that has occurred in the last 3 years.

At the present time there have been throughout the world 7,500 kidney transplants done. 4,800 of these people are alive and well walking around carrying the kidney of someone else and alive only because of that kidney. A kidney transplant is no longer an experimental procedure, but is now therapy, therapy for people with end-stage kidney disease, the best therapy presently available.

Kidney transplantation is being done at a success rate of approximately 90 to 95 percent of these individuals, alive and well with func-

tioning kidneys at the end of 5 years if they receive a kidney from someone who is related to them.

If they receive a kidney from someone unrelated, from a cadaver source, then under these circumstances, approximately 60 percent of these people are alive 5 years after transplantation.

It is a remarkable feat since 3 years ago the results of a cadaver kidney transplant operation resulted in a 20-percent salvage of individuals with functioning kidneys.

Individuals are walking around today with hearts that are paced by electronic devices. These individuals would also have died had it not been for the development of biomedical engineering, of pace-makers, with not only electronic sources, but atomic sources, that will continue to drive their hearts and regulate the right rhythm of these hearts that are diseased.

I can regale you all afternoon on the miracles of medicine today. This has been done this morning, however and it was done in the introduction that Senator Mondale has given to this bill, and it needs no further recounting to show you the medical miracles that are occurring at the present time.

I do feel that the need for a commission as proposed by Senator Mondale and the other Senators is essential at this time, but the reasons may be different from those that have been presented before, and perhaps there are reasons which I look for this Commission to have a strong role in the health care of our country.

Now, the bill itself, or the Commission addresses itself to three issues: social, ethical, and legal.

I would like to take each one of these individually and discuss what I think the Commission could do, and perhaps in some way provide us with a guiding force from the Federal Government. A leadership which is sorely needed despite the testimony we heard earlier this morning.

In the first place, as far as social implications are concerned, what is the health problem in the United States? There is a health problem, and we hear it stated over and over from the legislators, from politicians, and yet the solutions to these problems are in multifaceted bills that are currently before the legislature in the health delivery.

The rhetoric of our health delivery goes on and on and someday in the not too distant future, some reasonable health legislation will be accomplished.

Pragmatics has helped delivery, and I am not against developing better health delivery systems, but the real problem in the United States is not health delivery per se, but it is still disease, and disease goes on.

When you consider as far as the heart is concerned that 125,000 people in the United States die each year under the age of 65 from heart attacks, this is a deplorable statistic.

One million four hundred thousand people in the United States today have had one or more heart attacks; 800,000 deaths will occur this year related to heart disease alone. These are staggering figures. This is our medical problem, disease which we need further research on, further implementation as far as methods of detection and methods of treatment are concerned.

Cancer is obvious. Cancer is the second most feared killer in the United States, and it results in between 300,000 to 500,000 deaths each

year. There is a very strong desire to conquer cancer as urged by the President.

There is a bill which is going to provide money to do this. There is a Commission that will be established to do this, a crusade against cancer. This is important, and I think this kind of implementation should go on.

But we still have continuing health problems. Our mental hospitals are still filled, despite the fact that we have made tremendous advances in the use of drugs, antidepressant drugs and the like, in order to treat people with mental health problems.

So disease goes on, and yet we look at health delivery as our major health program.

What I say is, look back in history. As was once said, "those who don't recall history are doomed to repeat it," and it is so true. Polio was a classic example. If we had invested in the delivery of iron lungs for individuals with polio, at the present time, we could have several million iron lungs in the United States, and yet last year we had literally no deaths from polio, because of the development of a vaccine.

Tuberculosis sanatoria were built throughout the United States. This wasn't the way to treat tuberculosis. With the development of drugs, this disease is almost nonexistent in the United States as a public health problem today.

High blood pressure, one of the major killers in heart disease, is very nicely controlled with the use of antihypertensive medications developed through research.

So I say that we have problems when we address ourselves to health delivery. If we forget about the importance of medical research and sometimes ill-advised, well-meaning legislators will propose these kinds of approach, because it has a certain social and political impact, if you will, charisma for the people to talk about health delivery, and the same charisma perhaps does not occur when you talk about research.

A classic example was given this morning by Senator Kennedy when he asked whether or not, and I think he asked this question to provoke the answer that he received, whether or not there were individuals in the United States who have end-stage kidney disease who are going to die because their kidneys don't function, and could be salvaged if they did in fact have an artificial kidney.

When he asked this question, the answer was "Yes," but it should be a very firm yes.

Today, in the United States, 50,000 people die each year, 50,000 from primary kidney disease. These people die simply because their kidneys don't function. Today, in the United States, we transplant approximately 1,000 to 1,200 transplants year.

We place about 400 to 500 people on hemodialysis, on the artificial kidney per year. So we are treating less than 2,000 people out of 50,000 who die. What about these other 48,000? I was just mentioning to Senator Mondale before this testimony that I had a call from West Virginia from one of the Senators in West Virginia regarding a case there in which a patient had end-stage kidney disease and needed to be put on an artificial kidney, and asked if the patient could be transferred to our State of Minnesota.

We have no money to do that with. We do have some welfare money to place some patients on hemodialysis in our State, but unfortunately cannot take care of those out of State. There are no Federal funds.

In the State of West Virginia, there are no welfare funds for such, and as a result the question was asked, and what is going to have to happen is, someone is going to have to make an appeal, through the newspapers, to appeal, to plead, to beg for money in order to buy a machine so that someone can live, in a country as affluent as ours.

So this type of tragedy goes on, and that is just a classic example, but it occurs in 48,000 cases each year.

Senator MONDALE. This is a field in which you have been especially active—kidney transplants and hemodialysis work.

Dr. NAJARIAN. Yes; this is my particular field of emphasis.

Senator MONDALE. I think it is a classic example of a social issue. From what you say, they have developed kidney transplant technology to a point where approximately 90 percent of those transplants would be successful, and we have had enough experience with this so that is a pretty firm figure.

We have kidney dialysis which works well. But of an estimated 50,000 persons who could be saved, only about 2,000 are saved?

Dr. NAJARIAN. That is correct.

Senator MONDALE. So even though there was a report, as I understand it, in 1966 laying this out, we are still unnecessarily dooming 48,000 people to die yearly from this one, curable disease.

Dr. NAJARIAN. That is correct.

Senator MONDALE. How does a person, such as yourself make judgments among competing patients, as to who will be saved?

Dr. NAJARIAN. I am happy to say in the State of Minnesota we don't have to make such judgments, because we have a system in which we are able to find financing for patients in our State. We have never turned down a case since I have been there in the past 4 years, for lack of money. We have taken it from welfare, from various forms of assistance.

I have taken research grant money and put it into this area. There are many ways in which we have been able to accomplish this fact so that we, for instance, in last year, there were about 75 kidney transplants in the State of Minnesota. That just about serves all those who would have needed them at that time.

Senator MONDALE. Is Minnesota unique in this respect?

Dr. NAJARIAN. Minnesota is quite unique in this respect. There are support mechanisms in the State of California to the tune of about \$2 million, and I believe there is a similar system in New York State, but those are about the only ones I know of.

Senator MONDALE. What does a kidney surgeon do in one of the States that does not provide adequate financial support? It is a life and death decision.

Dr. NAJARIAN. That is true. Depending on the zeal of the surgeon involved, he will call around someplace and see where this treatment can be given. But we are still talking about only 2,000 people. The others are simply left to die.

Senator MONDALE. Are the judgments in the other States made on the ability to pay?

Dr. NAJARIAN. It is not only the ability to pay, but many times the facilities are not available in the State.

Senator MONDALE. Do you know how many skilled kidney transplant surgeons there are in the country?

Dr. NAJARIAN. I would hate to guess, but I imagine there are 50 of them working actively now.

Senator MONDALE. How many dialysis machines are there?

Dr. NAJARIAN. I don't know. There are about 4,500 people on dialysis, so there are half that many machines, and some more.

Senator MONDALE. You may proceed.

Dr. NAJARIAN. The reason why I bring this commission up with respect to this issue is because I ask the question socially "What are our obligations, what are our priorities?"

In 1966, when I was on the Gottschalk Commission, we came forward with a recommendation that could be implemented for the salvage, perhaps, within 10 years of almost all these patients with a progressive program in which we would build new units and train more doctors in this field so the patients could be cared for.

Unfortunately, this has not been permitted, and 5 years have passed since the Gottschalk Commission report was delivered to the President, and nothing has been done to legislate with respect to this particular recommendation.

So this is one of the things that the health commission could then address themselves to, where are our priorities as far as the medical social questions are concerned.

A simple way of handling this problem would be pushing forth legislation such as catastrophic insurance. This is one of the existing bills, or is tied on to one of the existing health bills as an amendment, but this could be done at this time, as it were, without overall health legislation.

This would at least resolve this problem of this catastrophic illness which affects a family and financially decimates that family, and could be used to save some of these patients.

So basically, as far as the social implications are concerned, I think it would be important for this Commission to lay down certain guidelines as to what our priorities in health should be.

Here, we spend \$70 billion a year in health, which is about \$315 per capita in the United States. Yet we spend about \$7 per capita in the United States for research. Should this be implemented? Should these figures be higher?

How should we approach this as far as the health of the country is concerned? Yet these decisions are frequently made on a political basis, not on the basis of what is the real need today, and I would hope that such a commission could focus on those priorities.

Senator MONDALE. This would provide a forum for that purpose, too, would it not?

Dr. NAJARIAN. It would be excellent.

So this is one of the social aspects I see that the commission could address itself to.

On the educational side of the problem, there are many things—the questionable things that have occurred in transplantation and which may occur in genetic engineering and human research. We work on a crisis basis, as Senator Kennedy said this morning. We establish com-

missions to meet a crisis, and here we are looking at a crisis that currently exists and another that we are perhaps not as aware of.

As I look back on the history of the ethics of medicine, we find that something precipitated a code or an ethic to be set up, dating back to 407 before Christ with the Hippocratic oath, which stated at that time that "I will abstain from whatever is mischievous or deleterious."

The William Beaumont code was the first in the United States, in 1833, at which time William Beaumont, a surgeon, worked on a patient who had a gunshot wound in the abdomen, and had a hole in his stomach, and Beaumont took this opportunity to study the secretions from the stomach as they relate to disease and as they relate to ulcer formation. The results of his findings were monumental in terms of gastrointestinal work. He wrote his own code, that stated that the subject should have proper, informed consent, and it should be given voluntarily, and any time the research protocol would be detrimental to the patient, it could be abandoned.

So this was our first attempt to try to get informed consent.

The Nazi atrocities lead to the Nuremberg code, which have served to guide our ethics as related to human research.

Subsequent to that, there was the declaration of Helsinki in 1964, which altered some of the code ethics described in the Nuremberg code.

It wasn't until 1967 when the National Institutes of Health required that all grants related to research on human subjects would in fact have full review at their own institution with an ethics committee, the kind of thing that Dr. Beecher talked about, and which he chairs at Harvard, and the kind of committee that currently exists at all universities.

What precipitated that admonition by the NIH? It was precipitated by the overt act of giving patients live cancer cells without telling them what they were receiving. This was given to some 250 unsuspecting patients. This was a travesty on research and science, and fortunately the NIH responded by this particular requirement that there be ethical committees established at each university that must oversee all research grants on human subjects before they are proposed to the National Institutes of Health for funding.

This is the first attempt, and each time each of these codes met a crisis and met that crisis with an appropriate group of guidelines or codes or rules on ethics and behavior.

Unfortunately, today you can still go down and pick from any of these codes, the Nuremberg code, the declaration of Helsinki, and you can describe a situation which will allow you to do human research in almost every form, because there is no one guideline present today as far as the United States is concerned.

The recent trouble that occurred when Dr. Saul Krugman injected hepatitis into children, led to a tremendous uproar of ethical reproach as far as his action was concerned utilizing these children as guinea pigs in whom he had received parental consent to inject the hepatitis virus.

The things he taught us about hepatitis could have been learned in no other way, but were the means correct?

In the United States, we have condoned this work by several of the major spokesmen for the U.S. ethical codes, we have given

many congratulations, and perhaps rightly so. Across the ocean in Great Britain, there has been a very strong hue and cry that this was an unethical thing to do, despite what we learned. An experiment is only ethical from its inception, and not after the fact if you learn something that is of importance.

Well, this kind of thing leaves us with an enigma. We don't have a specific code. This kind of commission could establish such guidelines, not to be restricted, and this is, I think, what bothers most people, concerns most physicians, concerns most scientists. Such a commission could lay down rules carved in stone that would make it difficult for us to deal with human experimentation, this is not what we are seeking.

What we are seeking are guidelines which we can look at and use in a helpful way in human experimentation.

All experiments must eventually come to the human being. The study of mankind is man, and as a result, after adequate laboratory investigation has been done, it must be translated to man. Human experimentation goes on today, will continue to go on, and human experimentation has led to the development of anesthesia, antisepsis, anything you want to name with respect to our general knowledge in our current level of medical competence.

So this must continue on, but we must have guidelines to follow, and these guidelines could be drawn up by such a commission not to be restrictive, but to be helpful.

In addition, I would hope that such a commission would establish an ongoing body, whatever that would be, that could be used as an appeal area, very much as we have our own legal appeals today.

So when medical ethics are judged by peers at the local university level as far as ethics are concerned, there would be a level where you could now respond to a national commission, with respect to specific guidelines for particular cases.

At the present time, the restrictions from the FDA are such that they say that no drug can be given to humans unless it has had adequate human trial. Yet try to get that human trial. It is practically impossible today. It is prohibitive today. I was told by some drug companies that they wouldn't develop a new "pill tomorrow, a pill like a contraceptive pill that we have, because it would be impossible to administer such a pill to a large majority of people without having human trial, without having adequate evidence to state that it is safe in humans.

Yet, where is this evidence going to come from? If you try to do it in foreign countries, then you have the problem of exploration in utilizing other countries in "experimentation."

What I am saying is that human experimentation must go on. It must continue. What it needs is guidelines, guidelines of behavior, and guidelines which I hope such a commission would address themselves to.

Senator MONDALE. The very fuzziness of this area may be a greater threat than the establishment of guidelines.

Dr. NAJARIAN. If there are guidelines and you could say, "All right, you have met these standards," let us set standards. Now, informed consent, Senator, is absolutely impossible. There is no such thing as informed consent. The only time I can do an experiment even to give a pill to somebody, another human being, and have properly informed consent is if that other human being perhaps is a physician, because he

has to have that much background in order to perceive all the risks apparent now and in the future, that could occur from such administrations, whatever it is, whatever the medication might be.

So this informed consent, *de novo*, is impossible to achieve.

Yet, some form of informed consent can be achieved and these kinds of guidelines could be given.

The commission will address itself to legal problems, and these are many. One of them I brought out as far as the Federal Drug Administration is concerned, which is now in the situation of requiring something which they won't allow to happen. We have recently come up against this ourselves. We have developed a serum at the University of Minnesota which has improved cadaver transplants, transplants from people who have recently died, kidneys, for example, from approximately 50 percent up to the range of 70 to 80 percent survival of these kidneys with the use of this serum.

It is raised in horses. This has resulted in 40 to 50 percent better salvage of kidneys.

Yet, today, we can't manufacture that serum, because we can't get anybody to support it, we can't sell it, we can't give it to anybody. We can give it within our own institution, but if we are to try to set it up for other institutions, we can't even receive cost recovery for it, so that we could make more of the serum to be distributed for further clinical trial, because the rules are that restrictive.

I think the rules and the legal implications must be defined much more clearly, and must be defined in a much less restrictive way so that these things, as new things come along, can be achieved.

If we had a serum, a vaccine against cancer tomorrow, you couldn't get money to support it. You couldn't give it to anyone, and you couldn't pass it across State lines, and it would be extremely difficult in order to develop such a vaccine, no matter how good, at least on preliminary trials, that appeared.

There are other obvious things in a legal sense, such things as a definition of death. We discussed that this morning. What has happened is that a variety of people and a variety of groups have looked at this, and they all have definitions of death, as far as brain death is concerned. The group at Harvard has set its standard, the AMA has a stand on this, and other groups do as well. They are all different, they are all relative, and in each institution perhaps a standard has been established.

What I am saying is that there ought to be, here, again, some specific guidelines on what we consider a definition of death in the modern sense with the advent of the machinery we have and the capability we have of extending life and continuing heartbeat and breathing in a patient who is "brain dead."

So these are the issues, basically, to have this commission study and recommend solutions to these problems. One, the social problems with respect to priorities, and hopefully this would have a meaningful input into the legislature if this is a Presidential commission.

Two, to address itself to the ethical problem, many of the ethical problems are fabricated, but many other ethical problems are real and do exist. They need some reasonable guidelines in order to follow, and perhaps some sort of appetite mechanism for local groups and universities to appeal to.

If the commission can do this, they will have done an awful lot, and they will have made a great stride forward with the Federal Government assuming a responsibility in putting a cohesiveness into the medical associations and medical institutions that are looking at the problem independently, none of which are really pulling us together in an amalgamated form. There could be one place you can go to find and answer, or at least an area of appeal or an area of definition.

In human experimentation, what are the benefits to society and the jeopardies of society. Therefore, I strongly urge the passage of your resolution, Senator.

Senator MONDALE. Dr. Najarian, I am pleased by your strong statement in support of this proposal. It is an excellent statement.

It is my impression that some of the research persons in medicine fear that there are more risks to be gained from public ventilation of these problems than it deserves.

Others, like yourself, seem to believe that great progress can be achieved through public ventilation.

How do you answer those who have this fear? As I understood Dr. Duval, he felt a public review would freeze and paralyze guidelines and rules and regulations, and thus we would not have the flexibility we need.

The assumption underlying that must be that the public would be unduly rigid and lack the understanding needed to respond intelligently. I think he saw it basically as a fear or a risk. You seem to see it as an important new possibility for public understanding, for support, for guidelines that would actually help research and treatment.

Dr. NAJARIAN. I think this is basically true. As we look back on medicine, and we find that, years ago medicine was practiced by pulling up a sack of digitalis leaves, and holding hands and reassuring patients. This was medicine, and there were very few things we could do.

Today medicine is different. Today we have a potential of doing an awful lot in medicine, and we do, and I think basically I give a lot more credit to the American people that this kind of public information is wanted, if they were to learn that experimentation is needed they can accept it. But the question always arises about human guinea pigs.

There are no human guinea pigs. If the guidelines are there, if you are not taking risks on these people that they are noninformed of.

Yes; there are skeletons in the closet, the travesties that we spoke about today, the injection of cancer cells and things like that, those exist. But they help us to draw up rules and guidelines. At the same time, the experimentation leads to the proper delivery of medicine to the people, and I think the people would respond to that.

I think your recent Amchitka thing is about as good an example as any. If people really knew the information behind that experiment, there probably wouldn't have been such a hue and cry against it.

The same thing is true of any experimentation. If you know the facts, you can't philosophize on what the potentials are, because they are presented to you, and it takes away the fantasies that allow for the fabrication of all kinds of Frankensteinian monsters.

Senator MONDALE. I don't like your Amchitka example at all. [Laughter.] Were you here this morning when I read Dr. Kornberg's

statement? I think it reflected a view that we are just interfering with scientific schedules, and there are great risks to a public study.

Let me read it to you. This is Dr. Kornberg, one of the great men of medical research.

He told the committee:

The biochemist who deals with molecules cannot afford any time away from them. Today, I am not in the laboratory. I do not know what is going on at the bench. Tomorrow, I will be less able to cope with the identity and behavior of molecules. The more I am estranged from the laboratory, the less competent I am to advise you regarding special problems in this field.

He felt the committee was imposing upon his research time.

Is that a standard view in the research fields of medicine, that the money should arrive in hundreds, tens and ones, to be spent in the research field, but there should be no dialog or information passed back?

Dr. NAJARIAN. No; that is not true.

Senator MONDALE. I think that is what he was telling us. He said he needed money, but "for crying out loud, don't ask me to come here and spend my time at hearings."

Dr. NAJARIAN. I think we will always have to have peer review, and that includes our lay peers as well, and I think we should be accountable for the research we do, and we should come to you, and when we appeal for more money for research, I think I can show you what we will do with that money, and I think it is important for us to come out with this kind of testimony to tell you what is going on, so you do know.

A lot of people in the United States still have the unfortunate idea that research is something that is very esoteric, something that is done on a bench that has nothing to do with disease, and why should we spend \$1.4 billion on research just to support a bunch of people who are investigating different events of molecular structure, or enzymatic processes, or chain reactions if it has no direct clinical application?

Well, that kind of decision is made by people at the National Institutes of Health in their peer review study sections.

Senator MONDALE. Most of the same people favor this commission, and they are the very people who fight hardest for those researchers.

Dr. NAJARIAN. Right. I don't look at this commission as restrictive. I think the fear that such a commission, and I think that as I read Dr. Duval's testimony this was his fear, the rules would be set up and would be so restrictive that it would be impossible to continue in the research much as we see it today.

I have faith that this commission would not come up with that alternative.

Senator MONDALE. I have a feeling that medicine does not want to explain its case partly because they went through the period with Lister Hill where they were in a preferred status, like the FBI. I think we are at a point now where American medicine has to explain itself.

I suspect very few people in this country are aware of the kidney situation that you referred to, unless they are a part of a family that suffered.

Yet, I think if they did know, there would be a far more adequate response than we have perceived.

Dr. NAJARIAN. As a practicing physician and surgeon, I feel the worst thing you can do with a patient is not explain what you are

doing, and by just sitting down and explaining what the patient has in the best terms that you can translate it to him and then tell him what operation that you are going to do and what is going to result and what you expect from it. I think it is a lack of information that the people resent. They feel like they are on the outside looking in, that we don't know what we are doing.

Skeletons will come up, we know that. On such a commission and looking into certain items such as medical research perhaps, this should be exposed.

I think what is going on, if the American public knows it and fully appreciates it and is cognizant of it, that they would accept it. Information is very important.

Senator MONDALE. One final point. I asked Dr. Duval whether in his opinion the medical schools today are providing adequate training, discussion and dialog in the social and economic implications of the professions. Do you feel that this is being given adequate treatment in medical schools?

Dr. NAJARIAN. Not in the way of a formal curriculum. We at the University of Minnesota recently had a series in the past 2 months at our medical staff conferences where we discussed the issues you are discussing today, human experimentation, because it must be discussed in this ad hoc way.

Whether it will develop into a formal course is hard to say.

Senator MONDALE. Don't you think your profession, and certainly it is true of my profession, suffers from failing to equip a highly skilled person with some social orientation? Isn't that increasingly important? We are in the midt of the most fundamental domestic debate concerning what we should do about medicine.

Yet, your national association—I am not sure if you are a member of the A.M.A.—comes up with the answer, “do as little as possible, stay out of our hair.”

Even in response to this little proposal for a study commission, some members of the profession say: “We will take care of that. You take care of your business, we will take care of ours.”

I think there is a tremendous amount of suspicion and fear about the public process as it relates to your profession.

Doesn't this reflect, among other things, a deficiency in training? I don't want to make social scientists out of every doctor, but it seems to me that we need Walter Heller kinds of physicians that may not be any good in a surgery room, but are good on the public policy questions that affect society.

Dr. NAJARIAN. We talked about this, but I think we are fortunate enough now that we are beginning to get a very socially involved group of students now, who went through their undergraduate curriculum, and are now in medical school, and this group is influencing our medical schools today.

They are asking us the social questions that we never discussed in medical school which, for the most part we were like a trade school. We teach them medicine, and this social awareness is increasing and through the students impetus, awareness of the social problems, is entering medical school discussed. I think this is a good thing, and it is occurring today.

What you are hearing from the AMA is perhaps the more conservative old line approach, which is "keep your hands off and we will do our job properly. We have done it before, and we will do it again."

But that is not what we are seeing today. The young physicians who are coming along, are socially involved and aware and interested, and as a result I think we will see improved insight in the near future.

Senator MONDALE. Thank you very much, Dr. Najarian, for a most useful contribution. We appreciate your willingness to come out here and participate.

Our next witness is Dr. Daniel Callahan, director of the Institute of Society, Ethics, and Life Sciences, Hastings-on-Hudson, N.Y., and author of books on ethics and conservation, and abortion.

#### **STATEMENT OF DANIEL CALLAHAN, PH. D., DIRECTOR, INSTITUTE OF SOCIETY, ETHICS, AND THE LIFE SCIENCES**

Dr. CALLAHAN. We share one condition in common with our ancestors. All of us were born and all of us will die. But unlike our ancestors, most of us were born and will die in the company of modern medicine, our birth made safer and our death delayed by greater medical sophistication, elaborate machines, and a never-ending array of drugs for our minds and bodies.

I count this as progress of an immensely beneficial kind. I am glad that my mother lives on in her seventies, that my wife did not die in childbirth, that my children will, barring accident, grow into adulthood, that the pain of my own operations was eased by tranquilizers, anesthesia, and painkillers.

Without modern medicine and the biological research upon which that medicine is based, none of these things might have been possible. I do not want to see biomedicine go back one step, not even to yesterday. And I don't want it to stay where it is today, with much still unknown.

But how is it to go forward? That is the central question. It can, of course, go forward blindly, a new drug here, a new machine there. But I hope I may be excused for a certain wariness about that process, however much we have benefited from it in the past.

We now know that medical progress can have two faces. The rapid, indeed staggering world population growth is one direct outcome of recent medical advances, which lowered death rates far more rapidly than birth rates. That is the kind of success which, if it won't kill us, may kill our children or grandchildren.

Our homes for the aged are filled with human beings who, but for obsessively effective lifesaving techniques, might long ago have passed to mercifully quick deaths, their faculties still intact.

Our hospitals are filled with physicians who, precisely because of the new powers given them, are often forced to make decisions far more agonizing than those faced by their predecessors: Whether and when to cease treating a dying patient whose life might artificially be extended for an indefinite period; whether to use a miracle drug at the possible price of devastating side effects; whether to try radical brain surgery at the hazard of making a person less than human.

The list could be extended, and it would run to many pages. The point, however, is an obvious one. It is increasingly difficult for medi-

cine to go forward with a heightened sensitivity to the fact that "progress" can carry a high price tag, the economic aspects of which may be the least of the problems.

On the contrary, the price I am referring to is that of increased confusion and uncertainty about goals; a sharp rise in painful, seemingly impossible ethical dilemmas about means; a geometric increase in power, but power now understood as a double-edged sword.

To take one example, as a technical problem, electrical stimulation of the brain and the production of desired behavior poses many unsolved scientific questions. But as an ethical and social problem, the questions are far more difficult:

Who would control such a power should it come to pass on a massive scale? What kind of a society would it produce, and would it be the kind of society we would want to live in? Perhaps Prof. B. F. Skinner is right in saying that if the human race is to survive, it will have to move "beyond freedom and dignity," into an engineered behavior control. But in that case survival may not be worth it. Some of our ancestors, we might recall, chose to engage in a revolutionary war rather than give up freedom and dignity.

In thinking about the implications of advances in the biomedical and life sciences, it is tempting to concentrate only on the most dramatic possibilities. In vitro fertilization, test tube babies, the cloning of genetically identical persons, sex determination, electrically controlled behavior rank high on the list of such possibilities. Depending upon our tastes and our thinking, we can contemplate them with hope or horror, secure in the knowledge that we still have a few years of contemplation left.

But I believe a serious mistake is made if anyone thinks that those are the only kinds of issues to worry about. Equally important at the present time are our present problems, not nearly so dramatic but far more pervasive in their immediate effects.

I have already touched upon the care of the elderly and the dying. No one who has reached adulthood will escape that problem, first with his parents and relatives, and then in his own case. We will turn to physicians for answers.

And where are they to get those answers? Most of us will have at some point, to face surgery, or radical chemotherapy, or both. Our chances will be better if the proposed treatment or therapy has been tested experimentally. But on whom should this experimentation be carried out? On those in prison, or the poor, or the helpless?

On those who give consent to the experimentation and only those, or on those who, consent or not, prove useful experimental subjects? Where and how should lines be drawn? And by whom?

I am only raising questions, and they are not very original ones at that. They are not original because the modern physician is being forced to think about them every day. For the physician is in the unenviable position of having tools and skills, the implications of which transcend his training and the wisdom of his profession.

He is being forced to ask the public what it wants him to do; what ethical standards does it want applied? What needs does it want met and what hazards avoided?

Needless to say, at a time when those closest to modern medicine, the physicians and scientists, find themselves in desperate quandaries, the

public may be even more at sea. As a nation, we pride ourselves on our pluralism. But it is becoming increasingly clear that, in making judgments on matters of life and death, of national medical policy, or research priorities, that something more than private, individual judgment is necessary.

Some minimal consensus is needed, some public mechanisms for wise decisionmaking, some means of bringing out into full public view the private dilemmas of physicians, of families, and of patients.

These are not the kinds of issues where each of us can just go off on his own. Even if we are happy to make an exception to this rule in our own case, we are not quite so likely to do so concerning our neighbor, particularly if, say, he has privately decided that we would make ideal experimental subjects.

I would not want to leave you with the impression that I minimize the importance of such dramatic possibilities as genetic engineering and massive control of human behavior. My point is simply that we are already faced with vast and difficult dilemmas.

How we choose to solve them will not only be important for the present and near future. No less importantly, the way in which society goes about deciding them is bound to establish important precedents for the solution of the dramatic issues of the future.

Public examination and discussion is essential for a number of reasons: to establish scientific priorities, which will bear heavily on the allocation of research and delivery funds; to bring some common wisdom to decisions which are too often unnecessarily private and isolated; to established ethical and social norms for assessing technological developments; and, finally, to enable the public to understand the exact nature of the issues at stake.

Let me seize on that last point. It is by now well known that the number of people suffering from inevitably fatal kidney disease far exceeds the number of available hemodialysis machines. In that instance, scarcity of medical resources places an impossibly heavy burden on physicians, who must literally choose who is to live and who is to die.

But there are actually at least two different problems here. One of them concerns the failure of legislatures and public authorities to provide funds sufficient to relieve physicians of the dilemmas posed by scarcity of those machines. There is no intrinsic reason why physicians should have to choose among lives, and the public needs to understand that.

At the same time, given the failure of society, they must choose—but neither the society nor traditional ethical codes provide clear guidance on the ethical basis of the choice to be made.

The dilemma is made all the worse by the fact that the American legal and political tradition has asserted that all lives are equal, that choices must not be made among human lives. For all that, choices are being made and must be made. Can we wonder that physicians find the burden an impossible one?

But understanding is needed for other reasons as well. For better or worse, the biological and medical decisions now being made—often in darkness—will radically change future conditions of life. The social impact of increased longevity can be as great as that of a political revolution.

The cultural impact of lifesaving antibiotics can be as shattering to the economic system as a bull or a bear stock market. The advent of widespread use of artificial procreation could introduce social changes which would make the present sexual revolution seem tame in comparison.

Where will we find the necessary good sense to deal with these developments? Where will we find ethical codes to enable us to make correct decisions? Where will we find the resources to develop an image of man, an understanding of his nature and his possibilities, which will save us from a descent into inhumanity?

Where will we find the wisdom to press forward scientific research and biomedical technology in that direction which most sensitively responds to genuine human needs and aspirations?

It would be foolish to promise that the needed ethical codes, the requisite intellectual resources, the imperative wisdom will inevitably be found. On the contrary, it is possible to imagine a permanent state of moral and social chaos, resting on jerry-built moral rules, and on ad hoc solutions and policies.

That may work for our generation—though there is no evidence to indicate that it is working—but it will almost certainly mean that we will bequeath to our children a mess of pottage. They will have to live with our mistakes, which in this case may be irreversible.

I am optimistic enough to think that progress can be made. The experience of our institute, and of a few others like it, is that a concerted effort can succeed in clarifying the issues, in specifying the social and ethical options, and, in general, providing both the public and the professions with a better grasp of the choices before them.

It takes time, it can be confusing and frustrating in the process, and it can and will take people out of their depth. It means that barriers between the professional disciplines must fall—physicians must learn to talk with philosophers, biologists with lawyers, historians with geneticists, social scientists with pediatricians. And all together must learn to talk with legislators, with the communications media, and with the man on the street.

Resistance will be met, sometimes from a few scientists and physicians who fear public discussion, who would prefer that the issues be handled behind closed doors; sometimes from segments of the public who would prefer that others make their decisions for them; sometimes from legislators, who would prefer to avoid hard issues and open controversy; sometimes from antitechnologists, who would simply prefer to condemn all scientific advance; sometimes from zealous protechnologists, who are willing to pay any price—usually someone else's—to keep the whole machine moving forward as fast as possible.

I believe, though, that the issues have now surfaced and that the public does want open discussion and debate, serious research and careful thought. A new generation of scientists, a new breed of physician, and a fresh corps of lawyers, and public policy experts are beginning to turn their attention in that direction. And, often to their surprise, they find far greater receptivity than they imagined possible, even among their elders.

For what is most evident is that we are all in the dark together, young and old, scientist and layman, physician and legislator. To-

gether we should act to admit some light, if not for our sake at least for that of our children.

Thank you.

Senator MONDALE. Thank you very much, Dr. Callahan. Personally, do you think a national commission would be helpful in trying to sort out these ethical and social issues?

Dr. CALLAHAN. Speaking for myself as an individual, I think it would be quite helpful. In the past years, I, along with a number of others have simply been working very hard to bring these issues out into public discussion.

It seems to me a commission would be one very effective way of publicizing the issues and, perhaps most importantly, trying to bring some systematic thought and investigation to the problems.

Senator MONDALE. Your institute has been in operation for how long?

Dr. CALLAHAN. We began initially in the spring of 1969, and it took us about a year to get ourselves organized. So actually, we haven't been going on a full-scale basis for much more than a year and a half.

Senator MONDALE. Do you fear that the creation of such a commission would unfairly impede responsible medical research and treatment or do you think it would be of assistance?

Dr. CALLAHAN. I think it would be of considerable assistance. I don't see any possibility of needed and important research being impeded by such a discussion. On the contrary, it would seem to me such a discussion might well serve to pinpoint where the actual research needs are.

It might serve to call public attention to areas of neglected research. It might make it clear to the public and the legislature just what kind of issues the scientist and the researcher faces in his daily work.

In many cases ethical issues impede scientific research and unresolved ethical problems hold up work which might go on. It seems to me, the chips fall both ways on this issue.

Senator MONDALE. How do you explain the reluctance of the medical profession to submit these kinds of obvious issues to public scrutiny?

Dr. CALLAHAN. My own impression is that it is by no means a universal feeling among physicians and scientists. I suppose my own impression is that physicians are responding not much differently from any other profession. There is no profession which seems to like the public to take a look at what it is doing; physicians, lawyers, academicians or what have you.

I think there is a fear that the public will not understand their problems. There is a fear that they may have to do something differently than what they are doing. I think it is almost an instinctive reaction of self-defense, one I think is unfortunate and unnecessary.

Senator MONDALE. What is your background?

Mr. CALLAHAN. I am a Ph. D. in philosophy with special training in the field of ethics. I have concentrated my work in recent years in the area of medical ethics.

Senator MONDALE. Thank you very much for your helpfulness.

Our final witness today is Prof. Hans Jonas, professor of philosophy of the New School for Social Research and the author of many works

in the field of philosophy and life sciences, including, "The Phenomenon of Life" and "Toward a Philosophical Biology."

We are very pleased to have you with us today and may I express my appreciation. I think you sat through a whole day's hearing.

**STATEMENT OF DR. HANS JONAS, PROFESSOR OF PHILOSOPHY,  
THE NEW SCHOOL FOR SOCIAL RESEARCH, NEW YORK**

Dr. JONAS. Mr. Chairman, the burden of my testimony in support of your resolution will be to plead the case of foresight versus hindsight, and to argue the supreme seriousness of the issues on which such powers of foresight as we can muster are in this case to be employed.

A plea for foresight against hindsight is less trite than it sound when we call to mind how thoroughly we have in the past allowed ourselves to be caught unawares by the long-range implications of our own deeds, the unchecked use of newly acquired powers.

One need only mention the ecological threat, which we are discovering so late in the technological game, when the crisis is already upon us, and when the sheer weight of what by now is already there makes remedy and redress exceedingly difficult.

By comparison, the mere fact of the present resolution is encouraging proof that some of us have learned something from the lesson of the past. So is the fact of unofficial bodies spontaneously forming to wrestle with the same subject at this incipient stage of the newest technology. I am a member of such a group—the one referred to in Mr. Callahan's testimony—and we have heard of another one this morning. For once, there is a will to know in good time what we are about to do, and to ask ourselves what we wish to be done and what perhaps not.

In other respects too, I would say, the comparison of the present case with the rather blind and automatic course of previous technological progress gives grounds for hope. This time, a sophisticated projection of potential consequences is possible to informed minds, which then was virtually impossible to anyone, even had the effort been made. The vulnerability of the environment came really as a new revelation which only the ravages already perpetrated could provide.

Moreover, this time, anticipation has a real chance to influence the course of future action—a chance nonexistent in the former case. I doubt whether even the truest prophecy, miraculously dropped into the onrushing stream, would have made any difference then. The industrial-technological tide which swept us into the ecological plight was all but irresistible: whoever wanted to stay afloat—and who didn't?—had to swim with it, and not the most enlightened forecast of the cost which posterity would someday have to pick up would have availed against the pressures of the hour.

Now, the better condition this time is that no such overpowering "must" is at work in the application of advancing biomedical techniques; no competitive necessity forces our hand here. We are not blinded by proximate pressures to the view of remoter responsibilities. And no vested interest has as yet preempted the freedom of decision over the use of the powers as they come within our grasp.

But this freedom will not last. Once the momentum of actually initiated practices comes into play, the field will develop its own dynamics

and take matters out of our hands. We are all too familiar with this kind of process. The moment of freedom, the moment for responsible deliberation is now; it is brief and must not be wasted. Senator Mondale's resolution comes at just the right time.

It also can count on the willing cooperation by the protagonists of the biomedical advance itself. Their's is, after all, an enterprise driven not by selfishness and greed, which tend to blunt sensibilities, but by high purpose, the altruistic will to help, to relieve, and to benefit other lives.

This, by nature, implies readiness to reflect on what will constitute benefits to man and what possibly the opposite; that is, to reflect on the human good in all its vulnerability. To have a well-grounded conception of it has become an indigenous commitment, objectively and subjectively, of the whole biomedical endeavor, as it passes beyond the confined terms of traditional medicine into areas which involve no less than the total image of man.

This kind of commitment is something new in the world of value-free science, and its presence is a great initial asset for the work of the proposed National Advisory Commission. In its shared objective, the members from all the represented fields can meet.

Thus, the possibilities are there, and the hour is propitious. And there is the supreme need. The depth of the interventions that are becoming feasible is such that they put the destiny of man at issue. A timely assessment of potential gains and losses, of promises and dangers, becomes imperative.

The picture is bound to be a mixed one. No simple yes or no to the use of the novel techniques is to be expected in most cases, though in some, such as human cloning, a firm no to even a first beginning may be deemed the appropriate verdict.

Mostly it is rather a question of how far to go and where to stop. Determining the critical boundary line will be a matter of wisdom for which we can only try, but try we must because of the seriousness of the stakes.

With the committee's permission, I will briefly illustrate the weight of the upcoming questions and the double-edged nature of the new powers on three selected examples: behavior control, extension of longevity, and genetic control.

First, behavior control. The new kinds of control that are being developed employ chemical means and direct electrical action on the brain, via implanted electrodes. The mixture of beneficial and dangerous potentials—or, put more neutrally, the possible use of such means for very different ends—is obvious here.

Least controversial will probably be the relief from distressing and disabling symptoms which the new methods promise to victims of mental disorder. This therapeutic application, I take it, is at present foremost in the researchers' minds and decision over its merits lies legitimately with the medical profession.

But, from the relief of the patient, a goal entirely in the tradition of the medical art, there is an easy passage to the relief of society from the inconvenience of difficult behavior among its members; that is, the passage from medical to social application, and this opens up an indefinite field with grave potentials.

The troublesome problems of rule and unruliness in modern mass society make the extension of such control methods to non-medical

categories extremely tempting for social management. Numerous questions of human rights and dignity arise. Shall we induce learning attitudes in school children by the mass administration of drugs, circumventing the appeal to autonomous motivation?

Shall we overcome aggression by electronic pacification? Candidates could be multiplied.

Senator MONDALE. I believe the head of the American Psychological Association, Ken Clark, proposed that pills be given to politicians. There is a lot of public criticism of that but a lot of private agreement.

It is a question of which pills and who takes them. That could be a good issue. I would like to be on the commission which decides.

Dr. JONAS. This is a good example from the political sphere. Also business firms might become very interested in some of these techniques for performance increase among their employees. Independently of the question of compulsion or consent—each time we thus bypass the human way of dealing with human problems, short-circuiting it by an impersonal mechanism, we have taken away something from the dignity of personal selfhood and advanced a further step on the road from responsible subjects to programmed behavior systems.

Social functionalism, important as it is, is only one side of the question. Decisive is the question of what kind of individuals the society is composed of, to make its existence valuable as a whole.

Somewhere along the line of increasing social manageability at the price of individual autonomy, the question of the worthwhileness of the whole human enterprise must pose itself. Answering it involves the image of man we entertain. We better pose it now while the instruments are being readied.

Second, extension of longevity. Prolongation, perhaps indefinite extension of life by counteracting biochemical processes of aging is a hope held out by certain advances in cell biology. A perennial craving of mortal man seems to come nearer fulfillment.

But how desirable is this? How desirable for the individual, and how for the population? Questions like these involve the very meaning of our finitude, the attitude toward death—a delicate subject in the American setting—and the general biological significance of the balance of death and procreation.

Even prior to such formidable questions are the more pragmatic ones of who should be eligible for the boon. Persons of particular quality and merit? of social eminence? those that can pay for it? everybody? The last would seem the only just course.

But in conjunction with the population problem it would call for a corresponding reduction of births, and this would result in decreasing proportions of youth in an increasingly aged population.

To take the extreme: If we abolish death, we must abolish procreation as well, the birth of new life, for the latter is life's answer to the former, and so we would have a world of old age with no youth.

But this is precisely the wisdom of our mortality that it grants us the eternally renewed promise of the freshness, immediacy, and eagerness of youth. There is no substitute for this in the greater accumulation of prolonged experience: It can never recapture the unique privilege of seeing the world for the first time and with new eyes—which may well be mankind's hope, its chance of retaining the spontaneity of life.

So it could be that what by intent is a philanthropic gift of science to man turns out to the detriment of man. Surely the perspectives it opens merit the most serious consideration by informed minds.

Thirdly, genetic control. This is too large a subject to be more than touched upon here, and only in one of its aspects. The more modest part of such control, not yet genetic engineering, falls in the class of preventive and preservative medicine; namely, avoidance of defective progeny; also inhibiting the increase of deleterious genes in the population, that is to say, counteracting the protection which civilization affords them from the rigors of natural selection; and so on.

These efforts aim at upholding rather than changing the norm of nature. They are essentially conservative. But there are more ambitious dreams abroad, summed up in the phrase that man will take charge of his own evolution, which means, not watching over the integrity of the species, but modifying it by improved designs.

This is what is properly called biological engineering and it is innovative in intent. Whether we are qualified for that creative role is the most serious question that can be posed to man finding himself suddenly in possession of such fateful powers.

Who will be the imagemakers, by what standards and on the basis of what knowledge? Also, the question of the moral right to experiment on future human beings must be asked. These and similar questions cannot be evaded before we embark on a journey into the unknown. The National Advisory Commission will have its work cut out for it.

To sum up, I think this Commission is necessary because for once we should make sure that the new powers we are acquiring shall not possess us but we possess them, and that they are employed for the benefit and not the injury of man. I sincerely hope that Senator Mondale's resolution will be adopted.

Thank you.

Senator MONDALE. Thank you very much, Dr. Jonas for your very strong statement in support of this proposal.

In your opinion, would the establishment of the proposed Commission diminish any of the ongoing public or private sector efforts in the field or would it stimulate greater interest and consideration of these vital ethical and social issues?

Dr. JONAS. Would you repeat the question?

Senator MONDALE. There was an earlier suggestion from the executive branch witness this morning, that such a Commission would inhibit local efforts and private committees and peer group efforts and would preempt the field.

Dr. JONAS. No, I don't believe so, if for no other reason than that the spontaneous interest and also worry in these matters is on the increase and there is not a surfeit of channels for that but rather a scarcity.

Also, I would anticipate that a committee of that official standing, with access to the highest level of policymaking, would rather stimulate efforts on the part of the more private or semiprivate agencies or bodies to articulate their own insights, even to increase their efforts so as to gain access to such a high synthesizing agency.

Senator MONDALE. You mentioned a point which has seemed obvious to me but which I was glad to see set out in the way that you did; namely, the timing of this matter. In many different areas it looks like we are on the threshold, or nearing the threshold, of this divide between therapeutic treatment and social applications and social manipulation, the point where behavior is designed and the length of life is determined; where we can order the characteristics of the next generation.

We are not there yet, but clearly it is in the works; new understandings which make it likely that we might arrive at that point some time in the near future, where such things are not just theory but possibilities. Is that correct, in your opinion?

Dr. JONAS. I cannot judge on how near the realization of some of these forecasts and anticipations is. The opinion of scientists is divided on that. I hear some younger biologists name a period of 5 to 10 years within which we will be able to perform human cloning. I hear other representatives of the field who say not within 50 years.

Senator MONDALE. Even to grapple with the enormity of the social consequences of this issue responsibly, a 50-year period would be a tight time frame, wouldn't it?

Dr. JONAS. Right.

Senator MONDALE. So we would be losing nothing to start right away. We could be risking a great deal if those young biologists are correct in the sense that we might set up a commission with the technology already underway and maybe be overwhelmed by it. Do you agree with that?

Dr. JONAS. Yes, definitely. I have a sense of urgency in the matter because we cannot be too early actually. We can only be too late, and generally we have had the experience of certain developments that went faster than even those that were engaged in promoting it anticipated themselves.

There came these surprising breakthroughs, and suddenly we have in our hands a whole arsenal for doing things without having previously pondered what to do with them or what is really involved in the full and unchecked employment of such powers.

I think it is none too early that we set about at least in the clarification. Incidentally, Mr. Chairman, if I may insert one note of caution here. I do not expect of such a commission, however distinguished its composition may be, that it will come up with a definite set of policy proposals, not even that it will achieve unanimity among themselves.

But I have an intrinsic faith in the power of light to spread and in the merits of clarification instead of letting things take their course.

Senator MONDALE. Very well. Thank you very much, Dr. Jonas, for your statement.

We stand in recess, subject to the call of the Chair.

At this point, I order printed all statements of those who could not attend and other pertinent material submitted for the record.

(The material referred to follows:)

## Statement Concerning S. J. Resolution 75

I would like to record my strong support for the resolution introduced by Senator Mondale and others to create a National Advisory Commission on Health Science and Society. The great advances in the sciences of physics and chemistry in the earlier part of this century have paved the way for equally great progress in the biological sciences and in our understanding of the nature of life - including human life. This progress has created the potential for change in and control of the living world comparable to the mastery we have already achieved over our physical environment.

Since the living world includes man, such potentials to influence man's biological nature must affect our entire perception of the nature of humanity and the meaning and purpose of human life. They thus affect our most profound philosophies and our most basic institutions.

Profound thought and reflection is thus warranted and indeed demanded before such potentials are unleashed and their consequences cast casually into the social vortex. The proposed commission could consider such issues - and all possible means for the effective deployment of social conscience in this field - before it is too late and the irreversible steps have been taken. There is a clear and present need for the establishment of ethical guidelines in this complex area.

I would hope that this commission could consider these problems not only in a national framework but also with regard to their international extensions - for science, like humanity, is international - and a world viewpoint must be developed (and soon) lest these great potentials be disastrously coupled to the virulent nationalism of our time.

I believe the questions as presented in Senator Mondale's introduction are urgent. And thus so is the need for this commission.

*Robert L. Sinsheimer*

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November 23, 1971

Hon. Walter F. Mondale  
Committee on Labor and Public Welfare  
United States Senate  
Washington, D. C. 20510

Dear Senator Mondale:

I am glad to support your proposal ( S. J. Res. 75) to establish a National Advisory Commission on Health Science and Society. The phenomenal progress of biology and medical science in our time raises difficult ethical issues of the utmost importance. It is, for instance, now possible to diagnose many genetic diseases by examining cells from a human fetus in its early stages, and to abort the fetus if a serious condition, such as Tay-Sachs disease, is discovered. (See for instance "Prenatal Diagnosis of Genetic Disease" by Theodore Friedmann, Scientific American, Nov. 1971, page 34). The technique requires a highly skilled operator, in order to avoid damage to the fetus. It also raises the question: how serious must the genetic or other abnormality be, to justify abortion? Indeed the whole question of abortion, and its justification, requires careful examination. Certainly I for one would consider it justifiable for a large variety of reasons, but our community standards in this matter are in a state of flux, and we must search for guiding principles of policy that would command wide assent.

At the other end of our lives, modern medicine has learned to prolong the life of vast numbers of people who would have died earlier. Often this prolongation brings only grief and misery to many old people, and their families, during their last years. Many would rather die far sooner than they do. Our ethical standards forbid mercy killings, yet the effort to prolong the patient's life is often an act of cruelty. We must face the very difficult ethical dilemmas involved; these involve the problem of insuring, if possible, that the patient dies with dignity and in association with his family and friends, not in an impersonal hospital surrounded

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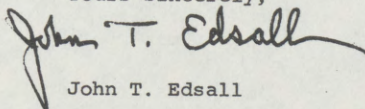
Hon. Walter F. Mondale -cont'd.

by medical machines and without people who care. There is also the difficult related problem of criteria of death, and the use of the dead person's organs for transplantation into other patients.

The cloning of human beings, which would permit the production of multiple copies of the same person, in unlimited numbers, is not yet technically feasible, although it may become so in the not very distant future. It would clearly raise extremely serious ethical issues, and it will be important to face these issues before such experiments on man become technically possible. Are we to ban certain type of experimentation, as my colleague James D. Watson has suggested might be desirable? Certainly experiments involving actual cruelty to the subject should probably be banned, although some people will and should undergo danger and suffering in experiments for sufficiently important ends. But here we must have the informed consent of the subject. What, indeed, is "informed consent"? How does it apply to the feeble minded or the mentally ill, or terminal cancer patients? Is it right that parents should give "informed consent" for experiments on their infant children? To state these problems is to reveal their complexity.

These topics do not exhaust the subject by any means, but they do illustrate the need for an authoritative commission of inquiry, such as your proposal calls for. I think it would probably be best, as the text proposes, that the commission should produce a report with recommendations, at the end of a specified interval, and then go out of existence. Such a report should clarify many important issues, for medical scientists and practitioners and for the public at large, and in doing so it could perform an immense service. However it will certainly not give what could be considered a final answer to many of the questions with which it would have to deal. These would have to remain the subject of continuing inquiry, but the level of the inquiry could be lifted to a higher plane by the analysis furnished by the Commission. It might be able to come up with what would be generally accepted as definitive answers on at least some matters. I believe that, if the commission could do this, for even a few of the questions, it would confront, it could perform a great service for the American community and indeed for other communities throughout the world.

Yours sincerely,



John T. Edsall

JTE:in

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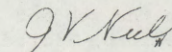
Office of Senator Mondale  
Committee on Labor and Public Welfare  
United States Senate  
Washington, D. C. 20510

Dear Senator Walter F. Mondale

I should like at this time to add my endorsement to the impending legislation to establish a National Advisory Commission on the Health Sciences and Society.

Enclosed please find a copy of a paper delivered at a Conference on Ethical Issues in Genetic Counseling and the Use of Genetic Knowledge sponsored by the Fogarty International Center and held on October 10-14, 1971. This paper is scheduled to be published as part of the proceedings of that Conference, but I understand that there would be no objection to inclusion in the record which you are building with respect to the above mentioned bill. I should think that it might be necessary to preface the paper by an explanatory sentence or two, to the effect that it was delivered in connection with this conference. While there are a number of references to events which had preceded the delivery of my paper, I do believe that it is a self-sufficient document.

Sincerely yours,

James V. Neel, M. D.  
Lee R. Dice University Professor  
of Human Genetics

JVN:gi

Enclosure

SOCIAL AND SCIENTIFIC PRIORITIES IN THE  
USE OF GENETIC KNOWLEDGE

by

James V. Neel  
Lee R. Dice University Professor of Human Genetics  
Department of Human Genetics  
University of Michigan Medical School  
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The title assigned this presentation, "Social and Scientific Priorities in the Use of Genetic Knowledge," at first glance reads innocuously enough. How do we proceed to set up priorities in the applications of the knowledge we have been discussing. But in fact, of course, what we are really discussing is the new eugenics, where I define eugenics simply as a collection of policies designed to improve the genetic well-being of our species. And I am sure the new eugenics will prove no less controversial than the old eugenics of the 1920's and 1930's. All of the value judgments and ethical issues that previously made eugenics so thorny an issue are still there, albeit with some added precision, while such recent developments as our ability to detect a variety of genetic carrier states and to engage in prenatal diagnosis have raised a number of important new social questions. In the following presentation, I shall for the most part skirt the ethical issues involved, and confine myself insofar as possible to the genetic problems.

#### CAN AND SHOULD WE ATTEMPT TO ESTABLISH PRIORITIES IN THIS FIELD?

Before we begin to consider how we might attempt to develop a rational system of priorities, we might do well to consider two antecedent questions which this Conference cannot afford to overlook. The first is, should society at this time try to develop priorities in this area? The second, assuming an affirmative answer to the first, is, can society develop priorities?

With respect to the first, I note only that many of the developments we have been discussing are so new that it is not clear we are yet ready to

set priorities. To some this will sound like the standard caveat of the paralyzed intellectual. The fact remains that we are discussing very recent developments, whose implications have yet to sink in on most of us.

With respect to the second, at this very moment the willingness of our society to assign priorities is being severely tested. While I take it that the priorities to which we are asked to direct our attention are primarily within the field of genetics, we cannot escape some concern with priorities between fields. I am sure we would agree that for the next 10-20 years, the impact of failure to apply the new genetic knowledge to human problems is far less than failure to solve such major issues as control of pollution, decay of the cities, or a sane energy policy. On the other hand, as I believe has been apparent from previous presentations, the potential of genetic knowledge for the good (or bad) of man is really very great. Furthermore, there is a symbolism about the use of genetic knowledge to influence the genetic composition of the next generation, which readily captures the public imagination. Herein lies one of our problems in setting priorities. Right now we are something of a glamour field, as witness the pages of Life, Time, and Newsweek. We do have important contributions to make to human well-being. However, we have caught the public imagination, and it's going to take a great deal of intellectual honesty and sobriety not to take advantage of this fact.

So--let the record show that before we began our discussion of the difficult issue of setting priorities in this field, we recognized that this discussion might be considered premature, presumptuous and naïve by some. Our discussion should deserve none of these adjectives as long as we recognize this as an exercise in social and scientific judgment, approached

with the necessary humility and objectivity. We will return to the "should" and the "can" of priorities after we have considered the issues involved.

WHAT ARE THE ACTIVITIES TO BE ASSIGNED PRIORITIES?

It might be well at this juncture to enumerate the sometimes inter-related developments in genetics to whose implementation we are attempting to assign priorities. We have in this Conference devoted almost all our attention to just three, namely:

1) Genetic counselling and its now logical extension, prenatal diagnosis.

To what has already been said, I would add only that our experience with counselling--which goes back to the establishment of an Heredity Clinic by the University of Michigan in 1941--is not quite so dramatic as the experiences presented here. For instance, among the last 100 cases to pass through the Heredity Clinic of the University of Michigan Hospital, 32 consulted us with the question of the likelihood of reoccurrence of a congenital malformation which had occurred in the kindred. This would include such entities as mental retardation, Down's syndrome, severe central nervous system malformation, and other entities not regularly fitting into a simple genetic pattern. The average risk of reoccurrence is around 5%, and these people will for the most part proceed to parenthood after hearing the fact. Another 43 cases involved familial occurrence of known genetic disease, both dominant and recessive. The questions raised covered a wide variety of risk situations--I imagine the mean risk of occurrence of disease in the individual of concern was 10-20%. For only two of the 43 situations which happen to be included in this particular sample (I-cell disease, galactosemia) can genetics

now offer intrauterine diagnosis in case of a pregnancy. There were 9 patients for simple karyotyping, largely possible translocation-Down's syndromes or questionable cases of Turner's syndrome, referred because of Dr. Bloom's special interest in this field (we do not routinely advise obtaining a karyotype on all patients with Down's syndrome). There were six cases involving hereditary anemia, which I put in a special category because Dr. Rucknagel's longstanding interest in this problem undoubtedly brings us a disproportionate number of referrals of this type. We had one problem of advisability of consanguineous marriage, one of racial ancestry, and seven rather miscellaneous problems. We had one patient for amniocentesis, but this is not representative of the Hospitals' involvement in this area. The most common genetic indications for amniocentesis, suspected Rh disease and pregnancy in women over 40, are not regularly referred to the Heredity Clinic; the patient contacts are handled by the Department of Obstetrics and Gynecology. However, our Department cultures the amniotic fluid obtained at amniocentesis from pregnant women over 40, and has done so 10 times in the past 6 months.

Much of our counselling, then, while certainly contributing to the understanding, acceptance, and control of genetic disease, will not produce spectacular results. You may argue that we are not putting our effort where it counts. However, in the practice of medicine one responds to the patients' perceived needs, and patients and doctors are requesting assistance with the kinds of problems just enumerated. Furthermore, it appears to me that even under the relatively favorable circumstances of highly accurate prenatal diagnosis, the impact of counselling on disease may also be modest. Consider a very simple hypothetical situation, of a replacement-type population in which everyone born survives, and marries, and each couple has two children.

Consider a recessive trait which lends itself to prenatal diagnosis. In the absence of the systematic and reliable detection of carriers, a "high-risk" sibship will be identified by the birth of an affected child. In our hypothetical population, half of all the affected children to be born will be first-born. If we monitor second pregnancies to mothers of first-born abnormal children, one-quarter will be affected, but for every one we might detect, there will be three born to mothers whose first-born child was normal. Thus, we could expect to detect prenatally (and possibly abort) 1 in 8 of such children (Neel, in press). More realistic schemes do not alter the proportions greatly (Motulsky, Fraser and Felsenstein, 1971). For prenatal diagnosis to be truly effective, we must be able to identify carriers and/or high risk marriages prior to reproduction. I believe it to be important that we ourselves make careful calculations of what prenatal diagnosis can accomplish before it is made for us by some pragmatic public health economist. On the other hand, I am sure that that economist would be well aware that the cost of maintaining an institutionalized child is approximately \$5,000 per annum, so that, were our hypothetical condition one requiring institutionalization, then quite aside from humanitarian considerations, amniocentesis for the pregnancy leading to that hypothetical second sibling of an affected child would even now be a sound procedure economically.

2) Genetic screening. Insufficient attention has been directed to the distinction between "genetic screening" for the detection of treatable hereditary disease, which is simply an exercise in responsible public health measures, and "genetic screening" to detect the carriers of deleterious genes, presumably for counselling purposes. With respect to the former, on the basis of experience with such diseases as phenylketonuria and, more recently,

galactosemia (Shih et al., 1971; Switkes, 1971; Gordon, 1971), there is already brisk debate concerning "false positives," problems in initiating treatment, cost, etc., and it is clear we are at the beginning of an involved subject. With respect to the latter, in assigning priorities to genetic programs, we must keep in mind that a screening program for carriers that does not alter the reproductive pattern of the population concerned, has failed its ostensible purpose, no matter how interesting the data collected. And at this point it is not at all clear just how anxious the people screened and found to be genetic carriers will be to alter their reproductive behavior on the basis of a finding which they presumably did not request. We badly need research on how the results of genetic screening programs can be used, but perhaps even before that, a good airing of the question of what constitutes an effective program whose benefits outweigh the costs. Furthermore, I continue to be concerned about the wisdom of programs that locate and possibly stigmatize the carriers of a few special genes, when in fact each of us is a carrier for several genes which undoubtedly do us no good and were best not transmitted to our children.

3) Genetic repair, either somatic or germinal. The repair of genetic damage has been mentioned several times at this Symposium. This is distinguished from simple substitution or replacement therapy by the concept of altering the genetic material of the individual concerned, in somatic or germinal cells. Of all the potential developments in human genetics, this is of course the one that is most provocative. Experiments on the transfer of genetic information between somatic cells are underway in a dozen cell culture laboratories. To my knowledge, no one has yet attempted to effect a genetic change in explanted somatic tissue, followed by reintroduction of

that tissue to the original donor, but this is surely to be expected within the next several decades. Conceptually, this is not too different from a renal transplant from a closely related donor to an individual with hereditary nephritis, or a marrow transplant from a sibling to a patient with lymphopenic hypogammaglobulinemia (Gatti et al., 1968). Purposive changes in human germinal tissue present very different issues, which, fortunately are much less immediate than the other issues we are discussing. So also are the issues presented by cloning, or the creation of chimeras composed of a carefully selected blend of genetically superior tissues. While if the recent scientific past is any guide, these issues will be on us sooner than we anticipate, there are in my opinion more pressing matters. I should like in the present context to point out that whatever the ethical implications, from the standpoint of setting priorities we should recognize that genetic manipulation of germinal tissue if handled legitimately will probably have substantially less impact on the human gene pool than the other developments we have just mentioned and those to which we now turn.

There are, however, four other "uses of genetic knowledge" which must be considered in any attempt to assign priorities. They have been only very briefly touched upon in our discussions thus far, so briefly I should devote a little time to each. They are--continuing our numerical sequence--4) prevention of mutation, 5) amelioration of genotype expression (euphenics), 6) "germinal choice," and 7) stabilization of the growth of the world's population, to each of which we now turn:

4) Prevention of mutation. With respect to the prevention of mutation, we have only the roughest of estimates of the contribution of the mutational process in each generation to human disease and disability. There is a

cluster of dominantly inherited abnormalities commonly used in estimates of human mutation rates (e.g., epiloia, achondroplasia, aniridia, retinoblastoma, multiple neurofibromatosis, Waardenburg's syndrome, multiple polyposis of the colon, Marfan's syndrome); their combined appearance each generation in consequence of mutation is in the neighborhood of 50 cases in each 100,000 births. These constitute the clearest case for the impact of mutation on human morbidity. In its 1956 Report, the Subcommittee on Genetics of the National Academy of Sciences' Committee on the Biological Effects of Atomic Radiation estimated that approximately 2 percent of all children born in the U.S. would prior to sexual maturity exhibit serious disease ultimately the result of mutation pressure. This estimate includes a number of diseases not so well understood as the abovementioned. In its 1962 Report, the United Nations Scientific Committee on the Effects of Atomic Radiation used a figure of 1 percent for the same phenomenon. The various entities comprising this 1-2 percent will not all increase in frequency following an increase in mutation rate as rapidly as will the subset of dominantly inherited diseases just enumerated against which there is high negative selection pressure, but they will respond in time.

The 1966 Report of the same U.N. Committee estimated that one child out of every 200 liveborn had a chromosomal abnormality responsible for gross physical or mental defect. For the most part, these abnormalities arise anew each generation, in consequence of "chromosomal mutation," in contrast to the "point mutation" thought to give rise to the types of conditions mentioned earlier.

As you all know, there has been a great deal of discussion as to whether man-made sources of radiation have increased these mutation rates; more

recently, attention has shifted to chemical mutagenesis. Without attempting to delve deeply at this time into what has become a very complicated problem in evaluation, let me say that in the context of priority-setting, it would be passing strange if while our left hand was working furiously to detect and abort genetically defective children, our right hand was condoning exposures resulting in an increase in the numbers of such children. The only excuse for such exposures is on the basis of the benefits gained; should there in fact be an increased mutation rate, very careful balancing of the over-all benefits to society from these exposures against the cost in human morbidity is called for. The monitoring of human populations for increase in mutation rates has in the past been quite unsatisfactory, but now large-scale screening for mutants at the biochemical level is possible (cf. Neel, 1971). While the mutants detected by these procedures would not be those responsible for human disease, it would appear reasonable to assume a correlation between these mutation rates and those responsible for human disease. However, again, as in previous presentations, I feel compelled to emphasize how difficult it will be to determine what particular agent in our environment might be responsible for an increase in mutation rates.

If society embarks upon a course which will result in an increase in the mutation rate, is there a coupled responsibility to the species, to decrease the transmission and manifestations of known inherited diseases, by whatever means we find ethically acceptable? This question raises the intriguing issue of the extent to which our collective gene pool is public property, which we hold in trust for the future, and the extent to which the very personalized packages into which it is subdivided precludes treating it as a public resource.

5) Amerlioration of genotype expression. I have previously referred to this as "cultural engineering," as opposed to "genetic engineering" (Neel, 1961). Lederberg (1963; see esp. 1970) has referred to it as "euphenics." This involves far more than the treatment of individuals with obvious hereditary disease. Very simply, we must recognize that we are blessed with a gene pool that evolved under very different circumstances than the present, and begin to devote much more thought than heretofore to the question of the circumstances facilitating the best expression of that gene pool. We already do this on a small scale, in the therapy of genetic disease, but the challenge is much greater. Individuals with  $\alpha_1$  anti-trypsin deficiency, determined by homozygosity for a "recessive" gene, appear to be unusually prone to death from chronic obstructive lung disease, an entity increasing at a striking rate. There is some evidence the predisposition is potentiated by air pollution and/or smoking. A very simple example of tailoring the environment to the person would be a survey which identified the susceptibles and, assuming the association is incontrovertible, made clear to these persons the consequences of smoking. Or, consider diabetes mellitus and hypertension. Familial and probably genetic factors are well implicated in the etiology of both. In some individuals predisposed to diabetes, obesity and lack of exercise undoubtedly contribute to realization of the genotype, while in persons predisposed to hypertension, the "trigger" may be excessive salt intake (e.g., Dahl and Love, 1954; 1957; Knudsen and Dahl, 1966). Ideally, the therapy of these individuals starts shortly after birth, with a program of physical activity or dietary restriction. And, since we cannot identify all the predisposed with accuracy, perhaps we encourage the total population to embark upon a regime which can only result in better health for the average person.

This is a kind of genetic counselling for populations rather than individuals. And the role of the geneticist in this area is as a member of an epidemiological team, trying to understand complex genotype-environment interactions. The examples I have cited apply only to physical disease. The opportunities with respect to the functioning of the mind are even more provocative. Galton (1892) in Hereditary Genius was one of the many who have drawn attention to the population base underlying the flowering of Greece. Between 530 and 430 B.C. the district of Attica produced 14 persons whom he would classify as illustrious, namely,

"Statesmen and Commanders--Themistocles (mother an alien), Miltiades, Aristides, Cimon (son of Miltiades), Pericles (son of Xanthippus, the victor at Mycale).

Literary and Scientific Men--Thucydides, Socrates, Xenophon, Plato.

Poets--Ashylus, Sophocles, Euripides, Aristophanes.

Sculptor--Phidias."

During that period Attica's population amounted to about 90,000 native free-born persons, 40,000 resident aliens, and a laboring and artisan population of 40,000 slaves. The abovementioned 14 persons were all drawn from the native free-born, who over a period of a century should amount to about 270,000 persons, or about 135,000 males, of whom only one-half would survive to the age of 26, and one-third to the age of 50. No matter how we criticize the sampling or the scoring process involved, or whether the estimate of population base is too low by a factor of 2, clearly here was an extraordinary flowering of genius. To Galton this was a genetic phenomenon, which somehow quickly ran its course. Aware as we now are of gene frequencies and slow rates of genetic change, surely we must see this extraordinary

manifestation of human capabilities as in whole or part the result of the creation of an unusual intellectual environment for unusually fine minds. It is sobering, how little we really know about the heredity-environment interaction in the realm of the mind--surely as knowledge becomes available in this field its application will have high priority.

Incidentally, I take it to be self evident that the principal beneficiaries of a program in euphenics would be certain minority groups; at the limit, a program in culture engineering is a program in social justice.

6) "Germinal choice."--This development was extensively discussed by the late H. J. Muller (see Muller, 1967). In its simplest form, it involves nothing more than an effort, for women for whom artificial insemination constitutes the necessary and desired avenue to parenthood, to ensure that the sperm employed be from genetically superior individuals. In its logical extension it involves a much larger fraction of the reproducing females. There would be considerable debate on the selection of genetically superior donors but otherwise, unlike some of the other developments we have been discussing the technology is at hand. As Muller recognized, this would involve a major change in societal attitudes towards parenthood, but, given the wide range of human behavior recorded by the anthropologist, such a major change is probably not impossible. Ramsey (1970) has presented cogent arguments to the effect that this development, as well as cloning, would place its practitioners outside the boundaries of the Judeo-Christian ethic, a viewpoint which a non-theologian like myself finds well buttressed. However, as a non-theologian, I find I prefer the somewhat broader statement of the issues involved in cloning, genetic surgery, etc., which is contained in Lord Kilbrandon's paper: "It is possible that the right of free men to acquire

and transmit knowledge must at some stage give place to the concept of the dignity and integrity of the human being, looked at as a fundamental requirement taking precedence of all law, learning, and ethical analyses."

With the proper selection of donors the result of artificial insemination will be better than the population average on whatever scale will be the basis for selection. However, because of genetic segregation, and because of difficulties in reproducing the environment which lead to the earlier favorable expression of the parental genotype, there will be many disappointments for parents who go this route. Here, as with other possible genetic developments, it will be important not to raise false expectations.

7) Stabilization of the gene pool. The last development to be discussed is more commonly known in other circles as population control. I take it we are in agreement that it is unwise to assume that the world's population can continue to increase at the rate prevailing during the past century, without a wide variety of problems. I take it that the geneticists here also agree that great though our concern for the individual unfortunate child tossed up by the vagaries of genetic segregation, we have an even greater concern for the corporate gene pool of our species. We simply cannot ignore the fact that any population policy--or for that matter, no population policy--may have implications more far reaching for the gene pool than all the genetic counselling of the next 100 years. Graham (in press) has recently been an especially persuasive spokesman for that viewpoint.

With no population policy, large-scale famine in certain especially susceptible areas could lead to quite specific die-offs, especially if the areas which normally respond to famile relief, struggling to feed their own swollen populations, find their corn attacked by blight and their wheat by rust. Some, of course, feel that with the present age structure of the

world's population, even with rather optimistic predictions about population control, it is already too late to avert localized famine. This might be, but surely we must make every effort to avoid or reduce such tragedy.

And if there is a population policy, what should it be? Elsewhere I have argued that anything other than a simple quantitative policy, of the same number of children for every couple, is unworkable (Neel, 1969, 1970). Broad-scale qualitative judgments are emotionally unacceptable to society; even if acceptable, we do not possess the wisdom or knowledge to make them. This argues for a policy that will have minimal qualitative or quantitative impact on the present gene pool--without arguing against some of the possible developments discussed earlier. However, this does not mean that every couple will in fact have the same number of children. Elsewhere we have pointed out that even if society set an upper limit of three children per couple, so many couples would probably have 0, 1, or 2 children that the realized mean would be close to 2 (Neel and Schull, in press).

Even such an apparently even-handed policy as this will not go unchallenged. Representatives of some of our ethnic minorities often refer to population restriction of this or any other type as "genocide." What I take to be the historical basis for this concern is shown in Table 1, taken from a United Nations publication of 1953. It is an effort to reconstruct the growth of the world's population since 1650. In 300 years the total population has increased by a factor of 5. However, let us consider the contributions of the major ethnic groups. To do so, I will commit some oversimplifications. I hope those who attack them will suggest improvements. We will equate Northern and Latin America and Oceania in 1650 with American Indians, Polynesians, and Australian aborigines. Even with a generous allowance for

hybridization, this subgene pool by 1950 had increased by a factor of perhaps 2. We will equate Africa with Negro; if one-sixth of the gene pool of the Americas were Negro in origin--a generous estimate--then the Negro gene pool has increased by the factor of 2.5. Equating Asia with Mongoloids and East Indians, this gene pool has increased by about a factor of 5. Finally, by this same reckoning, the Caucasoid pool has increased (last column) from an estimated 113 million persons to an estimated 935 million persons, a factor of 8. The role of the Caucasoids in the slow rate of increase of the American Indian, Polynesian, and Australian aborigine is a sordid and sickening record most of us prefer to forget. With respect to the historical role of Caucasoids in inhibiting the rate of growth of the Negro gene pool, there is no scarcity today of eloquent spokesmen, to whom I will leave the question.

Representatives of minority groups the world over will also point out that to the extent they suffer higher infant and childhood mortality rates, this uniform policy would be to their disadvantage. Clearly this legitimate objection must be met before we can expect to move towards any general population policy. Unfortunately, in some parts of the world the situation has already deteriorated to the extent that it will be very difficult to meet this demand while populations continue to grow at the present rate.

It is clear that the percentage composition in terms of ethnic groups of the world's gene pool today is very different from that of 300 years ago, and any stabilization of population numbers will tend to perpetuate that shift. However, with all due respect for the history involved, I see no way to turn the clock back. Moreover, simply because of the distribution of resources any failure to limit population growth now is apt to have the most dire consequences for those whose numbers have increased most slowly. I can

see no alternative but to live with history and attempt to forestall the even greater inequities which might result from failing resources unable to meet the needs of the people dependent on them.

#### WHAT ARE THE CRITERIA FOR PRIORITIES?

These, then are the seven principal present and potential genetic developments to which we might attempt to assign social and scientific priorities. What are the criterion by which we proceed? Where do we put the emphasis? Four kinds of scientific criteria present themselves, all of which of course have to be fitted into some kind of ethical framework, a framework whose definition--after the past several days--looks to be more difficult than the establishing of scientific criteria. We could judge the value of a development by the extent to which it accomplishes one or more of the following objectives:

- 1) The reduction of the proportion of persons with genetic disease, an objective with which we most readily associate genetic counselling, prenatal diagnosis, and, perhaps, genetic surgery.
- 2) The improvement of the expression of existing genotypes, by wide-ranging medical, social and nutritional measures.
- 3) The creation of genetically superior individuals, by artificial insemination (the germinal choice of Muller) or eventually, perhaps, cloning.
- 4) The protection of the present gene pool, by a world population policy which will at least ensure that as little as possible of what now exists is lost, and damage through exposure to mutagens be minimized.

These are all positive criteria. There is a fifth. It is becoming very clear that the human gene pool is much more complex and organized than seemed

to be the case 20 years ago. Man has by now adequately demonstrated his capacity to mess up complex biological systems. Our fifth criteria, then, is a negative one: a minimum of incalculable genetic and somatic risks. On this basis, for instance, I would rule out for the foreseeable future attempts at virus transduction in man--not because they are likely to have much effect on the gene pool, but simply on the philosophical grounds of so many unknown possible concomitants.

#### HOW WILL WE MAKE OUR PRIORITIES?

Thus far we have considered the real or pending developments in genetic knowledge which have practical implications for our species, and listed the kinds of criteria by which we might attempt to assign priorities to their implementation. Applying the criteria to the developments, what priorities emerge? There would undoubtedly be a very healthy diversity of opinion among us. In theory, we can consider each of the seven developments enumerated in the light of the four criteria for the evaluation of a development which I have suggested, and arrive at a judgment concerning the impact of that development on the quality of life. In fact, I doubt if we are ready for such an exercise. At the risk of sounding like a politician, I find all seven of the areas of possible applications of genetic knowledge we have enumerated to be high priority areas for investigations, and, excluding only genetic engineering, application, but immediately feel obliged to enter certain caveats. Genetic screening and genetic counselling combined with prenatal diagnosis should be available in every major medical center. The increasing interest in this area of individuals with good biochemical as well as genetic training ensures a healthy growth of the field, given reasonable financial encouragement. However, we must not oversell its actual impact on disease.

Firstly, as I pointed out earlier, much of the activity of a Counselling Service, even when it has a tangible impact on reproduction, is not directed towards high risk situations. Secondly, even when the situation permits of decisive intervention, the numerical impact on disease will be rather modest, short of large-scale detection of carriers and programs of moral suasion of carriers more extreme than the world seems ready for. Not only are there relatively few diseases with good biochemical or chromosomal handles, but even these present problems in ascertainment.

However, while genetic counselling with all its ramifications has made tremendous progress in this country, and is now attracting an adequate number of properly trained persons, I do not feel that some of the other areas which I enumerated are so well cared for. Let me be more specific. Firstly, the developments concerning the mutagenic effects of radiation and chemicals of the past 40 years make it clear there may have been an increase in human mutation rates. While I personally doubt that mutation rates have greatly increased, the subject has attracted widespread comment. Some type of monitoring is indicated. Utilization of the knowledge gained from an appropriate monitoring program will be admittedly difficult--given an increase, how do we identify and remove the offending agent--but this seems no reason to shrink from the necessary studies.

Secondly, population control represents an important area of application of genetic knowledge. Matsunaga's (1966) systematic enumeration of the probable genetic consequences of population control include a lowered frequency of Down's syndrome; a lower frequency of those congenital defects (exclusive of those due to chromosomal abnormalities) which contribute to the J-shaped curve relating maternal age to congenital defect; less disease due to

maternal-foetal incompatibility, such as erythroblastosis foetalis; and a relative decline in consanguineous marriage. Beyond this, it appears that some kinds of dominant, presumably point mutations (achondroplasia, Marfan's syndrome) may be more common in the children of older parents (refs. in Neel, 1969; Murdoch, Walker and McKusick, in press). However, if, with population control, the average age at reproduction decreases, so will the interval between generations, and some of the potential impact of population control will be lost. There must be some age at reproduction which is optimal both in terms of normality of child and low rate of population growth--say 25 to 30--and if society is ready to accept some of the developments we have been considering, it should be ready to plan not only the number of children but parental age at time of childbirth. This problem needs more attention.

Finally, and lastly, I return to a favorite theme of mine. Although with the diversity of human genotypes it is unlikely that any one environment could be best for the expression of all, there must be some environment which represents the best compromise for the most people, and in which the average person would do stunningly better than he does now. I use the term environment very broadly, to include diet, place of living, circumstances of school, conditions of working, and absence of minority groups because of full citizenship for all. The geneticist above all others is trained to analyze the heredity-environment interaction. Our new knowledge is sufficient to reveal the potentiality for reducing the unfavorable expression of genetic predispositions by this approach, but only a start has been made on accumulating the necessary detailed data. I would urge that one application of our new genetic knowledge, with high priority, should be in this area. And at this point, I take a stand in strong opposition to that developed at this meeting by my good friend Robert Sinsheimer,

concerning the imminence and inevitability of attempts at genetic engineering. I find it incredibly presumptuous to talk of improving genetic man when our knowledge of the potentialities of our present genotype is so limited. We do not begin to know what we are now capable of. Any program of genetic engineering will be carried on in a constantly changing environment which makes evaluation of the results of any genetic manipulation, other than the creation of monsters, impossible. If there is any absolute morality in science, it is that you do not undertake an important experiment whose results you cannot evaluate. In this case, the object of the experiment is the single most precious possession man has--the double stranded helix which against all odds, makes us human. Paul Ramsey (1970) has coined a most appropriate sentence in this context: "Men ought not to play God before they have learned to be men, and after they have learned to be men they will not play God." We're not losing our nerve, Bob--we're just realizing how complex the situation really is.

#### CONCLUDING REMARKS

These remarks have undoubtedly ranged further than the planners of this Symposium anticipated. In my opinion, a narrower treatment, which followed the obvious course of urging, for example, that high priority be given to establishing for each 200,000 persons a counselling center, with provision for prenatal diagnosis, would have been a mistake. This is a worthy and defensible objective, and it would provide a clean and simple goal on which a campaign or plea for funds could be based, but as I see it, given not only the avalanche of new genetic knowledge but the critical times in which our species finds itself, we geneticists have broader responsibilities to society.

Before we can assign priorities, we must have a clear view of where our special brand of knowledge can be effective. This brings us back to a thought raised at the opening of this presentation: are we ready to make priorities? I doubt that we are. What we have been considering is all so new and of such potential significance that we should proceed on all those fronts where compelling scientific and humanitarian arguments can be brought to bear. The actual costs involved, compared with expenditures in other areas, are a pittance in relation to the ultimate possibilities.

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Table I. Estimates of World Population by Regions, 1650-1950, (United Nations, 1953)

Series of Estimates and Date	Estimated Population in Millions						Area of European settlements <sup>g</sup>
	World Total	Africa	Northern America <sup>d</sup>	Latin America <sup>e</sup>	Asia (exc. U.S.S.R.) <sup>f</sup>	Europe and Asiatic U.S.S.R. <sup>f</sup>	
<b>Willcox's estimates:<sup>a</sup></b>							
1650	470	100	1	7	257	103	113
1750	694	100	1	10	437	144	157
1800	919	100	6	23	595	193	224
1850	1,091	100	26	33	656	274	335
1900	1,571	141	81	63	857	423	573
<b>Carr-Saunders' estimates:<sup>b</sup></b>							
1650	545	100	1	12	327	103	118
1750	728	95	1	11	475	144	158
1800	906	90	6	19	597	192	219
1850	1,171	95	26	33	741	274	335
1900	1,608	120	81	63	915	423	573
<b>United Nations estimates:<sup>c</sup></b>							
1920	1,834	136	115	92	997	485	701
1930	2,008	155	134	110	1,069	530	784
1940	2,216	177	144	132	1,173	579	866
1950	2,406	199	166	162	1,272	594	935

<sup>a</sup> Willcox, *Studies in...* (1940), p. 45. Estimates for America have been divided between northern America and Latin America by means of detailed figures presented *ibid.*, pp. 37-44.

<sup>b</sup> Carr-Saunders, *World Population* (1936), p. 42.

<sup>c</sup> United Nations, *Demographic Yearbook 1949-50* (1950), p. 10; and United Nations, "The past and future growth of world population..." (1951), Table II; the 1940 figures are unpublished estimates of the United Nations.

<sup>d</sup> United States, Canada, Alaska, St. Pierre and Miquelon.

<sup>e</sup> Central and South America and Caribbean Islands.

<sup>f</sup> Estimates for Asia and Europe in Willcox's and Carr-Saunders' series have been adjusted so as to include the population of the Asiatic U.S.S.R. with that of Europe, rather than Asia. For this purpose, the following approximate estimates of the population of the Asiatic U.S.S.R. were used: 1650, 3 million; 1750, 4 million; 1800, 5 million; 1850, 8 million; 1900, 22 million.

<sup>g</sup> includes northern America, Latin America, Europe and the Asiatic U.S.S.R., and Oceania.

[From the Congressional Record, Mar. 24, 1971]

## SENATE

By Mr. MONDALE (for himself) and Mr. BAYH, Mr. BROOKE, Mr. CASE, Mr. FONG, Mr. HARRIS, Mr. HART, Mr. HUGHES, Mr. HUMPHREY, Mr. JAVITS, Mr. KENNEDY, Mr. MCGEE, Mr. MCGOVERN, Mr. MOSS, Mr. NELSON, Mr. PELL, Mr. RANDOLPH, and Mr. SCHWEIKER):

S.J. Res. 75. A joint resolution to provide for a study and evaluation of the ethical, social, and legal implications of advances in biomedical research and technology. Referred to the Committee on Labor and Public Welfare.

## HEALTH SCIENCE AND SOCIETY

Mr. MONDALE. Mr. President, I introduce for myself and Senators BAYH, BROOKE, CASE, FONG, HARRIS, HART, HUGHES, HUMPHREY, JAVITS, KENNEDY, MCGEE, MCGOVERN, MOSS, NELSON, PELL, RANDOLPH, and SCHWEIKER for appropriate reference a joint resolution to create a National Advisory Commission on Health Science and Society.

Recent advances in biology and medicine make it increasingly clear that we are rapidly acquiring greater powers to modify and perhaps control the capacities and activities of men by direct intervention into and manipulation of their bodies and minds. Certain means are already in use or at hand—for example, organ transplantation, prenatal diagnosis of genetic defects, electrical stimulation of the brain. Others await the solution of relatively minor technical problems, while still others depend upon further basic research. All of these developments raise profound and difficult questions of theory and practice, for individuals and for society.

To consider and study the ethical, social, and legal implications of advances in biomedical science and technology, I propose in this measure the creation of a 15-member commission on Health Science and Society. This commission would also report on the public policy implications of its findings in interim reports and in a final report at the end of its 2-year study.

Mr. President, 3 years ago I introduced a joint resolution which was essentially the same as the one I am introducing today. At that time, heart transplants were a startling new medical breakthrough. Since then, several hundred heart transplants have been performed. When I reintroduced the resolution in the last Congress, the first successful test-tube fertilization of a human egg had just been reported. Now, just 2 months ago, Nobel Prize winner Dr. James D. Watson told the House Committee on Science and Astronautics that we will soon see the day when a baby will be conceived in a test tube and placed in a woman who will bear the child. As you may recall, Dr. Watson's reported prediction was that when such an implantation is successfully made, "All hell will break loose."

These brief comments indicate that the need for a sober and thoughtful analysis and evaluation of biomedical advance is even more urgent now than it was 3 years ago when I first proposed this commission.

The past 3 years have seen great advances in genetics. There have been major increases in the ability to detect genetic diseases, even in fetuses still unborn. By examining fetal cells present in fluid obtained from the wombs of pregnant women, diagnosis of diseases such as Mongolism are now being made. As treatment for most genetic diseases is not now available, the diagnosis is generally followed by abortion of the affected fetus.

But major steps have been taken toward developing a technology of genetic engineering which might eventually be able to provide a cure for diseases such as hemophilia, cystic fibrosis, or diabetes. Single bacterial genes have been recently obtained in pure form, both by isolation from biological material and by chemical synthesis from simple building blocks. And just 2 weeks ago, the Washington Post reported that British scientists had artificially corrected a genetic defect in mouse cells by inserting some healthy genetic material from chick embryos.

But these welcome prospects are accompanied by others which are frankly disturbing. In other areas of genetic research, work has progressed which may soon make possible the asexual production of large numbers of identical humans, by a technique known as cloning. Work is also in progress to make possible the predetermination of the sex of unborn children.

Research into the nervous system and behavior proceeds at an accelerated pace. The use of amphetamines on school children to treat the so-called "hyperactive syndrome," recently the subject of public concern and controversy, is only

a foretaste of things to come as the science of psychopharmacology becomes more sophisticated. New drugs offer possibilities both for novel therapies and for novel abuses. There has also been increasing experimentation with electrical stimulation and with selective destruction of certain areas of the human brain, in order to achieve desired behavioral changes.

In the area of clinical medicine, there has been considerable effort to resolve existing confusion concerning the definition of clinical death. This confusion is due to the fact that, thanks to medical progress, the traditional signs of life—heartbeat and respiration—can now be maintained almost entirely by machines. Since many human matters depend upon the distinction between a man alive and a man dead, the importance of resolving this dilemma cannot be overemphasized.

There is great ferment now in cancer research, and we may be nearing the day when men may live out their lives without fear of this dread disease. And while on the subject of longevity, we should not neglect the claims of some scientists that the time is now ripe for an attack on the biological processes of aging. If this attack is successful, the result could be many added years of healthy life for all.

While holding forth the promise of continued improvements in medicine's abilities to cure disease and alleviate suffering, these developments also pose profound questions and troublesome problems. There are questions about who shall benefit from and who shall pay for the use of new technologies. Shall a person be denied life simply because he does not have enough money for an organ transplant?

There will be questions about the use and abuse of power. When and under what circumstances can organs be removed for transplanting? Who should decide how long a person is to be kept alive by the use of a machine? Exactly what constitutes informed consent for a prospective transplant donor or recipient? The extent to which the consent is informed and voluntary may very well depend not only on what is said, but how it is said.

There will be questions about our duties to future generations and about the limits on what we can and cannot do to the unborn. Is it ethical for a man and wife, each carrying a gene for serious hereditary disease, to procreate, knowing that their children have a significant chance of acquiring the disease? Should the law enjoin certain marriages or require sterilization for such eugenic consideration? What rights do unborn children have to protect them in experiments involving genetic engineering or test tube fertilization? In a letter to the *Washington Post*, Dr. Leon Kass, executive secretary of the Committee on the Life Sciences and Social Policy of the National Research Council, warned:

"One must not forget that there is a human being (the child-to-be) upon whom these experiments are to be performed and who may suffer for our zeal and ignorance, an ignorance no more excusable because well-meaning."

We shall face questions concerning the desirable limits of the voluntary manipulations of our own bodies and minds. Some have expressed concern over the possible dehumanizing consequences of increasing the laboratory control over human procreation or of the increasing use and abuse of drugs which alter states of consciousness.

We shall face questions about the impact of biomedical technology on our social institutions. What will be the effect of genetic manipulation of laboratory-based reproduction on the human family? If laboratory fertilization can produce children for sterile couples, what will be the consequences for those orphaned or abandoned children who might otherwise have been adopted by these couples? What will be the effect on the generation gap of any further increases in longevity?

We shall face serious questions of law and legal institutions. What will the predicted new-fangled modes of reproduction do to the laws of paternity and inheritance? What would happen to the concept of legal responsibility if certain genetic diseases were shown to predispose to antisocial or criminal behavior? What would be done to those individuals with such traits?

We should expect that some people will try to have certain particularly frightening technologies banned by statute. Should this be done? Could such prohibition be effective?

Finally, we as legislators will face problems of public policy. We shall need to be informed of coming developments, of the promises they hold forth and the problems they present, and of public attitudes in these matters. We shall need to decide what avenues of research hold out the most promise for human progress. And we shall need to help devise the means for preventing undesirable consequences.

Mr. President, as serious and as vexing as these practical questions may be, there is yet another matter perhaps more profound. The biomedical technologies work directly on man's biological nature, including those aspects long regarded most distinctively human. Thus, we should expect major challenges to our traditional image of man as this technology unfolds. The impact on our ideas of free will, birth, and death, and the good life is likely to be even more staggering than any actual manipulation performed with the new technologies. These are matters of great moment, and we urgently need to take counsel from some of our best minds. I trust that the Congress will recognize this need by establishing this commission.

The questions raised require the competence of persons with different training and background. Accordingly, I propose that the commission include individuals drawn from the fields of medicine, law, theology, biological science, physical science, social science, philosophy, humanities, health administration, Government, and public affairs. The physician and the philosopher, the scientist and the theologian need to get together and to educate each other. We have much to gain from their collective learning. The commission I propose will provide the vehicle for this much needed exchange.

There is also a need for improved communication between laymen and scientists. The layman needs to learn more about the prospects and implications of expected developments. The scientist needs to acquire a broader understanding of the possible ramifications of his work and the concerns of the people it will affect. The Commission I propose will provide a vehicle for such communication.

Mr. President, we can ill afford to wait until the crush of events forces us to make hasty and often ill-considered decisions. We cannot again allow events to pass us by. We face an increasing number of new and far-reaching technological possibilities, touching the very nature of man. We face the need for some wise, deliberate, and sober decisions. These questions are not going to go away or answer themselves. They will become progressively more difficult as time goes on. As Dr. Watson said in his testimony:

"If we do not think about the matter now, the possibility of our having a free choice will one day suddenly be gone."

It would be foolish to expect the Commission to provide answers to all the questions we face, but we can expect that it will provide help in making some of our difficult decisions. The findings and considered judgments of excellent minds with a wide range of experience and training will be invaluable to individuals who must struggle with the awesome responsibility of coping with these new technologies.

We make no prejudgments. We do not call for controls. We ask only for a thorough and thoughtful consideration of every aspect of these complex, difficult, and profound questions and problems. I and the Senators who join with me in sponsoring this resolution sincerely hope that Congress will act with dispatch in creating this much needed Commission.

Mr. President, I ask unanimous consent that the text of the joint resolution, together with a number of articles, letters and statements bearing on these profound problems, be printed in the Record.

(There being no objection, the joint resolution and material were ordered to be printed in the Record, as follows:)

(The text of the bill appears on p. 3 of this hearing volume.)

[From the New York Times, Sept. 15, 1970]

#### CHIMP'S BRAIN SIGNALS ITSELF BY COMPUTER

(By Robert Reinhold)

NEW HAVEN, Sept. 14.—Direct two-way radio communication between an animal's brain and a computer has been established for the first time by a team of scientists at Yale University. It was used to enable the brain to control artificially one of its own functions.

In an experiment, electrodes implanted in a chimpanzee's brain picked up electrical brain waves, which were then transmitted to a computer by a small receiver-transmitter atop the animal's head.

The computer, programmed to recognize special characteristics of the wave, returned a control signal to another part of the brain through the receiver.

Stimulated by the control signal, the latter part of the brain internally turned off the brain activity originally sensed by the computer.

While the exchange is of the most rudimentary sort, the feat is said by the Yale team to suggest promising new ways of treating mental and physical disorders in human beings. Moreover, it raises the prospect of establishing direct electronic communication from one brain to another.

The head of the team is Dr. José M. R. Delgado, a 55-year-old Spanish-born neurophysiologist at the School of Medicine. Dr. Delgado, a pioneer in this field, has attracted both attention and controversy in the past for his experiments inducing anger, fear, affection, pleasure and other emotions in animals and human beings by telemetry stimulation of specific regions of the brain.

The new work represents the first time that a two-way radio network has been devised, in which the brain itself determines the outside signals it receives without using the senses as intermediaries to convey information to the brain.

"We are now talking to the brain without the participation of the senses," said Dr. Delgado in an interview at his laboratory. "This is a pure and direct communication—I call it 'nonsensory communication.'"

Dr. Delgado said he expected to use the new technique on human beings within a year. One possible application is in the treatment of epileptics.

Theoretically, the computer could recognize the pattern of brain waves associated with the onset of a fit and trigger the inhibitory areas of the brain or inject a chemical.

To simulate natural conditions, Paddy was placed on an artificial island in the company of three other chimpanzees at the 6571st Aeromedical Research Laboratory at Holloman Air Force Base in New Mexico.

Dr. Delgado's work was supported by the Air Force until recently, when it was decided that it had no direct military application. Congress recently forbade the armed forces from supporting nonmilitary research.

The transmitting and receiving equipment was mounted nearby, and Paddy's brain and motor activity were monitored 24 hours a day. The experiments hinged on the pattern of electrical activity in a small almond-shaped structure in the brain called the amygdala.

#### WAVE PATTERNS OF BRAIN

The amygdalâ spontaneously produces electrical wave patterns with a characteristic shape called spindles at the rate of about 1,000 an hour. Spindles are thought to be linked to olfactory, or smelling, functions and are one of the easiest patterns to recognize.

The spindles were converted by the stimo-Receiver into FM radio signals and fed into a Donner Analog computer. The computer was programed to recognize the spindles and to produce another signal for the duration of each spindle.

This signal was then converted into another FM radio wave and transmitted back to the animal, where it was picked up by the stimoceiver. The stimoceiver then triggered an impulse to the reticular formation, an area in the brain stem connected with arousal.

Thus the information received by the reticular formation was directly contingent on the pattern of electrical activity in a distant area, the amygdala.

The results showed that each impulse to the reticular formation inhibited electrical activity in the amygdala. After two hours of such feedback—that is, a signal is modified by its own deviation—the rate of spindling was cut to about half of normal. It disappeared almost completely after several days.

At the same time, behavior changed. The return impulses caused a slight grimace. Paddy became less aggressive and excitable, and lost much interest in food. After the computer was disconnected, these changes persisted for two weeks, after which behavior and spindling rate returned to normal.

#### ONLY ONE ANIMAL USED

The experiment was done on one animal only, but repeated successfully several times over a year and a half. The animal has suffered no apparent ill effects from the electrodes.

Collaborating with Dr. Delgado were Dr. Victor S. Johnston, Dr. Jan D. Wallace and Dr. Ronald J. Bradley.

The experiment, Dr. Delgado said, demonstrates the feasibility of artificial feedback between two cerebral structures and "on-demand" stimulation of the central nervous system.

According to Dr. Delgado, all of this has important implications for research and medicine. Various conditions, including multiple sclerosis, Parkinson's disease, anxiety, fear, obsessions, violent behavior, could conceivably be controlled by direct stimulation of the brain, which ultimately underlies all mental and physical activity.

Dr. Delgado has also experimented with imparting sight and hearing to blind and deaf persons through direct stimulation of specific areas of the brain.

A number of researchers, including Dr. Delgado, have permanently implanted electrodes in human beings. One of the leaders in this field is Dr. Robert Heath at Tulane University in New Orleans. Dr. Heath has been using the technique to correlate brain activity with behavior and to treat explosive and depressed patients.

#### NEW INSTRUMENTS NEEDED

To make such treatment practical, Dr. Delgado believes it will be necessary to develop radio instruments that can be completely buried under the skin. An experimental model of such a device is being tested in monkeys at his laboratory, but application is some years off.

The doctor recognized that the philosophical implications of this kind of work are as great as the medical. However, he says that brain stimulation should be treated much like other biological interventions we have become accustomed to—innoculations, tranquilizers, fluoride treatment of water, food additives.

He believes brain research can provide a window to the understanding of personality and social behavior—not to manipulate but to improve.

Technology, he says, has neglected man. So little is known of what goes on in the brain, he says, that "we are not civilized in human behavior."

In his recent book, "Physical Control of the Mind," Dr. Delgado wrote:

"We are now on the verge of a process of mental liberation and self-domination that continues our evolution. Its experimental approach is based on the investigation of the depth of the brain in behaving subjects.

"It's practical applications do not rely on direct cerebral manipulations but on the integration of neurophysiological and psychological principles leading to a more intelligent education.

"We must create a future man with greater personal freedom and originality—a member of a psychocivilized society, happier, less destructive and better balanced than present man."

[From the Washington Post, June 3, 1970]

#### SCIENTISTS CREATE FIRST GENE IN A TEST TUBE

U. OF WISCONSIN TEAM'S FEAT MAY LEAD TO CONTROL OF LIFE

(By Victor Cohn)

The first synthesis of a gene, the basic unit of heredity, was announced yesterday as the result of a momentous five-year effort at the University of Wisconsin.

The historic feat hastens the day of genetic engineering: mastery by man of the very control chemistry of life. It was accomplished by a team headed by Dr. H. Gobind Khorana.

Nobel-prize-winning geneticist Joshua Lederberg at Stanford University called the achievement a "milestone" and one that came "two years earlier than I expected."

On some future day, scientists may manufacture genes or parts of genes to order, and use them to cure or prevent diseases, or even change personality.

Some scientists even foresee—or fear—future production of "tailor-made" human beings as the result of such engineering.

Others call this unlikely. There is sure to be wide agreement however, that the shy, 47-year-old Khorana—a native of India who won the Nobel prize for several earlier steps in 1968—has probably opened an epoch.

In their Madison, Wis., laboratory, Khorana and his colleagues duplicated the structure of one of nature's simpler genes: one found in yeast RNA (for ribonucleic acid). Specifically, they synthesized an alanine transfer-RNA gene, one

that orders production of the RNA that carries some of the essential genetic information in yeast cells.

"Now that he has determined the rules" for chemical synthesis, "theoretically any desired gene could be made in the test tube," said a University of Wisconsin announcement that Khorana approved.

What Khorana did in more detail in his test tubes was to put a set of chemical building blocks called nucleotides into the sequence in which they occur in the natural yeast gene.

The Wisconsin group has yet to perform one ultimate—but hard—experiment checking the new gene for biological activity by introducing it into a living cell lacking this gene to transform the cell into a normal one.

Many other experiments are ahead. Khorana would like to know how the genes act more precisely in protein synthesis. He wants to know what chemical signals turn the gene on and off in a living cell. To do such things, he plans to modify specific parts of the synthetic molecule and observe the effects.

He has already started work on synthesizing a second gene—a transfer-RNA found in the bacteria *E. coli* and optimistically now expects to complete this work within a few months.

What Khorana and company have produced then is not a molecule to make better yeast—that would be a minor goal—but a methodology to assemble other genes and investigate the chemical structure of life.

Khorana shared the 1968 Nobel prize in medicine with Drs. Robert Holley (now at the Salk Institute) and Marshall Nirenberg of the National Institutes of Health at Bethesda. He talked to a few reporters yesterday but declined to hold a news conference.

"He expressly does not want a news conference; he wants to talk to scientists," a colleague said.

He plans to move with his team in the fall to Massachusetts Institute of Technology. Born in Raipur, India, he came to Wisconsin in 1960 as professor of biochemistry.

His efforts, he said when he received the Nobel prize might eventually lead to "manipulating biology" to cure cancer, diabetes or physical effects. Or "in the long distance future," he said, "the knowledge might allow for genetic planning of individuals—tailoring people to fit patterns, turning out athletes or intellectuals."

That, he insisted, is "a very, very long time off." But "in that context," he conceded, "we are in a very elementary but a necessary stage."

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[From the Washington Post, Mar. 12, 1971]

#### GENE IMPLANT SEEN STEP TO CELL CONTROL

(By Victor Cohn)

A long step toward genetic engineering—artificially correcting defects in human cells—has been taken at Oxford University.

Dr. Henry Harris and other scientists there have inserted into a deficient mouse cell some healthy genetic material from chick embryos, thus correcting the mouse cell deficiency.

The new genes remained part of the permanent cell machinery, moreover, and were duplicated as the now healthy cells grew and divided.

This has been done entirely in what biologists call "tissue culture": collection of cells in the laboratory. The next step will be to try to repeat the process in mice.

But, says the British journal *Nature* in an accompanying comment, "removing cells with some genetic defect from a (human) patient, treating them to introduce a new gene or genes "and replacing the cured cells in the patient" is now "possible in principle."

There are many equally long or longer steps ahead. Genetic engineering, *Nature* emphasized, is not "imminent." Yet "it is important to say," the eminent journal noted, that "these experiments offer the exciting prospect, in theory at any rate, of evolving a therapy" for mutant and defective human genes.

A vital part of the accomplishment was this: Only pieces of chick chromosome material (chromosomes are little rods which contain genes) were transferred.

## GENETIC ENGINEERING CURES DEFICIENCY IN A MOUSE CELL

These were too small to carry the chemical instructions for manufacturing antigens. This means they did not arouse antibodies—proteins which normally fight off all foreign tissue in the host.

It is this achievement (Nature calls it "most elegant") which raises the most hope that this kind of human cell therapy will one day be possible.

In their full scientific account, the British group—A. G. Schwartz, P. R. Cook and Harris, all of the Sir William Dunn School of Pathology at Oxford—tell how they:

Used an inactivated mouse virus as a kind of silent partner to carry the chick embryo material.

Thus incorporated small amounts of pulverized genes from chick red blood cells into a line of mouse cells unable to produce the enzyme IAP. This same deficiency in humans causes a rare and fatal hereditary disease, Lesch Nyhan syndrome.

Found that most of the hybrid cells thus produced still failed to make IAP and therefore died. But some survived because they now possessed the IAP that the chick genes coded. The chick genes were only loosely integrated in the mouse cell, yet integrated well enough to work this cure.

Is the chick-mouse synthesis a special case, or can the same thing be done in creatures? Nature asked the question and—in what seems to be advance notice of further laboratory progress—added: "It seems already that comparable cells derived from (other) organisms . . . can develop in a similar genetic transfer."

In the late 1940s, a National Cancer Institute scientist pointed out here, Dr. John Enders of Harvard got chick cells to grow polio virus by adding a carrier virus to get the polio virus inside them—after which they too accepted the polio virus's instructions.

Virus DNA (a genetic chemical) has been successfully introduced into cells in many other experiments.

What Harris and company have achieved, the scientist here explained, is an engineering advance: introducing a whole piece of chromosome that may have "hundreds and hundreds" of genes rather than the five or 10 of a small virus.

The Schwartz-Cook-Harris article in Nature was highly modest in wording. But its brief heading summed up their coup: "Correction of a Genetic Defect in a Mammalian Cell."

[From the Washington Post, Dec. 26, 1970]

BETHESDA, MD.,  
December 21, 1970.

## HUMAN REPRODUCTION

## LETTER TO THE EDITOR:

The report by Stuart Auerbach ("Lab Grows Embryo Ready for Womb," December 17, 1970) of the current success in the laboratory culture of human embryos and the anticipated success in implanting these embryos in prospective mothers prompts numerous moral and political questions. I wish to address but a few of these.

The article reports that the scientists are ready to proceed with implantation if tests on the embryos can rule out the presence of genetic defects. One should question whether the limited tests for defects now available can declare these embryos "genetically fit." Further, manipulation of the embryos to conduct such tests may itself introduce damages, some probably not detectable until after birth. One must not forget that there is a human being (the child-to-be) upon whom these experiments are to be performed and who may suffer for our zeal and ignorance, an ignorance no more excusable because well-meaning.

But one may go further and ask whether safety, even if adequately measured, would be a sufficient warrant for going ahead. Surely, there is more at issue than providing a child for an infertile woman. Once introduced for that purpose, the technique can be used for any purpose. Indeed, the work described is a giant step toward the full laboratory control of human reproduction. What are the implications of it is step, and of the others it makes possible, for the humanness of human procreation or for the human family? What are the implications of establishing as a precedent the passing of genetic tests as a prerequisite for a title to be born? Should not the weighing of ethical considerations concerning

the widespread use of the new technology enter into the decision to use it for the first time.

These ethical questions point to a political question. Laboratory control of fertilization and embryonic development is a major departure in human procreation whose human consequences, both private and public, are likely to be profound. It is no mere ordinary medical advance. Therefore, one must question the wisdom of leaving the decision to go ahead for the private judgment of a team of physicians and scientists (whose judgment I am not now questioning), or even for the collective judgment of the medical and scientific community. Is this not a decision which deserves full public deliberation and resolution?

We are all too often forced to cope belatedly with the untoward consequences of technological advance, consequences unanticipated because the primary goal was thought to be so obviously good, or because the decision to go ahead was made technocratically and without public deliberation. Let us not make the same blunders with respect to the awesome powers, now gathering, for manipulating the bodies and minds of men.

Sincerely,

LEON R. KASS, M.D.

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[From the Hospital Tribune, May 4, 1970]

#### DEFINITION OF DEATH: A DOUBLE STANDARD

(By Eliot Corday, M.D.)

Is the medical profession setting up a double standard of death? Can the transplant surgeon be charged with homicide or body robbing? Will new definitions of death cause a domino effect which dislocates relationship between everyday medical, legal, and clerical practices?

Farfetched as this may sound, there is the possibility that such questions may arise in the public mind—because exaggeration is sometimes a common currency in public discussion—unless the medical profession refines its definition of death. Already, in view of the known resuscitative methods and life-support systems that may revive a patient from apparent death, the public has begun to question the criteria by which a live heart is removed from a dead donor. And ultimately, we must have the support of the public.<sup>1</sup>

As matters stand now—in what Samuel Johnson called “the fury of innovation”—we are in danger of antagonizing the public by appearing to be moving toward a double standard. One standard would be to accommodate the transplanters—certifying that death has occurred when there are no reflexes and the EEG trace is linear—in other words, cerebral death. The other standard for the everyday practice of medicine would be to continue to accept the age-old definition of death as the irreversible cessation of perceptible heart beat and respiration. And today this may have to imply that cardiac resuscitation, assuming it was available, had been attempted and failed—a question that has come up in at least one court case.

If we adopted such a double standard in our everyday practice, will the public begin to fear that we are moving toward euthanasia?

Two lawyers, Houts and Hunts, recently wrote that as long as any heartbeat or respiration can be perceived, either with or without mechanical aids, death has not occurred. Obviously, this would preclude successful heart transplantation.

Also, obviously, we cannot maintain a double standard of death. It would dent public confidence in medicine and prevent transplantations. So it is around this irritant that some pearl of wisdom must be formed. Among the perplexities we need to look at are: (1) the financial trauma to a patient's family if we were obliged to keep him alive by mechanical means when there is no possibility of recovery; (2) a new concept to provide a single standard of death to avert the possibility, however remote, of a charge of homicide or wrongful action against a transplantor—and if not wrongful action, the accusation or samurai-like conduct. In feudal Japan a samurai warrior could test his sword against any passing peasant.

<sup>1</sup> From the American Bar Association Journal, vol. 55, pp. 629–632, July, 1969.

On the first point, there is no such legal requirement in this country. And in 1957, Pope Pius XII, while speaking out against euthanasia, also declared that there is a clear distinction between negative life and superior life with all the vital functions; the artificial prolongation of life, he said, is not "obligatory, particularly if it created too heavy a charge on the family." So it must be taken as a medical axion, legally and theologically, that the physician should not be obliged in every situation to use extraordinary life-prolonging procedures after it has been clearly established that there is no hope for the patient's recovery.

On the second point, an ad hoc committee of Harvard University has proposed criteria of irreversible coma: when respiration is maintained only by artificial means and this is withdrawn, spontaneous respiration would be impossible; a total unawareness of externally applied stimuli; no spontaneous muscle movement; no reflexes; a flat EEG. These have been generally accepted as a basis for the diagnosis of cerebral death to permit organ removal. Some transplant surgeons, however, have declared cerebral death while spontaneous respiration was still present.

Also in 1968, similar criteria were issued by 24 surgeons, immunologists, neurologists, and heart specialists called together in Geneva by the Council for International Organizations of Medical Sciences operating under the World Health Organization and UNESCO. They added two further guidelines: (1) the donor's heart must be in perfect condition at the time of removal; (2) an immunological examination should be made before the operation to determine the compatibility of donor and receiver. The scientists decided also that two independent teams should be deployed in heart transplant operations, one to establish the donor's hopeless condition, the other to perform the operation.

The Harvard criteria provide sound guidelines for the discontinuation of extraordinary life-prolonging procedures. But these and the Geneva guidelines still need to be ratified by the medical profession, the legal authorities, and the public. Otherwise we face the possible accusation that the concept of cerebral death is designed to meet the special interests of the transplanters; and we face the public's apprehension that this concept is a preface to euthanasia. We face, in short, an ethical crisis.

To avert this crisis, we need to determine whether there is adequate evidence that the moment of death may now be advanced to coincide with brain death, through cardio-respiratory activity is spontaneous. It would seem advisable to convene a Bethesda-type conference to try to arrive at this determination. Lawyers, clergymen, sociologists, perhaps even philosophers and cultural anthropologists should also be invited. The medical delegates, of course, would be the only ones to formulate scientific criteria. Any change requires careful study because it could start a chain reaction that might dislocate many relationships and standards of the everyday practice of medicine. But the advice of other professions may provide us with legal and historic precedent and with subtle moral guides to keep us from stumbling into some ethical or legal pothole.

Such a high-level conference would also give us the support that would increase the likelihood that our medical judgment, should we be able to arrive at one, will be accepted by the public. Certainly the public would be heartened by the fact that we have called upon other minds to share our moral responsibility and scrutinize our decisions.

Equally as important, we may harvest from such a meeting a new wisdom to accompany us should ethical problems arise from future scientific innovations.

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EXCERPTS FROM POTENTIAL CONSEQUENCES OF EXPERIMENTATION WITH HUMAN EGGS, A STATEMENT PRESENTED TO THE HOUSE COMMITTEE ON SCIENCE AND ASTRONAUTICS, JAN., 1971

(By J. D. Watson)

The Biological Laboratories Harvard University, Cambridge, Mass., and The Cold Spring Harbor Laboratory, Cold Spring Harbor, New York; Presented Before the Twelfth Meeting of the Panel on Science and Technology Committee on Science and Astronautics, U.S. House of Representatives, January 28, 1971.

Several years ago a most remarkable frog grew up in Oxford. Its origin did not lay in the union of a haploid sperm cell with a haploid egg, the fertilization process which ordinarily gives each higher animal a mixture of paternal and maternal genes. Instead this frog arose from an enucleated egg, into which had been inserted a diploid nucleus from the intestinal cell of an adult frog. Microsurgical removal of the maternal nucleus from this egg had denuded it of

any genetic material. But by subsequently gaining a diploid nucleus (as opposed to the haploid form found in a sperm) the egg acquired the chromosome number normally present in a fertilized egg. As such it could be activated to divide, thereby setting into motion the successive embryological stages which culminate in an adult frog.

The genetic origin of this frog was thus very different from that of all previous frogs, one half of whose chromosomes came from the male parent through the sperm, the other half from the female parent which produced the egg. Normal fertilization processes by combining genetic material from two different parents always generate progeny uniquely different from either parent. In contrast the Oxford frog derived *all* its genetic material from the individual whose intestinal cell was used as the nuclear donor. The genetic complement of all its diploid somatic cells (as opposed to its aploid sex cells) was thus identical to that in the donor frog. So, in effect, it was an identical twin of the donor frog born some months before. Furthermore, since every adult frog contains millions of cells capable of being used as nuclear sources, the original donor could have served as the genetic parent of thousands of progeny identical to itself.

This type of reproduction is generally referred to as a *clonal* reproduction.

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The question of course arises, will this same basic principle hold for the large majority of differentiated cells? Now I suspect most biologists will guess yes. In general, very fundamental phenomena, of which differentiation is one, do not have a difference molecular basis from one organism to another. Moreover, it is already clear that differentiation in several plant species does not involve irreversible nuclear changes. Now it is routinely possible to produce mature plants starting from highly specialized somatic cells of diploid chromosome number. For example, mature carrot plants can be produced from single callus cells that are placed in proper nutritional environments. Thus it is highly likely that the embryological development of most higher animals, including man, involves the creation of countless numbers of totipotent somatic nuclei each capable of serving as the complete genetic material for a new organism. This means that, *theoretically*, all forms of higher animal life may in effect be capable of clonal reproduction.

If true, this situation could have very startling consequences as to the nature of human life, a fact soon appreciated by many magazine editors, one who commissioned a cover with multiple copies of Ringo Starr, another who gave us overblown multiple likenesses of the current sex goddess Raquel Welch. It takes little imagination to perceive that different people will have highly different fantasies, perhaps with some imagining the existence of countless people with the features of Picasso or Frank Sinatra or Walt Frazier or Doris Day. And would monarchs like the Shah of Iran, knowing they might never be able to have a normal male heir, consider the possibility of having a son whose genetic constitution would be identical to their own?

Clearly even more bizarre possibilities can be thought of, and so we might have expected that many biologists, particularly those whose work impinges upon this possibility, would seriously ponder its implications, and begin a dialogue which would educate the world's citizens and offer suggestions which our legislative bodies might consider in framing national science policies. On the whole, however, this is not at all what has happened. Though a number of scientific papers devoted to the problem of genetic engineering have casually mentioned that clonal reproduction may someday be with us, the discussions to which I am party, have been so vague and devoid of meaningful time estimates as to be virtually soporific.

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The general impression exists among biologists that the cloning of any mammal will be far from a routine task, if not impossible, over the foreseeable future. In particular, the techniques of micromanipulation used to insert nuclei into frog's eggs cannot now be applied to eggs in the mammalian size range. They are likely to be irreversibly damaged by the introduction of a nucleus whose diameter is only some two or three times less than that of the egg itself. And if somehow a trick were ever found to successfully insert a diploid nucleus, the equally challenging task of finding conditions for the in-vitro growth of the modified egg through to the adult stage would still lie ahead. Thus the clonal production of human beings has seemed to most geneticists an event so unlikely as to not be worth stirring up public attention.

This assessment would be correct if the pace of research on human reproductive biology would continue at the current rate. With a few exceptions, work on the early developmental processes in man has not been seriously pushed either here in the United States or elsewhere. As a result, there exists a scientific lacuna so serious that it deeply disturbs those people who realistically worry about over-population problems. They believe that more basic biological knowledge about human reproductive processes would be very helpful in slowing down the fearful rise in the number of human beings. Consequently, already there is much "population" money available to induce more people to move into the field of reproductive biology, hopefully to learn in great detail the step-by-step processes by which a human egg is ovulated, fertilized, cleaved, and moves down the oviduct to implant on the uterine wall.

A key ingredient to obtaining this information is the development of methods by which the early embryological stages of mammals can be studied in-vitro. For as long as study is restricted to work on intact animals, experimental work, as to be distinguished from observational analysis will be virtually impossible. Most importantly, though unknown even to most biologists, the beginnings of first rate research on the in-vitro cultivation of mammalian eggs has already occurred. Techniques are in fact available for the isolation of mouse eggs, their fertilization in-vitro, and subsequent cultivation under test-tube conditions which permit growth to the sixty-four cell stage. At this point the embryonic body (called a blastocyst) can be surgically implanted back into the uterus of a living mouse, where it can eventually develop to the stage at which normal birth occurs.

This means that most of the techniques that will be needed for a clonal mouse are already available. The only serious obstacles remaining are the development of methods for the removal of the haploid maternal nucleus and the subsequent addition of a diploid adult nucleus. Now there are hints that the enucleation problem will not be serious. For some years it has been known that addition of the mitotic poison colchicine to preovulatory mice leads to abnormal meiotic divisions which frequently produce nuclear-free eggs. Moreover, very recent work suggests that colchicine in-vitro acts similarly. When it is added to unfertilized eggs which have been surgically removed from a living mouse, healthy enucleated eggs are produced.

And furthermore it looks like the nuclear insertion process might not be anywhere as tricky as first thought. This change of opinion is the result of the development of very simple methods for fusing two cells to yield a single cell containing the genetic compounds of both donor cells. Though the existence of rare examples of cell fusion was first clearly demonstrated in Paris by Barski in 1962, not until 1966 did Henry Harris and John Watkins working in the Pathology Department of Oxford University develop a routine method for easily fusing almost any two desired cells. Their contribution was the introduction of ultraviolet light-killed Sendai virus (a close relative of the common flu viruses). In some way not yet understood, absorption of large numbers of Sendai particles so modifies cell surfaces that when two so-treated cells touch each other, portions of the opposing cell surfaces effectively dissolve, thereby creating one much larger cell containing two nuclei. Subsequently these nuclei often coalesce yielding a single nucleus containing all the chromosomes present in both original nuclei.

During the past three years, Christopher Graham, also at Oxford, has been using Sendai virus to fuse mouse eggs with diploid adult mouse cells. The resulting cells still retain the essential features of an egg because even the relatively small mouse eggs are much larger than most diploid adult cells. While the fused eggs can divide several times, they so far has not yet developed into blastocysts, the stage necessary for successful implantation into the mouse uterus. Conceivably this limitation results from the need to remove the zona pellucida (a normal protective covering) for the Sendai virus fusing trick. Conditions must thus be found either to fuse eggs which retain the zona pellucida or which permit unprotected denuded eggs to develop normally to blastocyst. A reasonable guess is that Graham will succeed, if not this year, most likely within this coming decade. The clonal mammal then will no longer be science fiction.

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At first consideration, it would seem likely that cloning of many domestic species would have to occur before serious thought would be given to the development of clinical procedures which would make human cloning more than a theoretical possibility. This way of thinking presupposes that the primary purpose for such methodological development need be cloning itself. If this in

fact were the objective, the variety of moral and legal objections that would be bound to crop up most certainly would effectively prevent the legal granting of the medical facilities needed for extensive in-vitro experiments with human eggs.

If, however, the stated objective is to probe the human reproductive process so that better contraceptive methods can be obtained, the reaction of the general public will be much harder to predict. Though many people will look with horror at any test-tube work with human eggs, others will breathe more easily that something is being done to prevent the world from being crushed by over-population. Until several years ago, this latter group was numerically relatively small and without favor in virtually any political circle. Today, however, taboos which would have seemed unbreakable just a decade ago are rapidly being overturned, witness the recent action of the United States Congress in overwhelmingly passing legislation that would promote family planning. Even more significant was the action of New York State in making abortions the right of any women who so desire them.

Moreover, the development of a simple method for the predetermination of the sex of unborn children might generate considerable support, even if the methods involved the selective abortion of the not-wanted sex. At the same time I would foresee violent objections from other quarters, conceivably making the introduction of such sex-determining techniques illegal throughout much of the world. On the other hand, I would be surprised if all countries reacted unanimously. Most likely there would exist some countries where such sex-determining abortions were legal. If so, affluent families already having four sons could with absolute certainty have the pleasure of knowing that their last baby would be a girl.

The prognosis thus seems virtually inevitable that for one reason or another the number of people studying all aspects of human embryogenesis will greatly increase. Not only will the amount of classical observational analysis increase, but even more important, direct experimentation with human eggs most likely will soon be the main preoccupation of a number of intelligent, highly-qualified biologists.

Already there exists one such individual, R. C. Edwards, an English reproductive biologist now working in the Physiology Department of Cambridge University. Originally trained as an embryologist and with some ten years experience in growing mouse embryos in-vitro, he focuses his attention on the test-tube growth of human eggs.

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Edwards, together with his clinical colleagues, P. C. Steptoe of Oldham General Hospital, have devised a simple surgical method for the removal of healthy human eggs after they have completed much of meiosis, but before the ovulation step which releases free eggs from their follicles into the oviduct. Called laparoscopy, it is a relatively minor operation which, while requiring general anesthesia, generally only needs a twenty-four hour hospital stay. Prior to the operation, a regimen of hormone (gonadotrophins) treatment is given to induce follicle maturation and egg development through the early stages of meiosis. Laparoscopy is then performed, some four hours before ovulation would occur normally. The ovaries so exposed usually contain highly enlarged follicles with thinning walls, through which the desired oocytes can be carefully removed. Their procedures have now reached the state where they can obtain healthy eggs from over half the follicles examined.

Such pre-ovulating oocytes are very suitable for subsequent embryological investigations. Fertilization rapidly ensues after human sperm addition, and in contrast to those eggs which had undergone meiotic divisions in-vitro, these in-vivo matured eggs generally begin normal cleavage divisions. Already many embryos have developed into the eight-cell stage while a few have become blastocysts, the stage where successful implantation into a human uterus should not be too difficult to achieve. In fact, Edwards and Steptoe hope to accomplish implantation and subsequent growth into a normal baby within this coming year.

The question naturally arises why should any women willingly submit to such operations. There is clearly some danger involved every time Steptoe operates. Nonetheless, he and Edwards believe that the risks involved are more than counterbalanced by the fact that their research may develop methods which make their patients able to bear children. All their patients, though having normal menstrual cycles, are infertile conceivably because many have blocked oviducts which prevent passage of their eggs into the uterus. If so, in-vitro growth of their eggs up to the blastocyst stage may circumvent their infertility, thereby allowing

normal childbirth. Moreover, since the sex of a blastocyst is easily determined by chromosomal analysis, such women would have the possibility of deciding whether to give birth to a boy or a girl.

Clearly, if Edwards and Steptoe succeed, their success will be followed up in many other places. The number of such infertile women, while small on a relative percentage basis, is likely to be large on an absolute basis. Conceivably within the United States there could be 100,000 or so women who would like a similar chance to have their own babies. At the same time we must anticipate strong if not hysterical, reactions from many quarters. The certainty that the ready availability of this medical technique will open up the possibility of hiring out unrelated women to carry a given baby to term is bound to outrage many people. For there is absolutely no reason why the blastocyst need be implanted in the same woman from which the pre-ovulatory eggs were obtained. So, many women with anatomical complications which prohibit successful childbearing, would be strongly tempted to find a suitable surrogate. And it is easy to imagine that many women who just don't want the discomforts of pregnancy would also seek this very different form of motherhood. And of even greater concern would be the potentialities for misuse by a savage totalitarian government.

Some very hard decisions may soon be upon us. For it is not obvious that the vague potential of abhorrent misuse should weigh more strongly than the unhappiness which thousands of married couples feel when they are unable to have their own children. Different societies are likely to view the matter differently and it would be surprising if all come to the same conclusion. We must, therefore, assume that techniques for the in-vitro manipulation of human eggs are likely to be general medical practice, capable of routine performance through the world within some ten to twenty years.

The situation would then be ripe for extensive efforts, either legal or illegal, at human cloning. No reason, of course, dictates that such experiments need occur. Most of the medical people capable of such experimentation would probably totally stay clear of any step which in any way looked like its real purpose was to clone. But it would be shortsighted to believe everyone will instinctively recoil from such purposes. Some people may very sincerely believe the world desperately needs many copies of the really exceptional people if we are to fight our way out of the ever increasing computer mediated complexity that makes our individual brains so frequently inadequate.

Moreover, given the widespread development of the safe clinical procedures for handling human eggs, cloning experiments would not be prohibitively expensive. They need not be restricted to the super powers—medium sized, if not minor countries, all now possess the resources needed for eventual success. There furthermore need not exist the coercion of a totalitarian state to provide the surrogate mothers. There already are such widespread divergences as to the sacredness of the act of human reproduction that the boring meaninglessness of the lives of many women would be sufficient course for their willingness to participate in such experimentation, be it legal or illegal. Thus, if the matter proceeds in its current nondirected fashion, a human being—born of clonal reproduction—most likely will appear on the earth within the next twenty to fifty years, and conceivably even sooner, if some nation actively promotes the venture.

The first reaction of most people to these conclusions may be one of despair. The nature of the bond between parents and their children, much less everyone's values about their individual uniqueness, could be changed beyond recognition, and by a science which they never understood but which until recently appeared to provide more good than harm. Certainly to many, our most sensible course of action would be to de-emphasize all those forms of research which would circumvent the normal sexual reproductive processes. If this step were taken, experiments on cell fusion would no longer be supported by federal funds or tax-exempt organizations. Prohibition of such research would most certainly put off the day when diploid nuclei can satisfactorily be inserted into enucleated human eggs. Even more crucial would be to take steps quickly to make illegal, or reaffirm the illegality of, any experimental work with human embryos. With both these actions taken, our current value systems might survive somewhat longer.

Neither of these prohibitions, however, is likely to take place. In the first place, the cell fusion technique now offers one of the best avenues for understanding the genetic basis of cancer. Today all over the world, cancer cells are being fused with normal cells to pinpoint these specific chromosomes responsible for given forms of cancer. In addition, fusion techniques are the basis of many genetic efforts to unravel the biochemistry of diseases like cystic fibrosis or

multiple sclerosis. Any attempts now to stop such work using the argument that cloning represents a greater threat than a disease like cancer is likely to be considered irresponsible by virtually anyone able to understand the matter.

Though more people would initially go along with a prohibition of work on human embryos, many may have a change of heart when they ponder the real mess confronting us by the population explosion. The current projections are so horrendous that responsible people are likely to consider the need for more basic embryological facts much more relevant to our self-interest than the not-very-immediate threat of a few clonal men existing some decades ahead. So, scientists like Edwards are likely to get the go-ahead signal even if, almost perversely, the immediate consequences of their research may be the production of even more babies.

Complicating any possible effort at effective legislative guidance is the multiplicity of places where work like Edwards' could occur, thereby making most unlikely the possibility that such manipulations would have the same legal (or illegal) status throughout the world. We must assume that if Edwards and Steptoe produce a really workable method for restoring fertility, large numbers of women will search out those places where it is legal (or possible), just as now they search out places where abortions can be easily obtained.

Thus, all nations formulating policies to handle the implication of in-vitro human embryo experimentation must realize that the problem is essentially an international one. Even if one or more countries stop such research, their action could effectively be neutralized by the response of a neighboring country. This most disconcerting impotence even holds for the United States. If our congressional representatives, upon learning where the matter now stands, decided they wanted none of it and passed very strict laws against human embryo experimentation, their action would not set back seriously the current scientific and medical momentum which brings us close to the possibility of surrogate mothers, if not human clonal reproduction. This is because the relevant experiments are not being done in the United States, but largely in England. This is partly a matter of chance, but also a consequence of the advanced state of English cell biology. In certain areas it is far more adventurous and imaginative than its American counterpart. Now there is no American university with the strength in experimental embryology that Oxford possesses.

We must not assume, however, that today the important decisions lie only before the British government. Very soon we must anticipate that a number of biologists and clinicians of other countries, sensing the potential excitement, will move into the area and so even if the current English effort were stifled, similar experimentation could soon begin elsewhere. Thus it appears to me most desirable that as many people as possible be informed about the possible new ways of human reproduction and their potential consequences, both good and bad. Conceivably an international consciousness might be apparent and some form of international agreements might be negotiated before the cat is totally out of the bag. Admittedly, the vast effort, needed for even the most limited international arrangement, will deter those who believe the matter now is of such marginal importance that in effect it might be a red herring designed to take our minds off our callous attitudes toward war, poverty, and racial prejudice. But if we do not think about the matter now, the possibility of our having a free choice will one day suddenly be gone.

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[From the Washington Post, Feb. 4, 1971]

#### DNA AND THE SORCERER'S APPRENTICE

Man has come to be where he is in part because—at least until Hiroshima—he has considered anything that seemed possible by way of scientific discovery and technological capability to be *ipso facto* desirable. Lately, however, an increasing number of scientists has become increasingly worried that man, like the Sorcerer's Apprentice, may be unable to control the forces he keeps unleashing—that progress in science and technology is coming far faster and more easily than progress in our ability to deal with the social, political and moral implications of our discoveries.

One such worrier is Dr. James D. Watson, the Nobel-prize-winning co-discoverer of the structure of DNA, the heredity molecule and the author of "The Double Helix," a book that gave thousands of laymen a fascinating and human glimpse of these awesome scientific endeavors. Dr. Watson told the House Science Subcommittee a few days ago that any day now British scientists may produce a human embryo that can be placed inside a woman who will bear the child. "Then all hell will break loose," he said. For the next logical step will be to engineer biologically a human being by screening out "undesirable" characteristics and otherwise manipulating the female egg cells and male sperm cells before they are joined.

Scientists can see much obvious good resulting from these experiments. One might be an understanding of the genetic basis for cancer and other diseases. But Dr. Watson and others also have no difficulty imagining fearful abuse, not the least of which would be a drastic change in the nature of the bond between parents and their children and in the values we now attach to man's individuality. And worse. The "scientific" experiments in Hitler's concentration camps—the biological engineering for other than research purposes—are still too fresh on many minds to dismiss as mere nightmares. There is enough of what George Orwell called "double-think" even in our own, open society, to make it at least feasible that, once test-tube production of an unlimited number of duplicate embryos becomes possible (Dr. Watson deems this likely in 20 or 50 or perhaps five years) someone will set out to produce a master race or supermen.

Dr. Watson and a number of his colleagues, at any rate, fear that if we do not think about these matters now, "the possibility of our having a free choice will some day suddenly be gone." He suggested that the United States take the lead in forming an international commission to make this kind of biological engineering illegal.

*Illegal?* At first thought, a good many people will surely feel that this could only dangerously tempt another Sorcerer's Apprentice to invoke governmental control over some other quest for knowledge; international control, furthermore, seems a naive hope at best. So we share these first tentative thoughts. But we also urge second thoughts. And third and fourth ones, because the issue is incredibly complex, and therefore much too important to be allowed to become polarized between wishful thinkers and "realistic," first-thought-only thinkers. It is going to take broad, as well as hard, thinking, by which we mean, if you will pardon the cliché, that the application of these bio-medical developments is far too serious a matter to be left to the bio-medical scientists alone. This is why Dr. Jonas Salk is inviting philosophers as well as physical scientists to his Institute in La Jolla and why the Committee on Life Sciences and Social Policy of the National Research Council and the Institute of Society, Ethics and Life Science seek to draw lawyers and scientists in a variety of disciplines into their search for a middle ground between statutory limitations on certain research and pragmatic laissez-faire.

We desperately need this search. And to spur it along, we need broad discussion on the ever more urgent question of whether we dare continue to let material progress be our only guide.

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[From the Washington Post, Feb. 24, 1971]

#### EXPERIMENTS ON HUMANS

In your most thoughtful editorial of Feb. 4, you discuss many of the matters which I talked about recently before the House Science and Astronautics Committee. The International Commission on Genetic Engineering that I proposed be set up, however, would not have as its purpose the outlawing of human embryo experimentation. Instead its task would be to assess the state of the art, and so be in a position to advise the world's governing bodies of the particular consequences of any given technique in genetic engineering.

Some governments, upon thoughtful consideration, might wish to ban certain manipulations (e.g. human cloning). But in other cases, there may be general agreement that certain producers (e.g. test-tube conceptions to overcome infertility due to oviduct blockage) are in the national interest and should be actively promoted. In any case, I think the matter is much too important to be left in the hands of the scientists whose careers might be made by the achieving of a given experiment. In no case should we forget that the products of these experiments will be human beings, which we must afford the same opportunities for a meaningful life that are now given to children born of "God's" will.

J. D. WATSON,

*Professor, Molecular Biology, Harvard University; Director, Cold Spring Harbor Laboratory,*  
CAMBRIDGE.

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[From the New York Times, July 3, 1970]

#### RX FOR CHILD'S LEARNING MALADY

(By Robert Reinhold)

PROVIDENCE, R.I., July 2.—A few months ago Jackie D., a 6-year-old boy with big brown eyes, was so bad that his mother was at her wits' end.

He could not sit still, he fought with all the other children on the block, was so clumsy that he could not ride a bicycle, had trouble reading and got so frustrated with his first-grade arithmetic that he would tear up his lessons.

But today, Jackie was not his usual self. He deftly climbed up and down a ladder and did somersaults under the approving eyes of Dr. Eric Denhoff, a pediatric neurologist.

In fact, Jackie has not been himself for sometime now—ever since he started getting an amphetamine-like medicine called Ritacin a few months ago. Now he is quite, coordinated and has even done well enough in his lessons to be promoted to second grade.

Jackie is one of countless thousands of American youngsters with normal or even high intelligence who get Ritacin or amphetamines. The aim is to counter a complex and little-understood learning and behavior disorder sometimes called "minimal brain dysfunction" that afflicts as many as three million children.

#### GROWING ACCEPTANCE

The treatment is a widely accepted and growing one—if still somewhat controversial. It has been used throughout the United States for 10 or 15 years, often yielding results that one expert called "black magic when it works."

The change it induces, often within hours, is described by doctors, parents and teachers as "remarkable" or "amazing."

But amid mounting concern with pill-popping, many medical and laymen have expressed worry over the potential long-term effects of amphetamines, which are widely abused. Moreover, one side effect is loss of appetite, which is particularly undesirable in disadvantaged children who may be undernourished to begin with.

The practice has sporadically generated public dispute. A number of physicians and laymen have expressed fears about long-term effects. In Omaha black

parents were recently reported to have protested that their children were being drugged into submission.

According to the best estimates, from 5 to 20 per cent of American children suffer from this disorder, making it a problem of epidemic proportions.

Such children, usually boys, are all too evident in almost every classroom. They jump up and down, throw paper airplanes at the teacher, fight and shove on the lunch line, can concentrate for only a short time, frustrate easily and often do so poorly in school work that they eventually drop out despite good intelligence.

Very frequently this "hyperkinetic" behavior is linked to marked perceptual impairment; that is, visual and auditory signals are not assimilated properly. The child may read words and letters backward, a problem sometimes called dyslexia, or confuse the meaning of sounds.

This neurological disorder, possibly a result of subtle brain damage during or soon after birth, has been found in many but not all cases to respond dramatically to amphetamines, drugs that are normally used, and sometimes abused, to speed up bodily processes.

But for reasons that are not fully clear these stimulants have the paradoxical effect of calming hyperactive pre-puberty children, allowing them to concentrate for normal periods of time.

The drugs do have some side effects—largely loss of appetite and insomnia. Also, there have been reports of children swapping their pills in the school yard with unfortunate effects.

The most commonly used medications are Ritalin, made by CIBA, and Dexedrine and Benzedrine, made by Smith Kline and French.

"These drugs had been called the penicillin of children with learning disabilities," said Dr. Denhoff, director of the Meeting Street School, an Easter Seal-supported school for handicapped children here. Over the last 2 years, he has maintained 3,000 or so hyperkinetic children on drugs, often with spectacular results.

In fact, it was only a few miles from where Dr. Denhoff was examining Jackie D. that the value of amphetamines was discovered in 1937 quite accidentally by Dr. Charles Bradley, then director of the Bradley Hospital in East Providence, R.I.

Dr. Bradley noticed that drugs he had been giving to control weight problems in disturbed children also seemed to improve their behavior.

#### SYMPTOMS MASKED

The treatment, which may last for many years, can be likened to the use of insulin for diabetics. That is, it does not cure the underlying neurological disorder, but it masks the symptoms enough to allow the child to become organized, to cope with his environment and to respond to special therapy that is often needed in addition to the medication.

The treatment is not used for children with learning or behavior problems. It is connected with mental retardation, emotional disturbance or psychosis.

The dose varies, but is usually around 30 milligrams a day, about the same that an adult taking amphetamines to lose weight would get, but considerably less than hippies shooting "speed." A 10 milligram tablet of Ritalin costs about 10 cents, so that a week's treatment runs about \$2.

Various studies have shown that young children do not become addicted or develop tolerance for the drugs—and that the medication can be readily withdrawn after puberty, when minimal brain dysfunction often remits spontaneously.

While physicians have been using the drugs empirically for 30 years, there have been few controlled scientific studies. One of the first to start such studies was Dr. Leon Eisenberg, chief of psychiatric services at the Massachusetts General Hospital in Boston, and his associate, Dr. C. Keith Conners, a psychologist.

#### DRUGS HELD VERY SAFE

"When used properly, they are remarkably safe—even safer than penicillin," said Dr. Eisenberg, who has tested about 750 children.

Referring to fears that children were being doped up, he said:

"The basic confusion is to apply standards which were developed in adults to children without recognizing the very marked difference in response to his agent."

He and Dr. Conners have just completed an experiment in which 75 children were broken up into three groups. Twenty-five were given Ritalin, 25 Dexedrine

and 25 a placebo with no medicine. Each child was given a wide battery of intelligence and perception tests before and after medication.

#### SURVEY OPTIMISTIC

The experiment was "double blind", meaning that neither the children, parents nor testers knew which children were getting the drugs. The results showed "extremely strong" beneficial effects of the stimulants on a variety of cognitive, perceptual, attentional and learning tasks, including the so-called Draw-a-man test in which the child is asked to draw a human figure.

Similar results were obtained recently by Dr. Denhoff and Dr. Anthony Davids, a professor of psychology at Brown University, in a study of 42 children at the Governor Center School in Providence. However, Dr. Davids believes much more study is needed before he can say conclusively that the drugs aided learning.

In a survey of studies conducted through 1967, Dr. J. Gordon Millichap and Dr. Glenn W. Fowler of Northwestern University found that 83 per cent of 337 children given Ritalin by various scientists had shown improvement while only 1 per cent got worse from the drug. Undesirable side effects were reported in 14 per cent of the cases.

As for the amphetamines (benedrine and dexedrine), improvement was found in 69 percent of 610 cases and a worsening in 11 per cent.

In an attempt to measure the long-term effects, Dr. Eisenberg's group recently followed up on 100 children given drugs by Dr. Bradley in the nineteen thirties and nineteen forties. No indication of addiction or other drug-induced emotional or psychological damage was found.

Dr. William S. Langford, director of the pediatric language disorder clinic at Columbia's College of Physicians and Surgeons in New York, has been using the amphetamines since 1938 and Ritalin more recently.

"I don't think it's a learning pill," he said of Ritalin, "but our impression is that it is a safe drug—it keeps kids in school." Dr. Langford said that he had one child on it from age 3 to 13, the boy went on to complete college successfully.

The achievement has probably gained its greatest foothold in California. There, Dr. Sidney Adler, of Anaheim, a consultant to eight school districts in Orange County, has 2,000 children including 200 college students, on various drugs.

"I have saved many many kids from going down the drain," Dr. Adler said.

As elsewhere, school systems in California do not prescribe the drug. This is done by private physicians, often after a teacher or school nurse suggests that the parents seek medical help.

The chemical effects of the drugs are not clear. One theory holds that children with the disorder have immature nervous systems and that the stimulants affect certain immature parts of the brain, allowing the child to use his cortex, which controls logic and reasoning.

A number of pediatric authorities believe that some doctors have used the drugs too readily and have urged caution.

"No doctor should use any of these drugs lightly," said Dr. Robert Cook, of Johns Hopkins Medical School. "The whole drug culture of our society is a worry, but in appropriately selected patients it may be as effective as insulin in diabetes."

[From the Washington Post, Sept. 30, 1970]

#### FDA WARNS AGAINST USES OF "BEHAVIOR" AMPHETAMINES

(By Robert C. Maynard)

Federal Food and Drug Administration officials have warned physicians in Omaha, Neb., against the use of two drugs that had been commonly prescribed there for the "behavior modification" of schoolchildren.

The revelation was among several that emerged in a long day of testimony in Congress yesterday on the use of amphetamine-type drugs to curb the behavior of "hyperactive" children.

Minutes after the FDA warning was introduced to the Right to Privacy Inquiry of the House Government Operations Committee, a Little Rock, Ark., physician testified that once the drugs was among those used in his behavior modification program.

"That's one of the great concerns about the use of these drugs," said Rep. Cornelius Gallagher (D.-N.J.), chairman of the inquiry. "You are using drugs that FDA says are dangerous and you didn't even know the drugs were

dangerous. We should suspend the use of these drugs for this purpose until more is known."

His remarks were addressed to Dr. John E. Peters of Little Rock, who said he uses one of the drugs, Tofranil, for children with learning disabilities.

Neither Tofranil nor the other drug, Aventyl, should be used in children, and the FDA said it "now specifically warns against such use." The agency advised Dr. Byron B. Oberst of Omaha of this in a letter on Aug. 6. Dr. Oberst had been quoted in an article earlier in *The Washington Post* as saying that Tofranil and Aventyl were among several drugs he prescribed for modifying the behavior of children. The most common drug is Ritalin.

The FDA in its letter to Dr. Oberst emphasized that Tofranil's labeling specifically warns against its use in children. Its side effects include constipation, difficulty in focusing the eyes, precipitation of glaucoma, nausea, vomiting and mild symptoms of Parkinsonism among others.

Aventyl, the agency reminded Dr. Oberst, had been re-labeled to warn against its use in the treatment of children. Its known side effects include fall of blood pressure, tremors and bleeding into organs.

The FDA said in its letter that if Dr. Oberst wished to use these drugs in children, it would constitute an experiment and he would have to apply for a special permit.

Dr. Peters, head of the division of child and adolescent psychiatry at the University of Arkansas Medical Center, said he would suspend the use of Tofranil "until this is cleared up."

The discovery that the FDA had warned a doctor against the use of Tofranil in children came late in the day's testimony and after representatives of the agency had testified.

Dr. Dorothy Dobbs, the agency's director of the Division of Neuro-Pharmacological Drug Products, was asked whether she had investigated the use of drugs for behavior modification in Omaha. She said she had telephoned Dr. Oberst and determined that nothing irregular was taking place.

Dr. Oberst is one of several physicians in Omaha involved in a program for children with behavior and learning disabilities. Many of the children had been placed on amphetamines.

It was well after the testimony of Dr. Dobbs and several other FDA witnesses that the existence of the letter from the agency's legislative liaison, M. J. Ryan, was introduced by Theodore J. Johnson, a black chemist and Omaha resident. The letter had been addressed to Ernie Chambers, an opponent of the drug treatment approach to hyperactive children and an Omaha candidate for the Nebraska legislature.

"I am very disturbed," Gallagher said after Johnson introduced the FDA's letter. He charged that the agency had said that "everything is hunky dory" about using amphetamine-type drugs in children, only for the committee to discover later that two common drugs in such treatment are declared dangerous for children.

FDA officials could not be reached last night for comment, but Gallagher said before the hearing recessed that the agency would be recalled later.

Sally R. Williams, president of the Department of School Nurses of the National Education Association, was among those witnesses who said she felt stimulant drugs were safe if given to children under careful conditions.

But Gallagher hammered away throughout the day's testimony at the fact that amphetamines, commonly known as "speed," are a major cause of drug abuse in the United States.

The FDA witnesses had said there was no evidence of a link between drug abuse and the administration of such drugs to children.

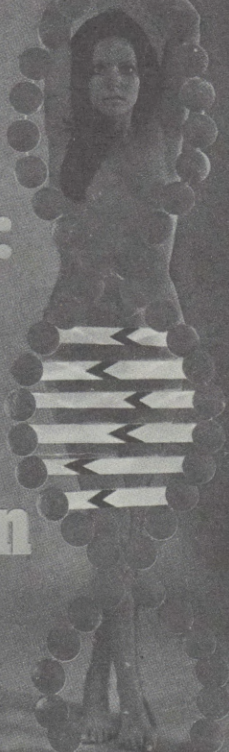
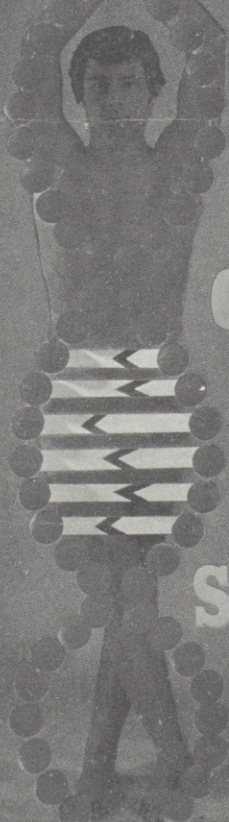
Don Warner, retired assistant superintendent of schools in Omaha, said he was concerned that the national attention had made it appear that the school system was dispensing drugs. He said only private physicians prescribe the drugs.

**SPECIAL SECTION**

# TIME

**The  
New  
Genetics:**

**Man  
Into  
Superman**



# MAN INTO SUPERMAN

## The Promise and Peril of the New Genetics

*Reshaping life! People who can say that have never understood a thing about life—they have never felt its breath, its heartbeat—however much they have seen or done. They look on it as a lump of raw material that needs to be processed by them, to be ennobled by their touch. But life is never a material, a substance to be molded. If you want to know, life is the principle of self-renewal, it is constantly renewing and remaking and changing and transfiguring itself.*

—Doctor Zhivago by Boris Pasternak

Perhaps it was simply a matter of chance, a random throw of the molecular dice. Perhaps some greater, transcendent force was at work in the earth's primeval seas. Yet from the moment of its miraculous genesis three billion years ago, life has been continually renewing and remaking itself, an evolutionary process that has led to the appearance of a unique creature quite unlike any of those before him. Thinking, feeling, striving, man is what Pierre Teilhard de Chardin called "the ascending arrow of the great biological synthesis."

Now, only some 35,000 years after the birth of modern man—a brief interval on the evolutionary time scale—the arrow is pointing in a dramatic new direction. Not only has man begun to unlock the most fundamental life processes, but he may soon be able to manipulate and alter them—curing such killer diseases as cancer, correcting the genetic defects that account for perhaps 50% of all human ailments, lessening the ravages of old age, expanding the prowess of his mind and body. Says Caltech's Robert Sinshemer, one of the architects of the biological revolution: "For the first time in all time, a living creature understands its origin and can undertake to design its future."

To an extent, man has already altered himself and his planet. Scientists can only guess at the genetic toll from radioactive fallout, chemical contamination and other assaults on the environment. Even man's noblest impulses are apt to offend against nature. While improved medical care assures the survival and reproduction of those with genetically caused mental and physical

defects, it also ensures that an increasingly larger percentage of the population will be heir to these illnesses in years to come. Geneticist Theodosius Dobzhansky succinctly expresses the ethical dilemma. "If we enable the weak

and the deformed to live and to propagate their kind," he says, "we face the prospect of a genetic twilight. But if we let them die or suffer when we can save or help them, we face the certainty of a moral twilight."

The biological revolution could make some of the choices easier. In the future, defective genes may be excised by pinpoint laser beams and replaced by viruses acting as man's genetic messengers in the body. Anguished man may also find his mental burdens lightened, as he turns to anti-aggression and knowledge pills, or learns to stimulate his brain's pleasure centers with electrodes.

### BUT OTHER ADVANCES

may only increase man's moral agony. By growing life in artificial wombs, for instance, or even rearranging enough molecules to create life itself, man will invoke comparison to the legendary Faust. He attained the power to create life—the tiny test-tube man, or homunculus—but only after he had bartered away his soul to the devil. If the new knowledge is used recklessly, Faustian man of the future may wonder if he, too, has not made a pact with dark forces.

In the long history of evolution, 100 million species of plants and animals have inhabited the earth.

Of these, 98% are now extinct, unable to survive the challenges of a changing environment. Man himself may face such a life-and-death test. Unlike his predecessors on the evolutionary ladder, he has the capability to meet it—and to fail it even more grandiosely than did creatures with lesser brains and imaginations.

Astonishingly, this capacity has been acquired only recently with remarkable advances in the life sciences. On the following pages, TIME describes the advances, including their promises and dangers. Some are distant, others close at hand. Together they may eventually shape *Homo futurus*, a creature resembling the Superman of the Nietzschean and Shavian dream—or at least one whose powers will be dramatically different from contemporary man's.



THE WISDOM OF MODERN MAN, RITE OF MAN VS. LUNAR LIFE

ARTIST ERNST TRÖVA'S "WALKING MAN"  
A pact with dark forces.

## THE CELL: Unraveling the Double Helix and the Secret of Life

Wildly excited, two men dashed out of a side door of Cambridge University's Cavendish Laboratory, cut across Free School Lane and ducked into the Eagle, a pub where generations of Cambridge scientists have met to gossip about experiments and celebrate triumphs. Over drinks, James D. Watson, then 24, and Francis Crick, 36, talked excitedly, Crick's booming voice damping out conversations among other Eagle patrons. When friends stopped to ask what the commotion was all about, Crick did not mince words. "We," he announced exultantly, "have discovered the secret of life!"



WATSON & CRICK WITH DNA MODEL AT CAMBRIDGE (1953)

*Mysteries of the master molecule.*

Brave words—and in a sense, incredibly true. On that late winter day in 1953, the two unknown scientists had finally worked out the double-helical shape of deoxyribonucleic acid, or DNA. In DNA's famed spiral-staircase structure are hidden the mysteries of heredity, of growth, of disease and aging—and in higher creatures like man, perhaps intelligence and memory. As the basic ingredient of the genes in the cells of all living organisms, DNA is truly the master molecule of life.

The unraveling of the DNA double helix was one of the great events in science, comparable to the splitting of the atom or the publication of Darwin's *Origin of Species*. It also marked the maturation of a bold new science: molecular biology. Under this probing dis-

cipline, man could at last explore—and understand—living things at their most fundamental level; that of their atoms and molecules. Once molecular biology was sardonically defined as "the practice of biochemistry without a license." Now it has become one of science's most active, exciting and productive arenas, taking the limelight (and some of the best talent) from that longtime favorite, nuclear physics.

Using laboratory skills that were unheard of a generation ago, scientists have isolated, put together and manipulated genes, and have come close to creating life itself. In 1967 Stanford University's Arthur Kornberg synthesized in a test tube a single strand of DNA that was actually able to make a duplicate of itself. Kornberg's "creation" was only a copy of a virus, a coated bit of genetic material that occupies a twilight zone between the living and inanimate. But many scientists have become convinced that they may eventually be able to create functioning, living cells.

Molecular biology, in part, is rooted in the science of genetics. Ever since Cro-Magnon man, parents have probably wondered why their children resemble them. But not until an obscure Austrian monk named Gregor Mendel began planting peas in his monastery's garden in the mid-19th century were the universal laws of heredity worked out. By tallying up the variations in the offspring peas, Mendel determined that traits are passed from generation to generation with mathematical precision in small, separate packets, which subsequently became known as genes (from the Greek word for race).

Mendel's ideas were so unorthodox that they were ignored for 35 years. But by the time the Mendelian concept was rediscovered at the turn of the century, scientists were better prepared for it. They already suspected that genetic information was hidden inside pairs of tiny, threadlike strands in cell nuclei called chromosomes, or colored bodies (for their ability to pick up dyes). During cell division they always split lengthwise, thereby giving each daughter cell a full share of what was presumed to be hereditary material.

A few years later, the suspicions were dramatically confirmed by the pioneering geneticist Thomas Hunt Morgan in

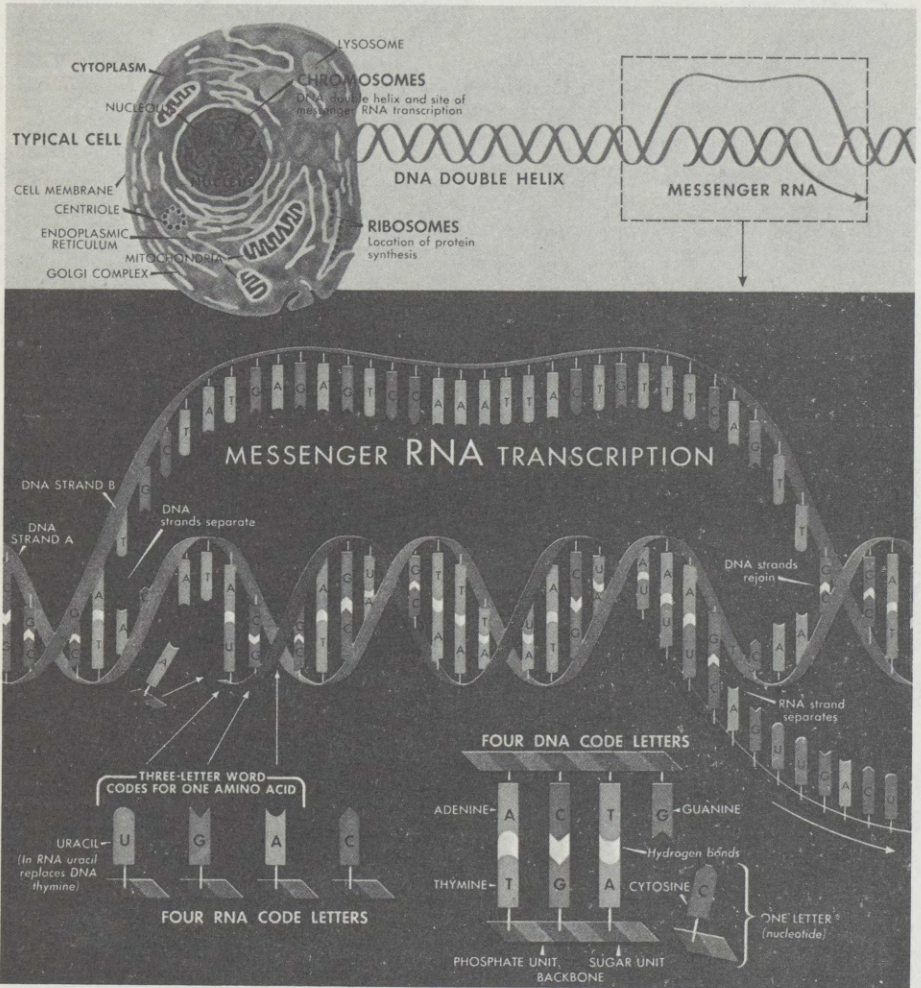
Columbia University's famed "Fly Room." Through ingenious crossbreeding experiments with the fruit fly *Drosophila melanogaster*, Morgan and his students were able to map the relative positions of the genes along the insect's four pairs of chromosomes. Still, the gene's physical nature remained as great a mystery as ever. DNA had been discovered in the nuclei of cells by the Swiss biochemist Friedrich Miescher a few years after Mendel did his work on peas. But since the chromosomes in which the DNA was found also contained proteins—the basic building blocks of life—few scientists had any inkling that DNA might be playing an even more central role to life.

By the 1940s, however, the molecular biologists had come on the scene, and they insisted that fundamental life processes could be fully understood only on the molecular level. In their investigations, some used the electron microscope, which revealed details of structure invisible to ordinary optical instruments. Others specialized in X-ray crystallography, a technique for deducing a crystallized molecule's structure by taking X-ray photographs of it from different angles. Physicist Max Delbrück turned to nature for his investigative tools: bacteriophages (literally, "bacteria eaters"), tiny parasitic viruses that invade their host bacteria and rob them of their genetic heritage.

### **B**UT THE HONORS

for making the breakthrough discovery went to a traditional bacteriologist. Taking purified DNA extracted from the chromosomes of dead pneumonia bacteria, Rockefeller Institute's Oswald T. Avery and his associates showed that it could transform other, normally harmless bacteria into virulent ones. The experiment indicated that it was DNA, and not protein, that carried the genetic message. So unexpected was that finding that even Avery was at first unwilling to accept it. Eight years later, Alfred Hershey and his assistant Martha Chase demonstrated that a virus DNA could, by taking over a bacterium, also nullify the cell's genetic instructions and replace them with its own. Only then was DNA finally accepted as the magic substance of the genes.

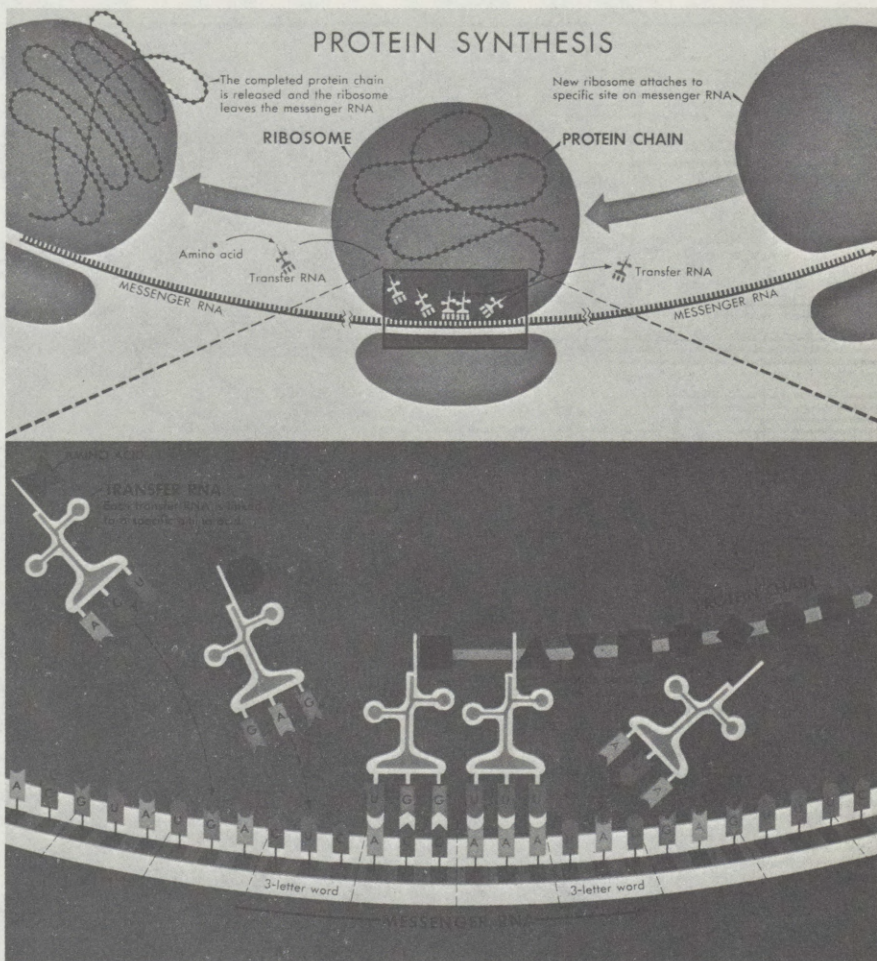
Inspired by these experiments, Watson, then a young Ph.D. in biology from Indiana University, decided to take a crack at the complex structure of DNA itself. The same thought struck Crick, a physicist turned biologist who was preparing for his doctorate at Cambridge. Neither man was particularly well equipped to undertake a task so formidable that it had stymied one of the world's most celebrated chemists, Linus Pauling. Watson, for his part, was deficient in chemistry, crystallography and mathematics. Crick, on the other hand,



The master molecule DNA passes hereditary information from one generation to the next and directs the manufacture of proteins, life's most important building blocks. Shaped like a spiral staircase, it spells out its vital messages in a complex code. Each of the steps that join DNA's twin spirals consists of two complementary chemical bases, each base-strand unit forming a nucleotide or single letter in the genetic code; three letters make up a "word." When the

human body requires a certain protein, that need is communicated to the cells that manufacture it. In their nuclei, a molecule called an enzyme unwinds and separates the section, or gene, or the DNA molecule that contains the coded instructions for making the protein. As the DNA strands unwind, their paired nucleotide links come apart. Other nucleotides floating freely in the cell fluid quickly attach themselves to complementary nucleotides on one of the

(continued on overleaf)



DNA strands and form a single-stranded molecule of messenger RNA. This molecule, imprinted with the DNA's message, then detaches itself and leaves the nucleus. The opening of the DNA molecule then rewinds.

After leaving the nucleus, the messenger RNA is picked up by a ribosome, which runs the RNA strand through itself like tape through a playback machine. It then reads off the messenger RNA's three-letter words—each of which names a specific amino acid necessary to form the protein molecule. As each word is read, another type of RNA, called transfer RNA, plucks the

appropriate amino acid from the cell fluid and arrives at the scene, carrying the acid at one end and three appropriate nucleotides at the other. These nucleotides are drawn to their complementary partners on the messenger RNA strand. Thus, the amino acids are brought to the ribosome in the proper sequence to form a long protein chain. When completed, the chain is released into the cytoplasm, where it organizes itself into a three-dimensional protein molecule. Meanwhile, the free end of the messenger RNA is picked up by another ribosome for the assembly of still another protein molecule.

## The New Genetics

was almost totally ignorant of genetics. But together, in less than two years of work at Cambridge, these two spirited young scientists showed how it is possible to win a Nobel Prize without really trying.

In 1968 Watson himself produced a highly irreverent, gossipy bestseller, *The Double Helix*, which revealed the human story behind the discovery of DNA's structure: the bickering, the academic rivalries, even the deceptions that were practiced to win the great prize. Out of Pauling's earlier work, Watson and Crick got the idea that the extremely long and complicated DNA molecule might take the shape of a helix, or spiral. From the X-ray crystallography laboratory at King's College in London, where Biochemist Maurice Wilkins was also investigating the molecule's structure, they quietly obtained unpublished X-ray data on DNA. Relying as much on luck as logic, they constructed Tinkertoy-like molecular models out of wire and other metal parts. To everyone's astonishment, they suddenly produced a DNA model that not only satisfied the crystallographic evidence but also conformed to the chemical rules for fitting its many atoms together.



### OUT OF THE

architecture of their precisely constructed double helix emerged the secret of DNA's awesome powers. The banisters of the staircase were fashioned of long links of sugars and phosphates; the steps between them were made of pairs of chemicals called bases, weakly joined at the center by hydrogen atoms. Only four different bases were used—adenine (A), thymine (T), cytosine (C) and guanine (G). But their sequence could vary so widely along the length of the staircase that they made up an almost limitless information-storage system, like the memory bank of a computer. In addition, because the bases were chemically complementary—that is, A paired off only with T, and C only with G—one side of the staircase was in effect a genetic mirror image of the other. Watson and Crick quickly recognized from the structure of their model how DNA worked. But their 900-word announcement in *Nature*, the international weekly published in Britain, concluded with one of the more coy statements in scientific literature. "It has not escaped our notice," they said, "that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material."

In a second letter, they described that mechanism: how the DNA molecule unwinds and unzips itself right down the middle during cell division, its base pairs breaking apart at their hydrogen bonds. Then by drawing on the free-floating material surrounding them in the nucleus of the cell, the two sep-



ALLFREY

DELBRÜCK

SPIEGELMAN

### Probing the process of cell differentiation.

arated strands link up with complementary base-and-strand units along their entire length, forming two exact copies of the original double helix. Thus DNA faithfully passes its genetic information on to new cells and to future generations.

Ingenious as the theory was, scientists still demanded proof that the molecule actually replicated itself. That proof was quick to come. By 1956, Arthur Kornberg, then at Washington University in St. Louis, discovered an enzyme, or natural chemical catalyst (which he named "DNA polymerase") that was apparently critical to some of the activities of the double helix. Once he obtained enough of the enzyme, he placed it in a test-tube brew with a bit of natural DNA, one of whose strands was incomplete, the four off-the-shelf chemicals. True to his expectations—and the Watson-Crick theory—the incomplete segment picked up its complementary nucleotides from the brew to form a complete double helix.

Implicit in the Watson-Crick model were the workings of DNA's other es-

sential function: how it orders the production of proteins. These are also long and twisted helical molecules, but they are the actual building blocks rather than the genetic blueprints for living things. As such, proteins are immensely varied; there are many thousands of different kinds in the human body alone. The distinctive proteins that make up the cells of the eye, for example, differ from those of the kidneys or muscles. Despite their variety, however, all proteins are built from some of only 20 smaller and simpler molecules, called amino acids. How then, scientists asked themselves, did the isolated double helix, locked in the nucleus of the cell, direct the assembly of amino acids into protein in other parts of the cell?

Scientists suspected that DNA had a helper, a single-stranded chemical first cousin called ribonucleic acid (RNA). Most of the cell's RNA is found in ribosomes. These are globular bodies in the material outside the cell's nucleus that seem to be highly active centers of protein synthesis. But if this ribosomal RNA played a role in protein making, how did it obtain and execute the



KORNBERG

NIRENBERG

PAULING

### Stealing the limelight from a longtime favorite.

## The New Genetics

instructions from the master molecule DNA inside the nucleus?

In 1955, after wrestling with the question, Francis Crick postulated (and Harvard Biochemists Paul Zamecnik and Mahlon Hoagland confirmed) a second form of RNA, which was later found to carry specific amino acids floating in the cytoplasm to the ribosomes; this substance became known as transfer RNA. Then in the early 1960s, biologists discovered a third kind of RNA—shortly after its existence had been theorized by Jacques Monod and François Jacob of France's Pasteur Institute. Called messenger RNA, it provided the missing piece in the molecular puzzle. It was formed on an uncoiled strip of DNA in the nucleus, imprinted with the particular "message" encoded in that portion—or gene—of the staircase, and then sent off with these instructions to the protein-making ribosomes.

Neat as it was, this scheme still left unanswered one more question: How could DNA or RNA choose from among 20 amino acids to produce complex proteins by using an informational system that had only four code letters—the four bases—at its disposal? An answer to this intriguing problem was suggested by Physicist George Gamow, who likened the four bases to the different suits in a deck of playing cards.

If the cards are dealt one at a time, disregarding the order of the cards within the suits, the player encounters only one of four possibilities on each draw (a heart, diamond, spade or club); clearly, if DNA's code worked this way, there would not be enough choices to encode 20 amino acids. If the cards are dealt in pairs, the number of combinations increases to 16 (since each card may combine with its own kind or one of three other suits). But such a two-unit system also would be inadequate. So Gamow reasoned that DNA's four bases had to be taken at least three at a time: this would yield 64 possible combinations ( $4 \times 4 \times 4$ ), more than enough to code for the existing amino acids.

**I**N 1961, CRICK'S team at Cambridge proved Gamow's ingenious "triplet" theory. They demonstrated that RNA formed from only one or two base units could not effect the manufacture of proteins. But when they added a third base unit, protein formation began immediately. It remained, however, for an unknown young biochemist named Marshall Nirenberg, at the National Institutes of Health, to crack the code itself. That some year Nirenberg had succeeded in building up short, synthetic strands of RNA out of only one type of base. Invariably, this artificial RNA induced the manufacture of chains of proteins consisting of only

one type of amino acid, phenylalanine. The conclusion was inescapable: in the genetic code, Nirenberg's triplet had to signify phenylalanine.

Using this clue as their Rosetta stone, Nirenberg and other researchers eventually found one or more three-letter code words, or codons, that could call up every single amino acid—plus other words that acted as punctuation, marking the start or completion of a message ordering the production of a protein. Even more remarkable, they learned that the code was universal: the same four letters, taken three at a time to form a single genetic word, code the same amino acids in all living things. Thus by the mid-1960s, scientists finally understood how DNA passes on genetic information with exquisite precision, and the way it orders up the fabrication of new cellular protein.



LUNGFISH (TOP) & SALAMANDER  
More richly endowed than man?

That process, shown in the accompanying color chart, was summarized by Crick in a series of rules that became known as the Central Dogma. Most scientists interpreted the key rule of that dogma to be that genetic information flowed in one direction: from DNA to RNA to protein. To the surprise of many molecular biologists, however, it has recently been shown that part of the process can sometimes be reversed. This finding, in the opinion of molecular biologists like Columbia's Sol Spiegelman, may offer an important clue to the workings of cancer cells (see box, page 44).

DNA is as complex as the system it directs. Even after two decades of in-

tensive study only about one-third of the genes have been mapped along the length of DNA in the chromosome of so elementary a creature as the digestive-tract bacterium *Escherichia coli*. The reason: just a teaspoon of *E. coli* DNA has information capacity approximately equal to that of a computer with a storage capacity of about 100 cu. mi.

## M

AN, FOR HIS PART, is even more generously endowed—with 1,000 times as much DNA as one *E. coli* in each of his reproductive cells.

Even so, the cells of such relatively primitive animals as salamanders, lungfish and even certain one-celled algae contain far more DNA than man's. Does this mean that such lowly beasts have a richer genetic capacity than man?

The Carnegie Institution's Roy Britten and David Kohne, after much painstaking investigation, may have found the answer to that embarrassing question. A few years ago they discovered that in the DNA of higher organisms many genes seem to be repeated. In calf cells, they calculated, up to 40% of the DNA consists of segments that are repeated as many as 100,000 times apiece. As a result of

this work, some scientists are now convinced that in this seeming redundancy of genes, rather than in the total number, lies the secret of the genetic sophistication of higher organisms.

How would such genetic repetition help man? Some theorists suspect that the "spare" DNA plays a regulatory role, perhaps switching other genes on and off at just the right moment during the involved process of protein manufacturing. Harvard Biochemist Charles Thomas, however, supports a more radical idea. He thinks that the repeated segments are actually "slaves" of a "master" gene from which they have been copied. Working in tandem, explains Thomas, such "slaves" could produce proteins more quickly and efficiently—though, he admits, not necessarily in greater diversity.

Molecular biologists are also probing ever more deeply into the process of cell differentiation. It has long been known that the DNA in every body cell of an individual organism is identical; this DNA contains all the information necessary to construct the whole organism. Why then, in a human being, for example, is a liver cell so different from a hair cell, a heart cell so different from a skin cell? The answer, Jacob and Monod theorized in 1961, is that only a small percentage of the genes in any cell are giving instructions

for the operation of that particular cell. The rest are "turned off" by protein repressors, which wrap themselves around long stretches of DNA and prevent them from transferring their coded information to messenger RNA.

A number of such repressors have since been found in bacteria. Scientists have also isolated enzymes that turn the genes back on. These inducers, as they are called, work by unlocking the repressors on the segment of DNA. But even in *E. coli*, such switching can become bafflingly difficult: the repressors and inducers, for example, require controlling enzymes of their own. These enzymes, in turn, apparently need the help of still other molecules, such as the recently discovered sigma, rho and psi factors, in recognizing the appropriate genes. In fact, it is because of the very complexity of these processes that leading molecular biologists like Crick find the questions arising from cell differentiation so fascinating. How in the human embryo, for instance, are certain genes switched on so that by the end of the first week after conception identical cells have begun to grow into cells with differing characteristics?

**S**O FAR THESE fundamental questions are largely unanswerable, although some clues have been uncovered. For one thing, it is thought that in higher, multicellular forms of life, repressors may be a special class of proteins called histones; these are not found in bacteria. When histones are removed, Rockefeller University's Vincent Allfrey has found, RNA production soars by 400%, evidence that formerly repressed segments of DNA have become active. In addition, it has been learned that the cell membrane itself appears to play a crucial part in switching genes on and off. When a membrane is merely brushed by certain hormones—a large class of molecules that serve as intercellular messengers—the membrane will respond as though jolted by an electric probe. It will instantly send off a signal to the nucleus, triggering RNA production by the genes. That finding could eventually have medical application for diseases—like diabetes—resulting from vital genes that are inexplicably turned off.

Many more puzzles remain unsolved. Why are there small bits of DNA located outside the nucleus in energy-producing cell centers called mitochondria? Does this mean that there are other, unknown repositories of hereditary information? In spite of such questions and complications, the basic structure of DNA postulated by Crick and Watson 18 years ago has withstood the test of time remarkably well. More important, it has given man a profound new understanding of basic life processes—and the means to control and alter them.

## THE BODY: From Baby Hatcheries To "Xeroxing" Human Beings

The remarkable advances in molecular biology during the past two decades have given man an understanding of the basic processes that shape his life and have placed within the realm of possibility medical achievements undreamed of a scant few years ago. As more and more of the once-mysterious life forces within the cell are defined in the logical language of chemistry, the way is being opened not only for permanent cures of genetic diseases but also for drastic changes in man's genetic makeup. The acquisition of the power to eliminate genetic imperfections and engineer entirely new characteristics for humans is, for all of its promise, a frightening prospect for those who be-

Fully 25% of all conceptions fail to reach an age at which they can survive outside the womb, and of these, at least a third have identifiable chromosomal abnormalities. Still, as many as five out of every 100 babies born have some genetic defect, and Nobel-Prizewinning Geneticist Joshua Lederberg believes the proportion would be even higher were it not for nature's own process of quality control.

The most obvious deformities result from chromosomal abnormalities. Down's syndrome, or mongolism, which occurs once in every 600 births, is caused when one set of chromosomes occurs as a triplet rather than a pair. Hydrocephalus, or water on the brain, polydactyly, the presence of extra fingers or toes, also result from faulty genes.

But the majority of genetic stigmas have somewhat more subtle symptoms and occur when defective genes fail to order the production of essential enzymes that trigger the body's biochemical reactions. Phenylketonuria (PKU) is caused by the absence of the enzyme necessary for the metabolism of the amino acid phenylalanine; as a result, toxins accumulate in the body and eventually cause convulsions and brain damage. Cystic fibrosis, which causes abnormal secretion by certain glands and respiratory-tract blockage that can lead to death by pneumonia, is the most common inborn error of metabolism; it is believed to be caused by a deficiency in a single gene.

Most people are unaware that they are carrying defective genes until they have a deformed, diseased or mentally retarded child. While medical science has not yet developed the techniques for repairing the bad genes, it can increasingly determine that they are present. Genetic counselors can thus advise prospective parents on the possibilities that their offspring will be born with genetic diseases. Properly informed, a couple that runs a high risk of producing a defective child may well decide to forgo having children.

If both parents carry genes for diabetes, for example, the chances are one in four that their children will inherit an increased risk for developing the disease. If either parent actually suffers from diabetes, the odds are even worse. Members of one large South Dakota family afflicted with a rare



LEONARD MC CONNELL—LIFE  
DIABETIC WOMAN UNDERGOING AMNIOCENTESIS  
Eliminating the uncertainty.

lieve that man should not tamper with his inheritance. Yet even before the structure of DNA was defined and the genetic code broken, doctors had begun, mostly by trial and error, to develop techniques of genetic medicine.

Man today is heir to a host of inherited imperfections, ranging from diabetes to degenerative nerve disease. Each individual, geneticists have determined, carries between five and ten potentially harmful genes in his cells, and these flawed segments of DNA can be passed down to his progeny along with the messages that determine whether a child will have red hair or blue eyes.

Nature itself takes care of the worst genetic mistakes. One out of every 130 conceptions ends before the mother even realizes she is pregnant because the defective zygote, or fertilized egg, never attaches itself to the wall of the uterus.

## The New Genetics.

degenerative nerve disease have been advised, for example, that the odds are 50-50 that any children they have will suffer loss of balance and coordination and die, probably of pneumonia, by age 45 (TIME, Jan. 25).

Genetic counseling once relied more heavily on mathematics than medicine to predict the chance of hereditary handicaps. But it is now possible for doctors to identify and catalogue chromosomes. If there are certain chromosomal abnormalities, the prospective parents are informed that they will almost definitely produce deformed offspring. While this knowledge may take some of the mystery and romance out of procreation, it also eliminates much of the uncertainty. As one geneticist puts it, "There is nothing very romantic about a mongoloid child or a deformed baby."

An even more important technique enables physicians to examine the cells of the unborn only months after conception and to determine with accuracy whether or not the infant will inherit his parents' defective genes. The procedure is known as amniocentesis, from the Greek *amnion* (membrane) and *kentesis* (pricking); it is performed by inserting a long needle through the mother's abdomen and drawing off a small sample of the amniotic fluid, the amber liquid in which the fetus floats. Physicians then separate the fetal skin cells from the fluid and place the cells in a nutrient bath where they continue to divide and grow. By examining the cells microscopically and analyzing them chemically, the doctors can identify nearly 70 different genetic disorders, most of them serious.

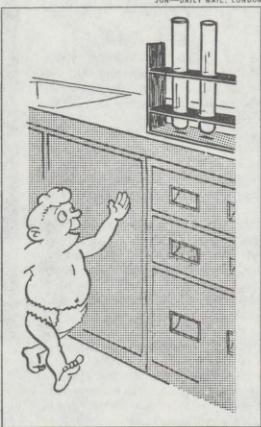
Amniocentesis, performed between the 13th and 18th weeks of pregnancy, is not without some risk to both mother and baby. But in cases where family history leads them to suspect genetic defects, physicians feel that the benefits more than justify the danger; for the tests, which have been carried out on more than 10,000 women in the U.S. alone in the past 40 years, have proved extremely accurate. Using amniocentesis, Dr. Henry Nadler, a Northwestern University pediatrician, diagnosed mongolism in ten of 155 high-risk pregnancies tested. Subsequent examination of the fetuses showed that his diagnosis was correct in all cases.

**A**T PRESENT, THE woman who learns through amniocentesis that she is carrying a seriously deformed fetus has only two choices: abortion or the heartbreak of delivering a hopelessly defective infant. But the mother whose unborn baby is found to have one of several hereditary enzyme deficiencies has a more acceptable alternative, for medicine has developed techniques for treating many such ill-

nesses. An amniotic test for fetal lung maturity, for example, has helped warn doctors when a child may be born with hyaline membrane disease, which blocks proper breathing. In those cases, birth can be delayed by sedation until tests show the baby ready to breathe on its own. Tests that permit prompt postnatal detection of PKU give doctors an opportunity to place babies so affected on special diets that prevent the accumulation of the deadly toxins and allow them to live relatively normal lives.

Some treatments are even possible before birth. Physicians routinely perform intrauterine transfusions on fetuses suffering from Rh disease, a genetic condition that results from the incompatibility of maternal and fetal blood.

Artificial insemination, once the exclusive province of livestock breeders, also offers escape from some genetic mis-



"GOOD MORNING, DADDY."

haps. An estimated 25,000 women whose husbands are either sterile or carry genetic flaws have been artificially inseminated in the U.S. each year, many of them with sperm provided by anonymous donors whose pedigrees have been carefully checked for hereditary defects. Some 10,000 children are born annually of such conceptions.

Doctors also see possibilities in artificial inactivation, a procedure in which an egg cell is taken directly from the ovaries, fertilized in a test tube and then reimplanted in the uterus. By carefully scrutinizing the developing embryo in the test tube, doctors could spot serious genetic deficiencies and decide not to reimplant it, thus avoiding an abortion later on. If the embryo is normal, it could even be reimplanted in the womb of a donor mother and carried to term

there, enabling the woman either unable or unwilling to go through pregnancy to have children that were genetically her own.

Even test-tube babies, once the stuff of science fiction, are now not only possible, but probable. Dr. Landrum Shettles of Columbia University and Dr. Daniele Petrucci of Bologna, Italy, have shown that considerable growth is possible in test tubes. Shettles has kept fertilized ova growing for six days, the point at which they would normally attach themselves to the lining of the uterus. Petrucci kept a fertilized egg alive and growing for nearly two months.

**I**NDEED, ONLY development of an "artificial womb" capable of supporting life stands in the way of routine ectogenesis, or gestation outside the uterus, and now even this problem may yield to solution. Scientists at the National Heart Institute have developed a chamber containing a synthetic amniotic fluid and an oxygenator for fetal blood, and have managed to keep lamb fetuses alive in it for periods exceeding two days. Once their device is perfected, the baby hatchery of Aldous Huxley's *Brave New World* will be a reality and life without birth a problem rather than a prophecy.

Man may eventually be able to abandon sexual reproduction entirely. That startling and perhaps unwelcome possibility has been demonstrated by Dr. J.B. Gurdon of Britain's Oxford University. Taking an unfertilized egg cell from an African clawed frog, Gurdon destroyed its nucleus by ultraviolet radiation, replacing it with the nucleus of an intestinal cell from a tadpole of the same species. The egg, discovering that it had a full set of chromosomes, instead of the half set found in unfertilized eggs, responded by beginning to divide as if it had been normally fertilized. The result was a tadpole that was the genetic twin of the tadpole that provided the nucleus. Gurdon's experiment was also proof of what geneticists have long known: that all of the genetic information necessary to produce an organism is coded into the nucleus of every cell in that organism.

Man, say the scientists, could one day clone (from the Greek word for throng), or asexually reproduce himself, in the same way, creating thousands of virtually identical twins from a test tube full of cells carried through gestation by donor mothers or hatched in an artificial womb. Thus, the future could offer such phenomena as a police force cloned from the cells of J. Edgar Hoover, an invincible basketball team cloned from Lew Alcindor, or perhaps the colonization of the moon by astronauts cloned from a genetically sound specimen chosen by NASA officials. Using the same technique, a woman could

## The New Genetics

even have a child cloned from one of her own cells. The child would inherit all its mother's characteristics including, of course, her sex.

Dramatic as cloning may be, it is overshadowed in significance by a technique that may well be practiced before the end of this century: genetic surgery, or correction of man's inherited imperfections at the level of the genes themselves. When molecular biologists learn to map the location of specific genes in human DNA strands, determine the genetic code of each and then create synthetic genes in the test tube, they will have the ability to perform genetic surgery.

Some molecular biologists envisage using laser beams to slice through DNA molecules at desired points, burning out faulty genes. These would then be replaced by segments of DNA tailored in the test tube to emulate a properly functioning gene and introduced into the body as artificial—and beneficial—viruses.

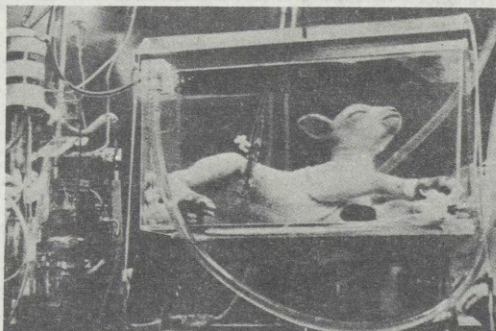
### THE CONCEPT IS

not as farfetched as it sounds. Real viruses are merely segments of DNA (or RNA) surrounded by largely-protein sheaths; they penetrate the cell nucleus (leaving their sheaths behind) and take over the cellular DNA.

The potential of the technique is already being tested by an international research team in the treatment of two children whose hereditary inability to produce the enzyme arginase had resulted in severe mental retardation. The team infected the youngsters with a natural virus, the Shope papilloma, which contains DNA that triggers arginase synthesis. Although the experiment is expected to produce no improvement in the children's mental condition, it may belatedly trigger the production of the missing enzyme and prove that viruses can carry beneficial messages to the cells.

There is other evidence that the beginning of genetic surgery is not far off. Dr. Sol Spiegelman of Columbia University has synthesized an artificial virus that is indistinguishable from its natural model and has used it to infect bacteria and produce new viruses. He and his colleagues have little doubt that they will also eventually create "friendly" viruses and use them to cure disease rather than cause it—by using the viruses to stimulate the production of the chemical products upon which health and life itself depend.

Prophylaxis is important, but man's molecular manipulations need hardly be confined to the prevention and cure of disease. His understanding of the mechanisms of life opens the door to genetic engineering and control of the very process of evolution. DNA can now be created in the laboratory. Soon,



LAMB FETUS IN ARTIFICIAL WOMB

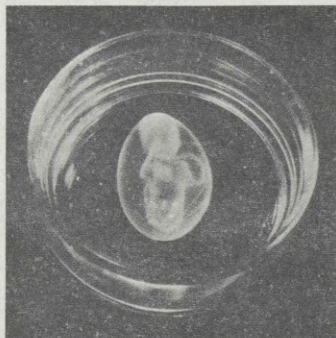
man will be able to create man—and even superman.

Researchers have found that they can increase the life span of laboratory animals by underfeeding them and thus delaying maturation. This phenomenon, they believe, occurs because a smaller intake of food results in the formation of fewer cross linkages—connecting rods that link together and partly immobilize the long protein and nucleic acid molecules essential to life. If scientists can retard cross linking in man, they may well slow his aging process. Scientists also hope that they can some day do away with disease, genetically breeding out hereditary defects while breeding in new immunities to bacterial and other externally caused ailments. Finally, they look forward—in the distant future and with techniques far beyond any now conceived—to altering the very nature of their species with novel sets of laboratory-created genetic instructions.

Current predictions about the appearance of re-engineered man seem singularly uninspired. Some scientists argue that man's head should be made larger to accommodate an increased number of brain cells. They do not, however, explain what man would do with this additional gray matter; there is good reason to believe that man does not use all that he presently possesses. A few others note that the efficiency of man's hands could be increased by an extra thumb and his peripheral vision enhanced by protruding eyes—improvements that seem unnecessary in the light of man's expanding technology.

### SOME FAVOR LESS

obvious alterations. They have suggested that man be given the genes to produce a two-compartment stomach (a cow has four) that could digest cellulose; that mutation could be advantageous if man fails to increase his food supplies fast enough to feed the planet's growing population, but superfluous if he does. They also want man programmed to regenerate other organs, such as he now does with the liver, so that he can repair his damaged or



SEVEN-WEEK-OLD HUMAN FETUS  
Acquiring Promethean power.

diseased heart or lungs if necessary.

Others call for even more specialized humans to perform functions that in reality will probably be done better by machines. British Geneticist J.B.S. Haldane called for certain regressive mutations to enable man to survive in space, including legless astronauts who would take up less room in a space capsule and require less food and oxygen (larger and more powerful spacecraft would seem to be an easier and less monstrous solution). Haldane also suggested apelike men to explore the moon. "A gibbon," he said only half-jokingly, "is better preadapted than a man for life in a low gravitational field."

Eventually, scientists fantasize, man will escape entirely from his inefficient, puny body, replacing most of his physical being with durable hardware. The futuristic cyborg, or combination man and machine, will consist of a stationary, computerlike human brain, served by machines to fill its limited physical needs and act upon its commands.

Such evolutionary developments could well herald the birth of a new, more efficient, and perhaps even superior species. But would it be man?

## The Search for a Cancer Cure

At present there are only three main ways of treating cancer, which will kill more than 335,000 in the U.S. alone this year. Doctors can cut tumors out with a knife, burn them out with radiation or kill them cell by cell with drugs. Though these treatments can be effective in combination, each has its drawbacks. Now, cancer researchers have turned to molecular biology, which shows promise of providing new and more effective means of dealing with the disease.

No one really knows what causes cancer, which is actually more than 100 distinct diseases, all sharing two common characteristics: rapid cell growth and a terrifying tendency to spread from one part of the body to another. Most researchers agree, however, that the vil-

min's discovery was at first believed to be unique to cancer cells infected by viruses. Thus when Columbia University's Sol Spiegelman and the National Cancer Institute's Robert Gallo found high enzyme activity in the cells of leukemic patients, medical science had a solid clue that leukemia might be caused by a virus. Even more important, some researchers speculated that if the Temin enzyme was found only in cancer cells, the spread of cancer might be halted simply by inhibiting the enzyme.

Their hopes for an immediate cancer cure were short-lived. The NCI's George Todaro and other researchers have since found similar enzyme activity in normal cells as well. They have also found evidence of these enzymes in human and animal embryonic tissues, thus helping to confirm the views of many scientists who believe that cancer is probably an aberration of normal cellular growth.

If it is, Temin thinks he knows why it occurs. According to his hypothesis, normal cells manufacture RNA, which moves to neighboring cells in the form of a provirus, or template, and stimulates the production of a new form of DNA. But, theorizes Temin, if this wandering RNA somehow transmits the wrong message after entering the cells, it can cause the production of altered DNA that orders the cells to grow abnormally.

Dr. Robert Huebner of the NCI speculates that cancer is caused by a noninfectious virus that is a normal part of every living thing. According to Huebner, the virus, which he has labeled the "C particle," is a part of everyone's genetic heritage, a tiny bit of RNA that is passed vertically from one generation to another and perhaps helps normal development by causing the cells of an embryo to grow. The C particle should become inactive as the fetus matures; if it fails to do so, the result is the rapid cell growth that characterizes cancer.

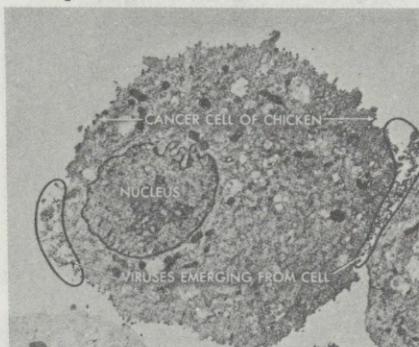
methods of administering medication impractical. But RNA viruses, which produce DNA, have proven their ability to move directly into the cells and could easily carry such communications. Scientists speculate that benign viruses could be made in test tubes with proteins and synthesized RNA. The viruses, injected into the body, would home in on the cancerous growth and shut down the cells' runaway reproductive mechanism.

### AVENUES OTHER THAN

virology are also being explored in the search for a cancer cure. Researchers have long been aware that animal cells growing in a culture medium will stop multiplying once they come in contact with one another. But in some recent experiments at Princeton, Biochemist Max Burger found that when he stripped normal mouse cells of their membranes, they continued to grow wildly—as do cancer cells—even after they had touched. Burger thus speculates that the loss of a cell's protective coating, possibly as a result of viral infection, could lead to cancer by exposing a sensitive area that signals the cells to continue growth. If the protective covering could be restored, he suggests, it might be possible to stop the genes of cancer cells from ordering further growth.

It may even be possible to use the body's immunological mechanism, which now helps to protect it against other diseases, to combat cancer. Some researchers note that organ transplant recipients, who take large doses of drugs to suppress their immune reactions and prevent the rejection of foreign tissue, may develop cancer. Also, the immune system often fails to respond to many cancer cells, although they have unique antigens that should alert the body to their presence. Accordingly, doctors have begun exploring ways of beefing up the body's defenses and immunizing man against cancer in the same way that he can now be vaccinated against polio and other viral diseases.

In a unique series of experiments, Dr. Loren Humphrey of Atlanta's Emory University inoculated patients with a vaccine made, at least in part, with tissues taken from tumors similar to their own. He then followed up the inoculations by cross-injecting the patients with white blood cells from fellow patients who had presumably been sensitized to the tumor antigens. Though only long-term testing will tell if Humphrey's approach is effective, the preliminary results appear promising. One patient with bowel cancer has been free of the disease for three years, while three others have evidenced definite remissions.



CELL INFECTED BY TUMOR VIRUSES  
*The defenses are down.*

lain is a virus, a miniature packet of nucleic acid with a membranous coat that was shown as early as 1911 to cause tumors in animals.

Unable to reproduce themselves, viruses invade normal cells and use their hosts' chemical mechanisms to produce more viruses. Eventually, the infected cell ruptures, releasing the newly formed viruses to infect other cells. Dr. Howard Temin of the University of Wisconsin has shown that some tumor viruses behave differently. They reverse the normal order of genetic transmission, and with the aid of a recently discovered enzyme, use their RNA messenger molecules to produce DNA, the double-helix master molecule. In a way not yet understood, this triggers the cellular genetic machinery to order cell division, causing the cancerous growth that is then perpetuated in succeeding cell generations.

The new enzyme associated with Te-

**M**ANY RESEARCHERS believe that the best method of attacking cancer is to use the body's own genetic mechanism to order cancerous cells to stop growing. Transmitting such orders may be difficult. DNA programmed to carry the command would be digested almost immediately by the body's enzymes if it were injected into the bloodstream, thus making conventional

## THE MIND: From Memory Pills to Electronic Pleasures Beyond Sex

In all of his 35,000-year history, Homo sapiens has found it harder to fathom the depths of his mind than to unlock the secrets of his body. But the discoveries of molecular biology may well show the way to a new comprehension; they may make it possible, through genetic engineering, surgery, drug therapy and electrical stimulation, to mold not only the body but also the mind.

Man cannot wait for natural selection to change him, some scientists warn, because the process is much too slow. Yale Physiologist José Delgado likens the human animal to the dinosaur: insufficiently intelligent to adapt to his changing environment. Caltech Biophysicist Robert Sinsheimer calls men "victims of emotional anachronisms, of internal drives essential to survival in a primitive past, but undesirable in a civilized state." Thus, by his own efforts, man must sharpen his intellect and curb his aboriginal urges, especially his aggressiveness.

To most laymen, the idea of remaking man's mind is unthinkable; "You can't change human nature," they insist. But many scientists are convinced that the mind can be altered because it is really matter. Explains Physicist Gerald Feinberg: "What sets us apart from inanimate matter is not that we are made of different stuff, or that different physical principles determine our workings. It is rather the greater complexity of our construction and the self-awareness that this makes possible."

That self-awareness resides in the brain, the organ about which scientists have the most to learn. To Physiologist Charles Sherrington, the brain's 10 billion nerve cells were like "an enchanted loom" with "millions of flashing shuttles." For some functions, M.I.T. Professor Hans-Lukas Teuber explains, brain cells are pre-programmed with "enormous specificity of configuration, chemistry and connection." Some are sensitive only to vertical lines, others only to horizontal or oblique ones. "Each of these little creatures does his thing," Teuber says.

### IN THE HOPE OF

deciphering this staggering variety, hundreds of scientists, including molecular biologists, in the U.S. and abroad, are now turning to brain research. One day in the distant future, their discoveries may help man to improve his already remarkable brain—for despite its dazzling versatility and subtlety, it is not without limitation. "Computers slashing from circuit to circuit in microseconds can cope with the input and response time of dozens of human brains simulta-

neously," Biophysicist Sinsheimer laments. Besides, the brain can call up only a limited amount of stored information at a time to focus it on a particular problem. And while it can grasp as many as 50 bits of visual information at once, it cannot file away more than 10 of them per second for later reference.

To most scientists, this reference system, or memory, is one of the most important tools of man's intelligence. Long before the development of molecular biology, Marcel Proust pondered the mystery of memory in *Remembrance of Things Past*. About a man's own

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PHYSIOLOGIST DELGADO STOPPING BULL IN MID-CHARGE  
Curbing violence with a radio transmitter.

past, he wrote that "it is a labor in vain to attempt to recapture it: all the efforts of our intellect must prove futile. The past is hidden somewhere beyond the reach of the intellect." In *Swann's Way*, it was a tea-soaked *petite madeleine* that touched off the hero's long-forgotten childhood memories. In the scientific world, the stimulus is sometimes a surgeon's probe. Montreal Surgeon Wilder Penfield, for example, while performing operations under local anesthesia, by chance found brain sites that when stimulated electrically led one patient to hear an old tune, another to recall an exciting childhood experience in vivid detail, and still another to relive the experience of bearing her baby. Penfield's findings led some scientists to believe that the brain has indelibly recorded every sensation it has ever received and to ask how the recording was made and preserved.

Initially, some brain researchers believed that memories were stored in electrical impulses. But scientists could not comprehend how a cranial electrical system, however complex its interconnections, could accommodate the estimated million billion pieces of information that a single brain collects in a lifetime.

### THEIR DOUBTS

increased when they found that a trained animal generally remembered its skills despite attempts to disrupt its cerebral electrical activity by intense cold, drugs, shock or other stress; only short-term memory—of recently learned skills—was impaired. There was an obvious conclusion: while short-term memory may be partly electrical, long-term mem-

ory must be carried in something less ephemeral than an electric current.

That something, theorists believed, was chemical. Scientists had long known that chemical as well as electrical activity goes on in brain neurons: these cells carry on metabolism and protein synthesis like other body cells. Researchers soon learned that the leap of message-carrying nerve impulses across the gap between one cell and another takes place only with the help of chemical transmitter substances. One of these, acetylcholine, was promptly identified, and investigators began to look for other brain chemicals, specifically for varieties that might contain memories.

Their reasoning was that just as DNA carries genetic "memories," so other molecules might encode and carry information plucked from transient electrical impulses. Some early researchers proposed the idea of a separate brain molecule for each memory. The

## The New Genetics

hypothesis of Swedish Neurobiologist Holger Hydén of the University of Göteborg was a bit more sophisticated; he thought that RNA was the key to memory formation and was encouraged in his belief by the results of his experiments with rats. When he taught them special tasks, he discovered that the RNA had not only increased in quantity but was different in quality from ordinary RNA. In short, what Hydén did was to lay the groundwork for a molecular theory of memory.

**A**S HYDÉN'S RAT experiments demonstrated, RNA itself does not store memories; instead, it may play an intermediary role, stimulating the brain to produce proteins that are perhaps the actual repositories of memory. In one experiment inspired by that theory, University of Michigan Biochemist Bernard Agranoff taught goldfish to swim over a barrier, then injected them with puromycin, an antibiotic that prevents protein synthesis. When the injection was given hours after learning, it had no effect, suggesting that memory proteins had already formed. Injected just before or just after training, the drug prevented learning.

Other experiments based on the RNA-protein theory may demonstrate actual chemical memory transfer. Among the most publicized are those of University of Michigan Psychologist James McConnell and Neurochemist Georges Ungar of the Baylor College of Medicine. McConnell works with planaria, or flatworms, conditioning them by electrical shock to contract when a light is flashed. He then grinds them up and feeds them to untrained worms. Once they have cannibalized their brothers, the worms learn to contract twice as fast as their predecessors. What may happen, McConnell theorizes, is that the first batch of worms form new RNA, which synthesizes new proteins containing the message that light is a signal to

contract. Having consumed these memory proteins, the second group of planaria presumably do not need to manufacture so much of their own; they have swallowed memory, as it were.

Ungar's experiments are similar. Using shock, he conditions rats to shun the darkness they normally prefer, then makes a broth of their brains. This he injects into the abdominal cavities of mice, which seem to react with a parallel unnatural aversion to the dark. Moreover, the more broth Ungar injects, the faster the mice seem to learn this fear. His theory: the memory message (that darkness should be avoided) is encoded by the rats' DNA-RNA mechanism into an amino-acid chain called a peptide, a small protein that Ungar managed to isolate and then synthesize. His name for it: scotophobin, from the Greek words for "darkness" and "fear."

The experiments done by both men are hard to repeat, and investigators are still trying to decide whether the few apparent replications are sound. There is controversy, too, over the meaning of results: critics say it is hard to interpret the behavior of worms and other lower creatures objectively. Some say that Ungar may have discovered not a memory molecule but a molecule that blocked a normal response (to seek darkness) instead of teaching a new reaction (to seek light). Most investigators doubt that a single memory molecule will be found, but they believe that molecular biology will eventually reveal the secret of memory. If so, the blue-sky possibilities are limitless. It might be possible to develop "knowledge pills" that would impart instant skill in French, tennis, music or math. McConnell jokingly proposes another idea: "Why should we waste all the knowledge a distinguished professor has accumulated simply because he's reached retirement age?" His solution: the students eat the professor.

Many less frivolous proposals for improving memory and other aspects of mental life are emerging from molecular biology and genetics. It is known that

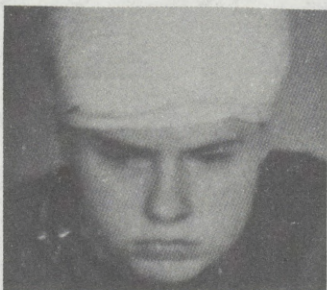
genes do not cause behavior. But they influence it and set limits to physical structure, temperament, intelligence and special abilities.

Psychiatrist Alexander Thomas of New York University finds that babies show a characteristic style (easy, difficult or slow-to-warm-up) from their earliest days. While he admits that this temperament may develop in the months after birth, he does not rule out the possibility that it is inborn. Other life scientists warn that "when we strive for equality of opportunity, we must not deceive ourselves about equality of capacity." For example, it is believed that genetic influence is especially great in such areas as mathematics, music and maybe acrobatics. Unless genetic potential is tapped by the environment, it will not develop: kittens prevented from walking will not learn normal form and depth perception. Says Geneticist Joshua Lederberg: "There is no gene that can ensure the ideal development of a child's brain without reference to tender care and inspired teaching."

**T**HIS INTERACTION between environment and heredity is one of the factors that make it so difficult to change human characteristics. Another is that nearly all behavioral traits are polygenic—dependent on several genes. But even so complex a trait as intelligence may eventually come under the control of molecular biologists. Some scientists fantasize that supergeniuses will some day be produced by increasing brain size, through either genetic manipulation or through transplantation of brain cells to newborn infants or to the fetus in the womb. (Such cells might be synthesized in the laboratory or developed by taking bits of easily accessible tissue from a contemporary Newton or Mozart and inducing them to turn into brain neurons.)

Another prospect is to alter genes so that babies will be born with rote knowledge—language skills, multipli-

BRAIN-DAMAGED GIRL'S HAPPY MOOD CHANGED TO ANGER (CENTER) & VIOLENCE (RIGHT) BY ELECTRIC PULSES



© 1970, HARTER & ROW, INC.—VIOLENCE AND THE BRAIN

TIME, APRIL 19, 1971

## The New Genetics

cation tables—just as birds apparently emerge from the egg with genetic programs that enable them to navigate. Some researchers hope to develop shared consciousness among several minds, thus pooling intellectual resources.

Most observers continue to feel that reining in man's aggressiveness is as important as spurring his intelligence. Harvard Neurosurgeon Vernon Mark advocates a non-genetic approach. "There are basic brain mechanisms that will stop violent behavior, and we are born with them," Mark asserts. To tap those mechanisms, scientists would like to develop an anti-aggression pill (estrogens, or female hormones, have already been used experimentally to inhibit aggressive behavior). Until they do, Mark and two Harvard colleagues—Psychiatrist Frank Ervin and Surgeon William Sweet—are fighting aggression by using surgery to destroy the damaged brain cells that sometimes cause violence in people with specific brain disease. Typical of their patients is a gifted epileptic engineer named Thomas, who used to erupt in rages so frenzied that he would hurl his children or his wife across the room. First, Mark and Ervin sent electric current into different parts of Thomas' brain: when the current sparked his rage, the doctors knew they had found the offending cells. Surgeons Mark and Sweet then destroyed them, and in the four years since, Thomas has had no violent episodes.

Physiologist Delgado has developed even more dramatic methods of aggression control in animals. In one famous experiment, he implanted electrodes in the brain of a bull bred for fierceness. Then, with only a small radio transmitter as protection, he entered the ring with the bull and stopped the angry animal in mid-charge by sending signals into what he believes was its violence-inhibiting center. Similarly, Neuroanatomist Carmine Clemente of U.C.L.A. has shocked cats into dropping rats they were about to kill. But neither man sees any early prospects for remote control of human aggression.



### OTHER MENTAL

problems may well succumb to molecular biology. Many therapists resist the idea that emotional problems have biochemical equivalents; yet Freud himself believed that they do and that they would one day be identified. Researchers are already convinced that schizophrenia has some genetic basis, although, as Psychologist David Rosenthal explains, it is not the disease that is inherited but a tendency to it. As a match must be struck before it will burn, so must the tendency be triggered by something in the environment. No one is yet sure whether the trigger is cultural or familial, electrical or chemical, but some investigators back the chemical theory

on the ground that certain drugs enable schizophrenics to live outside institutions, at least for short periods. To date, drugs for schizophrenia have been administered on a trial-and-error basis; as molecular biologists learn more, it will become possible to use specific drugs to achieve specific ends.

## FURTHER RESEARCH

may provide a bonus of new genetic, chemical and electronic ways to enhance sexual pleasure. Physicist John Taylor, in fact, professes to fear that sex will become so much fun that people will want to give up practically all nonsexual activities. Author Gordon Rattray Taylor predicts that it may become possible to "buy desire," or switch it on or off at will; the playboy might opt for continuous excitement and the astronaut for freedom from sexual urges during space flight.

Unlikely as it may seem, there are researchers who claim to have discovered something better than sex. At McGill University in Canada, Psychologist James Olds used electrodes to locate specific "pleasure centers" in the brains of rats, and then allowed the animals, electrodes still in place, to stimulate themselves by pressing a lever. Given a choice, the rats preferred this new pleasure to food, water and sex. Some pressed the lever as many as 8,000 times an hour for more than a day, stopping only when they fainted from fatigue.

Such experiments lead Herman Kahn of the Hudson Institute to predict that by the year 2000, people will be able to wear chest consoles with ten levers wired to the brain's pleasure centers. Fantasies Kahn: "Any two consenting adults might play their consoles together. Just imagine all the possible combinations: 'Have you ever tried ten and five together?' couples would ask. Or, 'How about one and one?' But I don't think you should play your own console; that would be depraved."

Author Taylor, on the other hand, sees nothing wrong with solitary pleasure. Some day, he writes, a man may be able to put on a "stimulating cap" instead of a TV set, and savor a program of visual, auditory and other sensations. He and other futurists envision "experience centers" or "drug cafes" that would replace bars and coffeehouses. There, perhaps with the help of "dream machines," one might order a menu of "enhanced vision, sensory hallucinations and self-awareness." One might also

be able to experience the mental states of a great man, or even of an animal. Molecular Biologist Leon Kass of the National Academy of Sciences projects a world in which man pursues only artificially induced sensation, a world in which the arts have died, books are no longer read, and human beings do not bother even to think or to govern themselves.

Some life scientists see even greater perils in man's new knowledge. "I would hate to see manipulation of genes for behavioral ends," warns Stanford Geneticist Seymour Kessler, "because as man's environment changes, and as man changes his environment, it is important to maintain flexibility." Professor Gerald McClearn of the Institute for Behavioral Genetics at the University of Colorado agrees, explaining that a gene that is considered

JOHN LOENHARD—LIFE



ELECTRICAL STIMULATION OF THE BRAIN  
Locating the pleasure center.

"bad" now might become necessary for survival in the event of drastic environmental change. "It is foolhardy to eliminate genetic variability," he says. "That is our evolutionary bankroll, and we dare not squander it. Species that ran out of variability ran out of life."

Such worries are probably premature. To some experts, the more radical forms of behavior control, especially genetic modification, belong to the realm of science fiction. Yet others believe that biological predictions are always too conservative, and that man will soon proceed, and succeed, with his experiments. If he does, he must prepare himself for a social and moral revolution that would affect some of his most cherished institutions, including religion, marriage and the family. With such possibilities in mind, Nobelist George Beadle has warned that "man knows enough but is not yet wise enough to make man."

## THE SPIRIT: Who Will Make the Choices of Life and Death?

The quantum leap in man's abilities to reshape himself evokes a sense of uneasiness, a memory of Eden. Eat of the forbidden fruit, God warns, and "you shall surely die." Eat, promises the serpent, and "you shall be like God."

That temptation—to be "like God"—is at the root of the ethical dilemmas posed by molecular biology. In one sense, the new findings have continued the work of Newton, Darwin and Freud, reducing men to even tinier cogs in a mechanistic universe. At the same time, it was man himself who deciphered the code of life and who can now, in Teilhard de Chardin's phrase, "seize the tiller of the world." If he is only a bundle of DNA-directed cells, more sophisticated but hardly dissimilar from those of animals and plants, he can at least use that knowledge to improve, even to re-create himself. But should he?

In his persuasive 1969 book *Come, Let Us Play God*, the late biophysicist Leroy Augenstein argued that man takes the role of God by default or design and has always done so. Ecologically, he changes the very face of the earth: first with plows, then with dams, insecticides and pollution, he has seriously upset the balance of nature. His humane instincts and scientific curiosity team up to preserve life so well that

the world faces a population crisis. Moreover, by extending the lives of those with defective genes, science increases the chance that damaging genes will be passed down to ever-larger portions of succeeding generations. Germany's pre-eminent Protestant ethicist, Helmut Thielicke, notes that men must recognize how "the act of compassion to one generation can be an act of oppression to the next." Thielicke argues that men must be willing to make hard choices. If society intervenes to keep alive the hereditarily ill (as he believes it should), then it must also be willing to intervene again, perhaps even sterilizing some with hereditary diseases.

**T**HIS IS ONLY ONE kind of ethical problem raised by the new genetics, and it is already close at hand. Other problems are still in the far future, but how the dilemmas of population control are handled will set important patterns for later issues.

Population pressures increase the likelihood of widespread government drives, or even coercion, to limit births. Couples who are warned by genetic counseling that they risk producing deformed offspring would face far greater pres-

sure than they do now to avoid having children; those with defective genes could become, in effect, second-class citizens, a caste of genetic lepers.

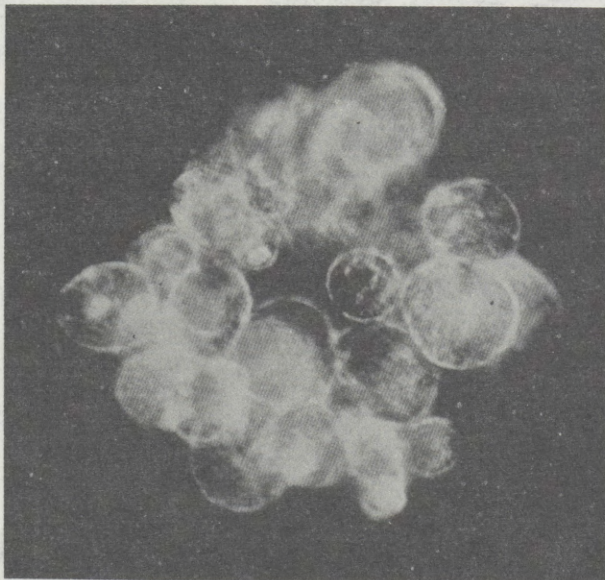
One current example illustrates the problem. Amniocentesis can now quite accurately predict whether a fetus is mongoloid; women carrying such abnormal fetuses are now encouraged, where it is legal, to have abortions. Already a number of medical planners are pointing up the cost-effectiveness of abortion in those cases. Unless the birth rate of mongoloid children is reduced, their care by 1975 may well cost some \$1.75 billion nationally.

Methodist Paul Ramsey, Professor of Religion at Princeton and one of the top Protestant ethicists in the U.S., protests the aborting of such abnormal fetuses as an unjustified taking of human life. But he does not think moral men can avoid the problems of population and genetic crises. Indeed, he urgently recommends that society develop an "ethics of genetic duty." The right to have children can become an obligation not to have them. Ramsey asserts; it is shocking to him that parents will refuse genetic counseling and take the "grave risk of having defective children rather than remain childless." Dead set as he is against abortion in all but the most serious cases, Ramsey would prefer to see one parent undergo voluntary sterilization. "Genetic imprudence," he says, "is gravely immoral."

To Ramsey and others, genetic surgery—repairing, replacing or suppressing a "sick" gene—could be profoundly moral. Depending on the defect, genetic surgery before or after birth could prevent abnormality, and also insure that it was not passed on. Moral Theologian Bernard Häring of Rome's Accademia Alfonsiana applauds basic remedial intervention as "corrective foresight."

**B**UT HÄRING IS ONE among many, both scientists and ethicists, who find it considerably harder to justify "positive" genetic engineering, restructuring the genes to make the "perfect" man. The prospect suggests apocalyptic possibilities: M.I.T. Biologist Salvador Luria approaches it "with tremendous fear of its potential dangers." Biologist Joshua Lederberg of Stanford University disowns such Utopian aims as a proper goal for serious biology, and even doubts that techniques sophisticated enough to achieve them could be perfected in the near future. But the possibility nonetheless tantalizes: Who would decide what qualities to preserve, and by what standards? Even remedial genetic engineering could pose a distressing problem if it achieved the ability to remove "undesirable" behavior tendencies. Asks Thielicke: "Would one try to eradicate Faust's restlessness, Hamlet's indecision, King Lear's con-

HUMAN BLASTOCYST 6½ DAYS AFTER FERTILIZATION (MAGNIFIED 400 TIMES)



DR. LAWRENCE R. SHETTLES

## The New Genetics

science, Romeo and Juliet's conflicts?"

Human cloning, the asexual reproduction of genetic carbon copies, raises similar questions. Who shall be cloned, and why? Great scientists? Composers? Statesmen? When Geneticist Hermann J. Muller first broached the idea of sperm banks in *Out of the Night* (1935), he suggested Lenin as a sperm donor. In later editions, Lenin was conspicuously absent, replaced on Muller's list by Leonardo da Vinci, Descartes, Pasteur, Lincoln and Einstein. Society could well be as fickle—or worse—about cloning. It might create a caste of subservient workers, as in 1984, or a breed of super-warriors out of a "genetics race" between the U.S. and the U.S.S.R. An even more hideous nightmare would be the "clonal farm," where anyone could keep a deep-frozen identical twin on hand for organ transplants.

Such fanciful fears tend to obscure deeper ethical and practical objections to cloning. The process could be used, for example, to allow a woman to produce a child without passing on her own or her mate's defective gene. A cell nucleus from the genetically sound parent could be substituted for the nucleus in her egg. But even that quite reasonable application could introduce a novel set of complications. Would the cloned child develop a sibling rivalry with its biological parent? Would he face a severe identity crisis, being someone else's "duplicate"? Beyond such considerations, a number of scientists and ethicists would list cloning among those things that men should never do, even if they can. Says Embryologist Robert T. Francoeur, author of *Utopian Motherhood*: "Xeroxing of people? It shouldn't be done in the labs, even once, with humans."

**T**O MANY CRITICS cloning is only one of several biological developments that threaten what Paul Ramsey calls "a basic form of humanity": the family. Ramsey thinks that artificial insemination by a donor, which is already fairly common, has opened the door to further invasions of family integrity. In his recent book *Fabricated Man*, he mentions other possible developments: artificial inactivation (the "prenatal" adoption of someone else's fertilized egg), "women hiring mercenaries to bear their children," and "babies produced in hatcheries." Beyond finding some of the possibilities repellent, Ramsey argues that they violate "covenant-fidelity," a bond of spiritual

and physical faithfulness, between wife and husband or parent and child.

Francoeur, on the other hand, feels that the new embryology can lead to a fresh flexibility in the family structure. He favors host mothers (Ramsey's "mercenaries") because some women want children but cannot carry them to term. In an opposite way, artificial inactivation could be the means for a sterile mother to bear a child, even if not from her own egg. But he draws the line at artificial wombs, which, he says, "would produce nothing but psychological monsters." Others emphasize that the family itself must survive to fill important psychological needs. Molecular

trucci embryo lived for 59 days before it died because of a laboratory mistake. The Vatican, which sternly forbids all experimentation with fertilized eggs, demanded that Petrucci cease his investigations. He agreed to comply.



"DON'T LAUGH, HARKNESS—BUT EVERY TIME I START AN EXPERIMENT THESE DAYS, I WONDER WHETHER IT'S GOING TO BE THE ONE DAY, I END UP FINDING RELIGION."

Biologist Leon Kass, who left the research labs to become executive secretary of the National Academy of Science's Committee on the Life Sciences and Social Policy, puts it effectively: "The family is rapidly becoming the only institution in an increasingly impersonal world where each person is loved not for what he does or makes, but simply because he is. Can our humanity survive its destruction?"

Beyond population control, beyond "Xeroxing" and patterning people, beyond the survival of the family lies the ultimate ethical question: the sanctity of life itself. The move toward new knowledge requires experimentation. The new generation of experiments, however, involves human life, and many moralists suggest that many of those experiments are intrinsically evil because they toy with life. They point, for example, to the experiments by Italian Biologist Daniele Petrucci, who in 1961 announced that he had kept a fertilized egg alive for 29 days *in vitro* (in the glass) before letting it die because it was monstrously defective. Another Pe-

## I N A RECENT

experiment conducted by Landrum Shettles at Columbia University, a 100-cell human embryo growing in a petri dish was unceremoniously pipetted in a salt solution onto a glass slide. For those who believe that human life begins with fertilization, Shettles' simple laboratory procedure was an act of unjustifiable killing, even though such experiments might help perfect a morally justified technique like genetic surgery. Even in the case of laboratory mistakes that might produce monsters, argues Bernard Häring, only those that are clearly inhuman should be destroyed. A number of scientists, on the other hand, subscribe to an alternate ethical view that an embryo is not human until later in its development—perhaps as early as two months or as late as six months.

Most scientists, naturally, fight what they see as arbitrary limits on their right to experiment. But not all. Testifying before the House subcommittee on science in January, Molecular Biologist James Watson took time off from his cancer investigations to express concern about developments in embryo research. Predicting that many biologists would soon join Britain's R.G. Edwards in experimenting with human eggs, Watson suggested that one course of action could be to prohibit all research on human cell fusion and embryos. Failing that, he proposed international agreements limiting such research before it becomes widespread and irresponsible, and before "the cat is totally out of the bag."

Watson is not alone in his worries. Last summer Biologist James Shapiro, one of three young scientists who successfully isolated a bacterial gene, gave up his promising career to take up social work because he feared government misuse of genetic achievements. An Episcopal priest, Canon Michael Hamilton of Washington (D.C.) Cathedral, called Shapiro's action a "loss of nerve." Yet the looming issues are enough to test the nerve of any thoughtful man. Central is the question: Who will decide? Who will make the choices not only of life and death, but what kind of life?

To consider such issues, Roman Catholic Lay Theologian Daniel Callahan

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and a number of like-minded ethicists and scientists have set up the Institute of Society, Ethics and the Life Sciences. Among the 70 members are Geneticist Theodosius Dobzhansky, Psychiatrist Willard Gaylin, Theologian John C. Bennett, and U.S. Senator Walter F. Mondale of Minnesota, who three years ago introduced a bill to establish an interdisciplinary committee to examine new scientific problems. It did not pass, but Mondale is trying again this year. "There may still be time," he says, "to establish some ground rules."

The long-term goal of the institute, says Callahan, is "legitimizing the problems," making the study of ethical issues a respectable part of the scientific curriculum. Too many scientists, says Gaylin, "see this as something mushy, something for Sunday morning, beyond the realm of science." To change that situation, the institute is trying to educate legislators on the importance of ethical considerations, and is encouraging universities to offer a solid background in ethical studies for "every scientific professional." At the Texas Medical Center in Houston, a similar interdisciplinary effort has been started by the Institute of Religion and Human Development and the Baylor College of Medicine. The Sunday School Board of the Southern Baptist Convention has developed a thorough adult-education course on biomedical issues as one of its electives for this spring.

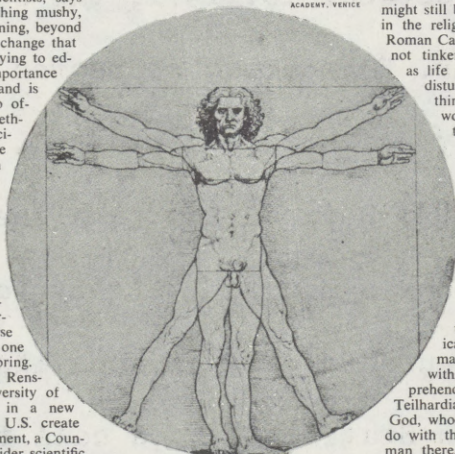
Cancer Researcher Van Rensselaer Potter of the University of Wisconsin has suggested in a new book, *Bioethics*, that the U.S. create a fourth branch of Government, a Council for the Future, to consider scientific developments and recommend appropriate legislation.

Indeed, some form of super-agency may be the only solution to the formidable legal problems sure to arise. Already, laws relating to artificial insemination by a donor are in confusion; developments such as donor mothers and cloning will raise even more complicated questions. If a mother had herself cloned without her husband's permission, for only one example, would he be legally responsible for the child?

**S**OME SCIENTISTS, however, frankly believe that laymen are ill equipped to discuss issues with them, let alone share control of what they do. The matters, they contend, are technical and should be decided by the technical men who understand them. Even if government does enter the field, points out Daniel Callahan, much of the

success of any ethical policy will depend on a responsible professional code. "If you depend solely on laws, sanctions and enforcements," says Callahan, "the game is over." Molecular Biologist Francis Crick is confident that basic morals and common sense will prevail. Some of the wilder genetic proposals will never be adopted, he claims, because "people will simply not stand for them."

Some ethicists and scientists argue that the worries, the plans and the proposals are premature, that ethics has always been an *ad hoc* thing, dealing with the world as it is, not as it might be in the future. Given the enormosity of the new problems and the speed of change, that attitude may be a luxury.



LEONARDO DA VINCI'S MAN  
Seizing the tiller of the world.

Beyond the sanctity of human life, the single criterion that ethicists most often mention as an absolute, or nearly one, is human freedom. Scientific advance, as they see it, can either promote freedom or inhibit it, but the distinctions are not always obvious or easy. The danger is that a democratic society might therefore fail to act at all, and by default pass the problems—and the solutions—to a small, uncontrolled elite, leading perhaps ultimately to a totalitarian government. The late author C.S. Lewis warned more than a quarter century ago that "man's power over Nature is really the power of some men over other men, with Nature as their instrument."

Despite the urgency, there can be no single ethical approach to the problems posed by the new genetics. The mecha-

nists may want simply to deal with the facts of molecular biology, exploiting its discoveries as well as they know how, but not quite willing to look beyond to spiritual considerations.

**A**MONG MANY religious thinkers, there is an affection for the futurist philosophy of Teilhard de Chardin, who wrote glowingly of a coming scientific age when men would exult in "fathoming everything, trying everything, extending everything" on their road to an ultimate Omega Point of shared godhood. Finally, there are those, believers and unbelievers, who know man to be a victim of what might still be called original sin. Those in the religious community, especially Roman Catholics, warn that man must not tinker with such sacred values as life and the family for fear of disturbing the natural order of things. Those in the scientific world, more pragmatically, tend to mirror Potter's warning about "dangerous knowledge"—knowledge that accumulates faster than the wisdom to manage it.

There is hardly a chance for complete consensus among the three schools, but it may help to borrow a lesson or two from each. From the mechanist, his conviction that there is an order in the physical world, discoverable and manageable if it is approached with enough humility to comprehend its mysteries. From the Teilhardians, the confidence that God, whoever he is, has something to do with the future and may yet meet man there. From those who still believe in man's propensity for error, the willingness to put on the brakes a bit and reflect on values and consequences—but also, as Helmut Thielicke counsels, the courage to act despite almost certain knowledge that man will make serious mistakes.

As they look back toward the time when man stood on the threshold of a biological revolution, troubled and uncertain, but determined to push ahead, what will the beings of the future say about their ancestors? Caltech Biologist Robert Sinshemer suggests an optimistic—and poignant—answer in his essay "The Mind of Pooh": "Perhaps, when we've mutated the genes and integrated the neurons and refined the biochemistry, our descendants will come to see us as we see Pooh: frail and slow in logic, weak in memory and pale in abstraction, but usually warmhearted, generally compassionate, and on occasion possessed of innate common sense and uncommon perception."

"CHOICES ON OUR CONSCIENCE"

THE KENNEDY INTERNATIONAL SYMPOSIUM  
ON  
HUMAN RIGHTS, RETARDATION, AND RESEARCH

On October 16, 1971, the Joseph P. Kennedy, Jr. Foundation sponsored an international symposium in Washington, D. C. on Human Rights, Retardation, and Research. Following the symposium, eighty-four of the distinguished participants issued the "Timberlawn Statement" as a call to action. Reprinted below are the "Timberlawn Statement", the list of signers of the statement, and the program of the symposium.

## "CHOICES ON OUR CONSCIENCE"

A CALL TO ACTION FROM THE KENNEDY INTERNATIONAL SYMPOSIUM ON  
HUMAN RIGHTS, RETARDATION AND RESEARCH

Timberlawn Statement

October 17, 1971

Science and technology have added immeasurably to human knowledge, health, well-being, and possibility for good. Inevitably, they have also radically changed the conditions of life and altered the choices that individuals and society have to make. Nowhere is this more evident than in relation to the dramatic advances being made in biological, genetic and medical science. In this field choices may be made, dogmatically or in ignorance, by inadvertence or by default, that can have an irreversible effect on our human future. We believe that moral thinkers and social critics have an obligation to start a process that might help the societies to which they belong to make these decisions in as responsible a manner as possible. They share this obligation with lawyers, physicians, social workers, natural and social scientists and the rest of our fellow citizens.

There are two dangers in which, as individuals or as a society, we can fall. One is to ignore old wisdom, the experience of the human race as incorporated in the great religions, philosophy, literature, history, the law, and the common sense of mankind. The other is to imagine that the old wisdom in its entirety is still valid in new conditions. When new options are available for human choice, this is not true. Inquiry is needed -- informed inquiry -- into the significance for human life and human good of the new changes in our knowledge and power.

The purpose of the inquiry should be to explore the options which growing knowledge of man's biology and of human society have made possible, and to consider the standards and the legal and social frameworks by which the choice among these options should be guided. To do this we need concerted inquiry, and the growth of a body of informed discourse, to which people from many different fields contribute. But we need much more -- a change in education and in public attitudes.

Physicians are inadequately educated with respect to the social and moral implications of decisions they are called upon to make. Lawyers know too little about the pressures, actual and potential, exerted by new biological and medical technology on the legal framework. Those who address themselves to ethical questions concentrate too often on abstract generalizations uninformed by close knowledge of the facts and complexities of actual moral choices. The sense that our moral standards need reconsideration, and that our laws and institutions are inadequate for the exercise of responsible moral concern, has much to do with the widespread feelings of frustration that exist in our society. We believe that professional and graduate education needs fundamental reform if the moral concerns of this and future

generations are to be properly guarded. For this public support, psychological and financial, are needed. But they are not sufficient. What is required is a recognition by educators of the depth of the problem, and the serious will to do something about it.

We also believe that the various publics of which this country is comprised should register their concern for these issues through their political representatives. They can give support to inquiry, to educational innovations, and to programs that improve the quality of our thinking and acting in matters so laden with potential for human welfare or woe, for human decency or human callousness.

What can the public do? We propose the following concrete steps for public discussion:

#### 1. PUBLIC AWARENESS

a. Greater assistance should be given to the media in the gathering of facts, viewpoints, new developments, and future consequences of decisions taken in the life sciences.

b. Greater support should be given to the development and training of reporters and public commentators on the social and ethical implications of scientific developments.

c. There is an urgent need for public forums, adult education programs, and open discussions among scientists, lawyers, physicians, clergymen, public officials, and educators on the concrete moral pressures each is under as they confront the decisions they must take.

d. Understanding of the problems requires open access to public institutions, especially those which deal with the sick, the mentally ill, the retarded and the handicapped. Mutual understanding requires public sensitivity to the daily dilemmas faced by institutional administrators and staff.

#### 2. CURRICULUM DEVELOPMENT

a. Primary and secondary school science courses should introduce children to the social implications of science as early and as thoroughly as possible.

b. College, university, and professional schools should examine social and ethical issues as an integral part of the educational process, both for the purposes of general education and for the training of professionals.

c. Special provision should be made for the students to gain actual experience in a clinical setting, so that the complexities of daily decisions will be early impressed upon them.

d. Special training programs should be developed to enable professionals to develop skills in analyzing ethical issues and in proposing solutions to them.

### 3. PROFESSIONAL EXAMINATION

a. Professional bodies engaged in the medical, behavioral, and life sciences should examine and continually re-examine professional codes of conduct, changing and improving these codes when necessary. Where codes do not now exist, they should rapidly be developed.

b. Understanding the nature of professional work requires painstaking re-examination in the light of new social needs and ethical dilemmas. Good professional practice and moral sensitivity cannot be separated.

c. Professional bodies should make systematic efforts to provide continuing opportunities for in-service training programs, special institutes and post-graduate education designed to keep professionally abreast of, and competent to deal with, perplexing scientific and clinical developments.

### 4. LEGISLATIVE ACTIVITY

a. Legislators should develop effective means of open communication between the public and scientific experts, concerning the social and moral implications of new scientific developments. Scientists and physicians should be prepared to make known to legislators the ethical problems they face.

b. Scientific development with social and moral implications often require legislative or judicial decision about which political leaders, on the one hand, and scientists, on the other, have an obligation to inform the public in advance.

### 5. SPECIAL TRAINING AND RESEARCH

a. Congress should allocate funds for research on the social and ethical consequences of scientific decision.

b. Progress for the development of skills in discerning the options facing us and the consequences of our present decisions need to be designed, funded, and implemented if expertise in social and ethical reflection is to be equal to the expertise in scientific developments.

### 6. THE PUBLIC INTEREST

Present legal structures must be examined to ascertain whether, under the conditions established by new technologies, some persons, especially among the powerless and the helpless, such as infants, the sick, the retarded, and the elderly, have rights that stand in need of defense, and by what means.

SIGNERS OF TIMBERLAWN STATEMENT

February 1, 1972

- Raymond D. Adams  
Harvard Medical School  
Boston, Massachusetts
- Thomas F. Anderson  
The Institute for Cancer Research
- David L. Bazelon  
Washington, D. C.
- George W. Beadle  
Chicago, Illinois
- Paul Berg  
Stanford University
- Royal A. Brink  
University of Wisconsin
- Daniel Callahan  
Hastings-on-Hudson, New York
- Mrs. Sydney Callahan  
Hastings-on-Hudson, New York
- Leonard Carmichael  
National Geographic Society
- Charles H. Best  
University of Toronto
- Dr. James Cheek  
Washington, D. C.
- John Cogley  
Center for the Study of Democratic Institutions
- Robert E. Cooke  
Johns Hopkins Hospital
- Andre F. Cournand  
Columbia University
- William Curran  
Harvard University
- Gilbert Dalldorf  
Oxford, Maryland
- Theodosius Dobzhansky  
University of California at Davis
- Philip Dodge  
St. Louis, Missouri
- Albert Dorfman  
University of Chicago
- Paul M. Doty  
Harvard University
- Father John Dunne  
University of Notre Dame
- Arthur Dyck  
Harvard University
- Sir John Eccles  
State University of New York at Buffalo
- John T. Edsall  
Harvard University
- Reverend John Fletcher  
Washington, D. C.
- Charles Frankel  
Columbia University
- Paul Freund  
Harvard University
- James Gallagher  
University of North Carolina, Chapel Hill
- Willard Gaylin  
Columbia University
- Edward S. Gleason  
Dedham, Massachusetts
- Robert A. Good  
University of Minnesota Medical School
- Harry H. Gordon  
Albert Einstein College of Medicine
- Reverend Canon Michael P. Hamilton  
Washington National Cathedral
- Albert B. Hastings  
La Jolla, Calif.
- Andre Hellegers, M.D.  
Georgetown University
- Father Theodore Hesburgh  
The University of Notre Dame
- Ernest R. Hilgard  
Stanford University
- C.H.W. Hirs  
Bloomington, Indiana

Bernard L. Horecker  
Albert Einstein College

Dwight J. Ingle  
University of Chicago

Nathan O. Kaplan  
Univ. of Calif., San Diego

Paul Kurtz  
New York State University, Buffalo

Lawrence M. Langer  
Indiana University

Philip Lee  
University of Calif. Medical School  
San Francisco

Albert L. Lehninger  
Johns Hopkins University

Fritz A. Lipmann  
Rockefeller University

Oliver H. Lowry  
Washington University

Reverend Richard McCormick  
Loyola University, Chicago

William McElroy  
National Science Foundation

Dr. John Meier  
Denver, Colorado

Robert K. Merton  
Columbia University

Karl Meyer  
Yeshiva University

Vernon B. Mountcastle  
Johns Hopkins University

James V. G. Neel  
University of Michigan

Dr. John T. Noonan, Jr.  
U. of Calif., Berkeley

Ralph Potter  
Harvard University

Dr. Dominick Purpura  
Yeshiva University

John C. Raines  
Temple University

Paul Ramsey  
Princeton University

Reverend Warren Reich  
Georgetown University

Dr. Howard Rusk  
New York University Medical Center

Dr. Bert Schmickel  
Baltimore, Maryland

James A. Shannon  
New York, N. Y.

Seymour J. Singer  
U. of Calif. San Diego

Robert L. Sinsheimer  
Calif. Institute of Technology

Tracy M. Sonneborn  
Indiana University

Curt Stern  
U. of Calif. Berkeley

Albert Szent-Gyorgyi  
Institute for Muscle Research

Dr. George Tarjan  
UCLA School of Medicine

Dr. Luther Terry  
University of Pennsylvania

James M. Gustafson  
Yale University

Maurice B. Visscher  
Minneapolis, Minnesota

Leroy Walters  
Georgetown University

William B. Wood  
Calif. Inst. Tech., Pasadena

Julius B. Richmond, M.D.  
Judge Baker Guidance Center

Marvin Karno, M.D.  
University of California

Nicholas Hobbs  
Vanderbilt University

Robert Loeb  
New York, New York

Dr. Louis Jolyon West  
Professor and Chairman  
Department of Psychiatry  
UCLA School of Medicine

Dr. Robert J. Stoller  
Professor of Psychiatry  
UCLA School of Medicine

Dr. Donald A. Schwartz  
Associate Professor of Psychiatry  
UCLA School of Medicine

Dr. James Q. Simmons, III  
Associate Program Director of Mental  
Retardation

Dr. Bernard Towers  
Professor of Anatomy and Pediatrics  
UCLA School of Medicine

Dr. Herbert J. Grossman  
Director, Illinois State Pediatric  
Institute

*"Choices on our Conscience:"*

THE JOSEPH P. KENNEDY, JR. FOUNDATION  
INTERNATIONAL SYMPOSIUM  
ON HUMAN RIGHTS,  
RETARDATION, AND RESEARCH



The John F. Kennedy Center for the Performing Arts  
and  
The Shoreham Hotel  
Washington, D. C.      Saturday, October 16, 1971

**MORNING**  
THE EISENHOWER THEATER

9 A.M.

**Plenary Session — Who Should Survive: Is Survival a Right?**

This case study involves a child born with both Downs Syndrome (mongoloid) and an intestinal block. The latter could be corrected through a fairly simple operation without which the child could not be fed and would die. The parents were asked for permission. They refused, saying that it would be unfair to their other two (normal) children to be brought up with a mongoloid sibling. The hospital sought the advice of a judge, who indicated that the court would not likely overturn the parents' decision under these circumstances. Subsequently the child was put in a side room and, over an eleven-day period, allowed to starve to death. The hospital staff was greatly upset, but took no action to hasten the child's death.

*Moderator:* ROGER MUDD, News Commentator, CBS, Washington, D.C.

*The Legal Aspects*  
*Essayists:* PAUL A. FREUND, S.J.D., Carl M. Loeb University Professor, Harvard Law School.

*The Moral and Ethical Aspects*  
JAMES GUSTAFSON, Ph.D., Acting Chairman, Department of Religious Studies, Professor of Ethics, Yale University.

*The Social Aspects*  
MICHAEL HARRINGTON, Author of *The Other America*, Social Critic, Lecturer, New York.

*The Psychological and Familial Aspects*  
MRS. SYDNEY CALLAHAN, Mother, Psychologist, Author, Columnist, Hastings-on-Hudson, New York.

*The Public Policy Aspects*  
THE HONORABLE WALTER F. MONDALE, U.S. Senate—Minnesota; Chairman — Select Committee on Equal Educational Opportunity; Member — Select Committee on Nutrition and Human Needs.

*Mental Retardation and Motherhood*  
RENÉE SYLVIE PORTRAY, M.D., Mother, Secretary General, Association Nationale Pour L'Aide Aux Enfants Retardés Bruxelles; Kennedy Award Winner 1966.

The Plenary Session will commence with a 30-minute documentary film pertaining to the case study. Participants in the film will join with the Essayists above in the discussion. Filmed participants are:

MRS. SYDNEY CALLAHAN.

ROBERT E. COOKE, M.D., Pediatrician-in-Chief, Johns Hopkins Hospital, Baltimore; Chairman, Kennedy Foundation Advisory Board; Kennedy Award Recipient, 1968.

WILLIAM CURRAN, Ph.D., Francis Glessner Lee Professor of Legal Medicine, School of Public Health, Harvard University; Kennedy Inter-Faculty Program in Medical Ethics at Harvard University.

REVEREND JOHN FLETCHER, Th.D., Director, Inter-Met Theological Institute, Washington, D.C.

RENÉE FOX, Ph.D., Professor of Sociology, Department of Psychiatry, University of Pennsylvania, Philadelphia.

## AFTERNOON

SHOREHAM HOTEL

**Panel #1—Who Should Be Born: Is Procreation a Right?**

AMBASSADOR ROOM

A case study of the Tay-Sachs disease. Tay-Sachs is a genetically based disease, which can be deciphered both before and during pregnancy. It is a fatal disease, the child being born normal, but beginning a terminal decline about the second year of life. The institutional care during the final two years of life is roughly \$25,000 a year. The obvious questions: Should we require a chromosome test before marriage, as we now require blood tests? Should two carriers of Tay-Sachs be allowed to have children? Is genetic abortion morally permissible?

*Moderator:* JOHN CHANCELLOR, News Commentator, NBC, New York.

*Essayists:* JAMES CROW, Ph.D., Professor of Genetics, University of Wisconsin, Madison.

DANIEL CALLAHAN, Ph.D., Director, Institute of Society, Ethics, and Life Sciences, Hastings-on-Hudson, New York.

JOHN T. NOONAN, JR., Ph.D., Professor of Law, University of California at Berkeley.

*Respondents:* JOSHUA LEDERBERG, Ph.D., Nobel Laureate; Professor of Genetics and Director of the Joseph P. Kennedy, Jr. Laboratories of Molecular Biology, Stanford University, Palo Alto, California.

JEROME LEJEUNE, Ph.D., Professor of Genetics, University of Paris, France; Kennedy Award Recipient.

CLAUDINE ESCOFFIER-LAMBIOTTE, M.D., Medical Editor, "Le Monde"; Director of the French Foundation for Medical Research, Paris, France.

WILLIAM STYRON, Author of *Confessions of Nat Turner*; Martha's Vineyard, Massachusetts.

2 P.M.

**Panel #2—The Human Rights of the Retarded: An Inquiry Into the Personal Freedom of the Retarded in Sexual, Educational, Social and Political Activities.**

REGENCY ROOM

Beginning with a case study in the sexual rights and/or lack of rights of an adult retarded person (isolation/sterilization, marriage, children, etc.), the larger question of the personal freedoms of the retarded will be examined. What kind of education do the retarded have a right to? What social and political freedoms do they enjoy or should they enjoy?

*Moderator:* THE RIGHT REVEREND PAUL MOORE, JR., Bishop Coadjutor of New York.

*Essayists:* NICHOLAS HOBBS, Ph.D., Provost and Professor of Psychology, Vanderbilt University, Nashville, Tennessee; Past President, American Psychological Association; Kennedy Foundation Advisory Board.

REVEREND RICHARD McCORMICK, S.J., Professor of Christian Ethics, Bellarmine School of Theology, Loyola University, Chicago.

GEORGE TARJAN, M.D., Director, Neuropsychiatric Institute, Professor of Psychiatry, U.C.L.A. School of Medicine; Kennedy Foundation Advisory Board.

DAVID L. BAZELON, Chief Judge, U.S. Court of Appeals of the District of Columbia, Washington, D.C.

*Respondents:* BERT W. SCHMICKEL, Director, Mental Retardation Administration, Maryland Department of Health and Mental Hygiene, Baltimore.

ELYCE FERSTER, Ph.D., Professor of Law, George Washington University, Washington, D.C.

MICHAEL NOVAK, Ph.D., Provost and Professor of Religion, State University of New York, Old Westbury, Long Island.

ANDRÉ HELLEGERS, M.D., Professor of Obstetrics and Gynecology, and Director, Kennedy Institute for the Study of Human Reproduction and Bioethics, Georgetown University.

**Panel #3 — Fabricated Babies: The Ethics of New Technologies in Beginning Life.**

**EXECUTIVE ROOM**

Beginning with a case study of the new technologies in procreation, this panel will study the ethical implications of procedures, such as implantation, cloning, and extra-uterine fertilization and maturation of human fetuses. To what extent do these technologies represent a quantum jump in man's capacity to control man? To what extent should these lines of research be continued or discouraged? What are the social implications of being able to determine the sex of one's offspring? Who controls the controllers?

*Moderator:* WILLIAM D. McELROY, Ph.D., Director, The National Science Foundation, Washington, D.C.

*Essayists:* ROBERT EDWARDS, Ph.D., Professor of Physiology, Cambridge University, England.

PATRICK STEPTOE, M.D., Professor of Medicine, Cambridge University, England.

ELIZABETH BOGGS, Ph.D., Past President, National Association of Retarded Children, Hampton, New Jersey.

PAUL RAMSEY, Ph.D., Professor of Christian Ethics, Princeton University.

ANNE McLAREN, Ph.D., Senior Principal Scientific Officer, University of Edinburgh, Scotland.

*Respondents:* LEON KASS, M.D., Executive Secretary, National Academy of Sciences and National Research Council, Washington, D.C.

HOWARD JONES, M.D., Professor of Gynecology and Obstetrics, Johns Hopkins University, Baltimore.

DAVID DAUBE, Ph.D., Professor-in-Residence, School of Law, University of California, Berkeley.

JAMES G. WATSON, Ph.D., Nobel Laureate; Professor of Molecular Biology, Harvard University; Director, Cold Spring Harbor Laboratory, Long Island, N.Y.

**Panel #4 — The Use and Misuse of Labeling Human Beings: The Ethics of Testing, Tracking and Filing.**

**BLUE ROOM**

Beginning with a case study in mental retardation, the panel will consider problems of labeling, testing and tracking which arise in a more general way in our society today. By what actual practice does a child in our society come to be labeled "retarded," "handicapped," or "culturally deprived?" Are there class or racial distinctions made, however unconsciously, in actual practice? Once a child is labeled, how does that affect the attitude of teachers, the child's own attitude in creation of his self-image? As a child leaves the educational process to enter the adult world, what problems face him because of prior labeling, tracking and filing? What about "right to privacy" in the issue of access to the filed information? Do the retarded possess the "right to work?"

*Moderator:* FRANK MCGEE, News Commentator, NBC, New York.

*Essayists:* CARL HAYWOOD, Ph.D., Director, the John F. Kennedy Center for Research on Education and Human Development; Kennedy Professor of Psychology, Peabody College, Nashville, Tennessee.

RALPH POTTER, Ph.D., Professor of Social Ethics, Harvard University Divinity School.

JANE MERCER, Ph.D., Professor of Sociology, University of California at Riverside.

JAMES GALLAGHER, Ph.D., Professor of Education, and Director, Institute of Learning, University of North Carolina, Chapel Hill.

*Respondents:* CHARLES G. HURST, JR., Ph.D., President, Malcolm X College, Chicago, Illinois.

SISTER MARIA AUGUSTA NEAL, SND, Ph.D., Professor of Sociology, Emmanuel College, Boston.

NORMAN ST. JOHN-STEVAS, Member of Parliament, Author, Lawyer, Journalist, Chelmsford, England.

BERNARD POSNER, Ph.D., Deputy Executive Secretary of the President's Commission on Employment of the Handicapped, Washington, D.C.

PROFESSOR RICHARD HERRNSTEIN, Department of Psychology, Harvard University.

**Panel #5 — The Modification of Human Behavior: The Ethics of Human Control.**

EMPIRE ROOM

Beginning with a case study of the use of operant conditioning in the control of the behavior of retarded people, this panel will examine broader ethical issues involved in various forms of the control of human behavior. What kind of conditioning and control is it morally acceptable for a society to exercise? What is the concept of man engaged in various sides of this debate? Who is to decide which behavior is to be modified and in which way?

*Moderator:* NORMAN PODHORETZ, Author and Editor, "Commentary" Magazine, New York.

*Essayists:* B. F. SKINNER, Ph.D., Edgar Pierce Professor of Psychology, Harvard University.

JEROME KAGAN, Ph.D., Professor of Psychology, Harvard University.

JOSÉ M. R. DELGADO, M.D., Professor of Neurophysiology (Psychiatry), Yale University.

ROBERT SHINN, Ph.D., Professor of Christian Ethics, Union Theological Seminary, New York.

WILLARD GAYLIN, M.D., Professor of Psychiatry and Law, Columbia University School of Law; President, Institute of Society, Ethics and Life Sciences.

*Respondents:* PAUL KURTZ, Ph.D., Professor of Philosophy, New York State University, Buffalo; Editor of "The Humanist."

GERMAINE GREER, Ph.D., Author of *The Female Eunuch*, Theatre Critic, Columnist of *The Sunday Times*, London.

BETTYE CALDWELL, Ph.D., Professor of Child Development, University of Arkansas, Little Rock.

EDWARD ZIGLER, Ph.D., Director, Office of Child Development, Department of Health, Education and Welfare, Washington, D.C.

THE REVEREND CANON MICHAEL P. HAMILTON, Washington National Cathedral.

NICHOLAS N. KITTRIE, Professor of Criminal and Comparative Law, the American University; Director, the Institute for Studies in Justice and Social Behavior; Author, *The Mentally Disabled and the Law*, *The Right to Be Different*; former Counsel to the Judiciary Committee of the United States Senate.

**Panel #6 — Why Should People Care?**

## TUDOR ROOM

This panel will discuss that dimension of moral, philosophical and religious questions which have been implicit throughout the panels of the day. Namely, why is it that people should care, in the first place? What is the situation of man that it is appropriate for people to respond with care for their fellow human beings? Or, does that represent a profound naivete? Should we, perhaps, not care? Would a stronger society then result? What are the various ways in which men seek to persuade themselves and others today that we should care about each other — the competing world-views and definitions of reality?

*Moderator:* CHARLES FRANKEL, Ph.D., Professor of Philosophy, Columbia University.

*Essayists:* LESZEK KOLAKOWSKI, Ph.D., Professor of Philosophy, All Souls College, Oxford University, England.

JACQUES MONOD, Ph.D., Nobel Laureate; Author of *Chance and Necessity*; Director, Pasteur Institute, Paris, France.

ELIE WIESEL, Author of *Night, Dawn, and Beggar in Jerusalem*, New York.

JEAN VANIER, Ph.D., Director, L'Arche, France.

ANATOLE SHUB, European Editor, Harper's Magazine, Paris; Moscow Correspondent (1967-1968), Paris Correspondent (1969-1971), both for the Washington Post.

*Respondents:* FATHER JOHN DUNNE, Ph.D., Professor of Christian Theology, University of Notre Dame.

REVEREND ANDREW YOUNG, Chairman, Atlanta Community Relations Committee.

MOTHER TERESA of Calcutta (India), Founder, Missionaries of Charity; Recipient of the Pope John XXIII Peace Prize.

SIR JOHN ECCLES, Nobel Laureate; Professor of Neurobiology, New York State University at Buffalo.

**Panel #7 — How Should People Care? The Ethics of Medical Services.**

## LOWER LOBBY

This panel will examine the issue of possible over-professionalization and systemization of medical service in the United States. Is a patient viewed and treated too simply as a "client" of the medical delivery system? What of the enormous problems of health care, especially for the poor — with the attendant need for system adjustment and control?

*Moderator:* PHILIP HANDLER, Ph.D., President, National Academy of Sciences, Washington, D.C.

*Essayists:* REVEREND IVAN ILLICH, Author, Educator, Morelos, Mexico.

MYRON WEGMAN, M.D., Dean, School of Public Health, University of Michigan.

E. FULLER TORREY, M.D., Assistant to the Director, National Institute on Mental Health, Bethesda, Maryland.

RASHI FEIN, Ph.D., Assistant Director, and Professor of the Economics of Medicine, Harvard University Center for Community Health and Medical Care.

*Respondents:* CHARLES SCHULTZE, Ph.D., Author, Senior Fellow, Brookings Institute; Former Director, Bureau of the Budget.

JOHN KNOWLES, M.D., General Director, Massachusetts General Hospital, Professor of Medicine, Harvard Medical School; President-Elect The Rockefeller Foundation.

ERIC CASSELL, M.D., Clinical Professor of Public Health, Cornell University, Medical College.

YVONNE POSTERNAK, M.D., President, International League of Societies for the Mentally Handicapped, Geneva, Switzerland.

WILBUR COHEN, Dean, School of Education, University of Michigan, Ann Arbor.

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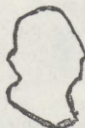
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THE PUBLIC HEALTH SERVICE GUIDELINES  
GOVERNING RESEARCH INVOLVING HUMAN SUBJECTS:  
An Analysis of the Policy-Making Process

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GUIDELINES GOVERNING RESEARCH INVOLVING HUMAN SUBJECTS:

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Introduction

The Public Health Service (PHS), largely through its National Institutes of Health (NIH), is the federal government's chief agency for supporting and conducting medical research. For the 1970 fiscal year NIH appropriations totaled \$1.5 billion<sup>1</sup> and NIH support for medical research was approximately 53% of total federal support for such research.<sup>2</sup> Thus, the tempo, character and direction of the nation's medical research effort is preeminently influenced by NIH programs and policies. Involved in this major research effort is a significant amount of clinical research using human subjects. In 1970 there were more than 11,000 research grants awarded by NIH and "slightly over 30%" of these involved human subjects.<sup>3</sup> The NIH, of course, is responsible primarily for the support of a national program of research in the health sciences. In implementing this responsibility, the NIH maintains its own intramural research program, issues contracts for particular research studies, and distributes research grants to non-profit research institutions and their investigators.

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<sup>1</sup>United States Department of Health, Education and Welfare, Public Health Service, National Institutes of Health. NIH Almanac 1971 (Washington, D.C.: GPO, 1971), p. 99.

<sup>2</sup>Ibid., p. 109.

<sup>3</sup>Interview with Donald T. Chalkley, Chief, Institutional Relations Section, Division of Research Grants, NIH, Bethesda, Maryland, June 22, 1971.

While other PHS components maintain similar, though smaller programs, policy related to the administration of the extramural research program is largely determined by NIH. This study is concerned with one of these policies, the PHS Guidelines regarding the protection of the individual as a research subject. Part I of the study examines the evolution of the first issuance of the PHS Guidelines and subsequent revisions through the promulgation of the Protection Of The Individual As A Research Subject<sup>4</sup> on May 1, 1969. Part II of the study analyzes the process by which these Guidelines were developed and examines the values, motivations and other underlying factors which led to their formulation. This analysis is constructed in the context of various theoretical and conceptual frameworks of decision-making and attempts to explain why the policy evolved as it did. It is not the purpose of this study to evaluate the Guidelines in principle or to assess their effectiveness. While the author recognizes the worth of a study "testing" the validity of many of the key decisions as well as of evaluating the efficacy of the Guidelines, such an effort would probably require another study equal to or greater in scope than this one.<sup>5</sup>

The importance of the PHS Guidelines is found most of all in their relationship to society, its health and its values. The Guidelines represent the government's attempt to protect the interest and investment

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<sup>4</sup>United States Department of Health, Education and Welfare, Public Health Service, Division of Research Grants. Protection Of The Individual As A Research Subject (Washington, D.C.: GPO, 1969), Publication No. O-348-095.

<sup>5</sup>Dr. Bernard Barber and his Research Group on Human Experimentation at Barnard College, Columbia University, have made such a study. Their findings were presented in a series of four papers at the American Association for the Advancement of Science (A.A.A.S.) Annual Meeting in Chicago, Illinois, December 1970.

of the American people. Such interest and investment are evidenced by the nation's annual commitment of more than one billion dollars to the NIH, which is "a decision by the American people, expressed through the Congress, to invest a substantial share of the nation's resources in research leading to the improvement of health."<sup>6</sup> But while the American people accept health as an important value, they also recognize the value of individual worth and dignity. The Guidelines reflect the fact that society assigns great importance to protecting the individual against possible injury while simultaneously desiring to maximize the freedom of scientific inquiry. "This policy seeks to avoid the danger of direct federal intervention, case by case, on the one hand, and the dangers inherent in decision by an individual scientist on the other."<sup>7</sup> The knowledge explosion has brought to the policy-making process a confrontation of scientific knowledge, ethical values and political responsibility. The Guidelines represent an attempt on the part of an administrative agency to reconcile those factors as they relate to a specific area of the quest for new knowledge and to develop a climate in which clinical research can prosper.

Examination of the Guidelines also focuses attention on public policy-making by a federal agency. By identifying the important substantive issues as well as the key decision-makers and the critical values which supported their policy decisions, one can more easily account for the

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<sup>6</sup>William H. Stewart, Former Surgeon General, United States Public Health Service, in Committee on Government Operations, National Commission on Health Science and Society. Hearings before the Subcommittee on Government Research, United States Senate, on S.J. Res. 145, 90th Congress, 2nd session, 1968, p. 210.

<sup>7</sup>Ibid., p. 211.

resultant policy. At a time when new scientific and technological developments have rekindled the debate regarding the merits and feasibility of various approaches to making public policy, an analysis of this policy-making process may help one to evaluate this debate. At the very least, it should provide valuable insight into one instance of public policy as it was actually developed.

## PART I: THE EVOLUTION OF THE P.H.S. GUIDELINES

In the Foreword to the Protection of the Individual as a Research Subject, former Surgeon General William H. Stewart wrote that "I believe that we have taken important steps toward protecting the human being who is a subject of research, while encouraging the conduct of excellent research on man."<sup>8</sup> The steps of which Surgeon General Stewart wrote evolved over a long period of time. While the first official statement of government policy concerning its extramural research program was issued only in 1966, the issues underlying the development of the policy extend some years further back in time. In order to understand more fully the basis upon which recent policy decisions were made, it will be useful first to examine the thinking and practices relevant to medical research prior to the initiation of formal government involvement

Historical Antecedents

Experimentation on man for scientific purposes dates back to the beginning of recorded history. Justification for such experimentation lies in the belief that, before any new technique may be considered acceptable medical practice or procedure for use in man, it must first be tested on a human being. "While prior experimentation in animals is

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<sup>8</sup>William H. Stewart, Protection of the Individual as a Research Subject, p. iv.

absolutely necessary when possible, the crucial study of new techniques and agents must be carried out in man. The current development of human biochemistry, human physiology, human pharmacology has made it plain that man is the 'animal of necessity.'<sup>9</sup> Paralleling this need for experimentation on man is the constant need to evaluate the procedures involved.

Prior to 1950 there were no specific federal or state statutes designed to regulate research institutions or investigators in their use of human beings for experimental purposes.<sup>10</sup> In fact, there existed some uncertainty among those involved in medical research about what the law did say about medical research. In general, most hypothesizing about what such legal doctrines might state with respect to human experimentation derived from a long line of British and American court decisions involving common-law actions of medical malpractice. As far back as 1767, in Slater v. Baker and Stapleton,<sup>11</sup> an English court concluded that "many men very skillful in their profession have frequently acted out of the common way for the sake of trying experiments . . . they have acted ignorantly and unskillfully, contrary to the known rule

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<sup>9</sup> Henry K. Beecher, Experimentation in Man (Illinois: Charles C. Thomas, 1959), p. 9.

<sup>10</sup> William J. Curran, "Governmental Regulation of the Use of Human Subjects in Medical Research: The Approach of Two Federal Agencies," Daedalus, vol. 98, No. 2, of the Proceedings of the American Academy of Arts and Sciences, Spring 1969, p. 54.

<sup>11</sup> 2 Wils. [K.B.] 359, 95 Eng. Rep. 860 (1767).

and useage of surgeons." The Court then disciplined the chief surgeon for failure to obtain the consent of the patient permitting the use of a new procedure. In the leading American case, Carpenter v. Blake (1871),<sup>12</sup> the Court cited the Slater opinion and concluded that "when the case is one as to which a treatment has been followed for a long time, there should be no departure from it . . . The rule protects the community against reckless experiments." The general conclusion drawn from these examples as well as subsequent decisions was that the scope of a physician's practice did not include the right to experiment with human beings. However, in a 1935 case, Fortner v. Koch,<sup>13</sup> the Court did recognize the importance of clinical investigation for medical progress. "We recognize the fact that if the general practice of medicine and surgery is to progress, there must be a certain amount of experimentation carried on." The Court stated further that such experimentation must be done with the patient's knowledge and consent and "must not vary too much from the accepted methods of practice." This case, similar to the ones before it, appears to indicate that the judiciary associated experimentation with irresponsible behavior and professional negligence. "Experimentation was seemingly equated with ignorant and unskillful departure from approved methods."<sup>14</sup> Yet none of these cases actually prohibited experimental procedures which took place in a controlled environment and which were directed toward the

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<sup>12</sup>60 Barb. 488 N.Y. (1871).

<sup>13</sup>272 Mich. 273; 261 N.W. 762 (1935).

<sup>14</sup>Elwyn L. Cady, Jr., "Medical Malpractice: What About Experimentation?," Annals of Western Medicine and Surgery, vol. 6, March 1952, p. 164.

discovery of new knowledge not necessarily of direct benefit to the patient or subject. Past court decisions simply "failed to recognize the important distinction between poor medical practice and legitimate research."<sup>15</sup> Yet, by the very nature of medical practice, physicians have always been involved in experimentation. "Every treatment is, in a sense, an experiment. There is no certainty that there will be complete safety for every patient, nor is there certainty that every diagnostic procedure will be safe. Each patient presents a unique and different research problem."<sup>16</sup> Even no treatment at all can be a form of experimentation. In these instances the traditional safeguard was the fidelity of the physician to his patient. However, medical research directed primarily at the acquisition of new knowledge, like all other activities in our society, is subject to the application of the law. While the law regarding the liability of the investigator involved in clinical research remained undeveloped, it appeared that some experimentation was permissible and that,

since the courts rely on what the profession develops as acceptable practice, the principles and methods established by reputable public and private organizations will be employed as guidelines in determining whether the research has been properly performed and whether the patients or subjects have been safeguarded.<sup>17</sup>

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<sup>15</sup>Irving Ladimer, "Human Experimentation: Medico-legal Aspects," New England Journal of Medicine, vol. 257, July 4, 1957, p. 23.

<sup>16</sup>Chauncey Leake, "Top Scientists Probe Dilemmas of Research Ethics," Medical World News, May 5, 1967, p. 37.

<sup>17</sup>Report of the National Conference on the Legal Environment of Medical Science. Published jointly by the National Society for Medical Research and the University of Chicago, Chicago, Illinois, May 27-28, 1959, pp. 82-83.

Thus, it was apparently in the best interest of the medical community to develop acceptable standards of care in their research.

#### Initial PHS Involvement

The PHS first became involved with the development of such standards with the opening of the NIH Clinical Center in 1953. The Center brought together talented young scientists and outstanding research leaders from throughout the world in order to seek new knowledge for the benefit of mankind. Edward J. Rourke, formerly of the Office of General Counsel, Department of Health, Education and Welfare (DHEW), emphasizes this primary goal. "If the Clinical Center meant anything at all, it was doing nonstandard things for more than therapeutic purposes . . . it sought to acquire new information."<sup>18</sup> Individuals admitted to the Clinical Center were categorized into two classes: (1) Normal Volunteers--healthy persons who had volunteered to serve as normal controls for clinical investigation. Most of the volunteers were members of religious sects who served in this capacity as an obligation of service to their particular faith; and (2) Patients--individuals who had a disease that required further investigation, diagnosis, or treatment.

With the establishment of the Clinical Center, the ethical and moral problems connected with research on human subjects came sharply

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<sup>18</sup>Interview with Edward J. Rourke, former Assistant General Counsel, Public Health Grants and Services Division, Office of General Counsel, DHEW, Arlington, Virginia, June 18, 1971.

into focus. The issues first arose "with respect to what limits should be applied in the case of normal subjects or volunteers."<sup>19</sup> At that time it was felt that the use of experimental procedures for patients was part of the doctor-patient relationship; "a positive decision was made that it would be intrusive for an administrative body to interfere with that relationship."<sup>20</sup> That relationship, of course, did not apply to the normal volunteer and this was an important area of concern among NIH officials. "A fairly extensive effort was made to devise a set of guidelines and procedures governing the use of normal controls in clinical investigations within NIH and the clinical research programs."<sup>21</sup> There were two important issues which came to the attention of NIH officials. "First, there was the degree of hazard or risk which we felt it was appropriate to subject anyone to. The second major question was the kind of information . . . which we felt should be made available to these people."<sup>22</sup> To answer those questions, the NIH, on November 17, 1953, issued a set of principles and procedures for the protection of the individual. The guidelines, referred to as "Group Consideration of Clinical Research Procedures Deviating From Accepted Medical Practice or

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<sup>19</sup>Interview with Joseph S. Murtaugh, former Director of the Office of Program Planning, National Institutes of Health, Washington, D.C., March 26, 1971.

<sup>20</sup>Interview with James A. Shannon, former Director of the National Institutes of Health, New York City, May 13, 1971.

<sup>21</sup>Interview with Joseph S. Murtaugh.

<sup>22</sup>Interview with Irving Ladimer, former Assistant Director of Research Planning, National Institutes of Health, New York City, May 14, 1971.

Involving Unusual Hazard,"\* placed primary responsibility for the formulation and conduct of clinical research and medical care on the principal investigators. However, "in order to assist the principal investigator in making determinations with respect to research projects and medical procedures which may involve deviation from accepted medical practice or potential hazard to the life or well-being of the patient or subject, methods for obtaining group consideration and advice are established."<sup>23</sup>

Such group consideration was instituted in the following manner. Each Institute Director and the Director of the Clinical Center was to establish a committee to review and make recommendations to him concerning clinical projects proposed by his staff that involved unusual hazard to the patient. A Medical Board, composed of representatives of each research institute and of the Clinical Center staff, established a Clinical Research Committee for the purpose of reviewing and reporting to the Medical Board on clinical research procedures involving unusual hazard or deviating from accepted medical practice. Cases were referred to the Committee by an Institute, by the Director of the Clinical Center, or by the Director of the NIH. This Committee reviewed the medical, scientific and ethical propriety of any questionable procedure. This procedure differed depending upon whether the project involved patients or normal volunteers. Projects involving patients were considered by the

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\*These guidelines were revised in July 1966.

<sup>23</sup>Stuart M. Sessoms, "Guiding Principles in Medical Research Involving Humans," Hospitals, Journal of the American Hospital Association, vol. 32, January 1, 1958, p. 62.

Clinical Research Committee only if referred to it for the reasons cited above. On the other hand, all research projects involving normal volunteers were referred to the Committee. Recommendations of the Committee were submitted, through the Medical Board, to the Director of the NIH, who had the final authority to decide such matters. With respect to the question of how much information was to be given to the research subject, the guidelines provided that "the patient or subject of clinical study shall be considered a member of the research team and shall be afforded an understanding suited to his comprehension of the investigation contemplated, including particularly any potential danger to him." Where there was the possibility of an unusual hazard, the written consent of the subject was required and a statement was entered on the patient's chart or on a separate memorandum, indicating his understanding of the procedure and its purpose, including the potential hazards to him, and his consent to participate. Through these 1953 Guidelines, the general problems that one might experience in clinical research were discussed and means for avoiding those problems were established.

#### The Extramural Research Program

In its early years, the extramural research program was not subject to the same guidelines adopted for the intramural program. To cope effectively with the processing of these research grants, applications were subjected to a review process initiated at the request of the National Advisory Health Council in 1946. A grant application was first reviewed by the Division of Research Grants (DRG) to assure

basic compliance with NIH requirements. The grants were then assigned to various Study Sections made up of scientists with acknowledged competence in the scientific disciplines involved in the proposed research project. These panels passed judgment on the relative scientific merit of the proposal. Following the Study Section review, the proposals were forwarded to the Advisory Councils of each of the respective Institutes. These groups, composed of highly qualified individuals representing diverse backgrounds, provided the NIH with a mechanism of peer judgment augmented by wider considerations of social needs essential to a balanced and effective research program. Their concern was with the relevance and importance of the proposed project to the mission of the Institute. Since there was never any requirement that a Study Section or Advisory Council employ any particular set of ethical principles or guidelines, these official bodies

relied primarily on the collective experience and judgments of their members. Almost without exception, they were members of a profession which had established a code or set of principles, or they had subscribed to a particular code such as those developed by the American Medical Association or the World Health Organization.<sup>24</sup>

Once a research proposal received approval, its conduct became the responsibility of the investigator and his institution for a period of up to seven years. The investigator was free to pursue his objectives, limited only by his own knowledge and ethical considerations and by any guidelines provided by his institution. In the late 1950's the NIH

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<sup>24</sup>Interview with Donald T. Chalkley.

explored the possibility of adopting the Nuremberg Code,<sup>25</sup> or one similar to it. This Code had developed from the trials of Nazi doctors who were tried for criminal action because of the experiments they had performed upon captives held in concentration camps and hospitals. The Code permitted some experimentation using human subjects, but explicitly enumerated the guidelines which should be followed when conducting such experimentation. "The effort foundered largely because of the difficulty of devising a single code that would cover with equal adequacy and equal flexibility the entire range of biomedical experimentation."<sup>26</sup> The pervasive posture of the NIH during these years was to permit researchers "to be guided by their own professional judgment and controlled by their own ethical standards as well as those of their institution."<sup>27</sup>

While the NIH did not issue formal regulations or guidelines governing medical research, this is not to suggest that officials were unconcerned with ethical problems or with protecting human subjects from potential research hazards. There was a continuous flow of advice from the NIH to individual investigators and institutions. In addition the National Advisory Councils had discussed some of these problems. "The questions constantly arose, is the institution aware of what this

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<sup>25</sup>United States v. Karl Brandt, et. al., United States Adjutant General's Department, TRIALS OF WAR CRIMINALS BEFORE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10 (October 1946-April 1949), The Medical Case, vol. 2 (1947).

<sup>26</sup>Interview with Donald T. Chalkley.

<sup>27</sup>Curran, *op. cit.*, p. 549.

individual investigator is intending to do? Have they really read this application over carefully?"<sup>28</sup> Former Surgeon General Stewart writes that "the National Advisory Heart Council had had discussions on human experimentation before I became Surgeon General (in 1965) and there had been developed at least a certification on grant applications that human subjects were protected."<sup>29</sup> Such concern developed primarily because of the rapid growth of medical research in the United States. By the latter part of the 1950's public expenditures for medical research had increased considerably as the NIH by expanding its extramural research program increased the capability for more clinical investigation throughout the country. Accompanying this expansion in medical research was a rapid increase in research involving human subjects. The nature of experimental procedures was also changing. The development of new surgical techniques made possible more complex and invasive surgical actions, culminating in the processes of organ transplantation. Initial efforts in the field of kidney transplantation had a special impact. Dr. James A. Shannon, Director of the NIH from 1955-1968, recalls an incident that occurred at a University hospital where a surgeon transplanted, without success, an animal kidney into a human being. What distressed Shannon most was that the surgeon "did it on his own without prior consultation with anybody" connected with the medical school or the University "and that the procedure as performed on the

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<sup>28</sup>Interview with Donald T. Chalkley.

<sup>29</sup>William H. Stewart, in a letter to this author, February 16, 1971.

basis of then current information had neither likelihood of therapeutic benefit to the patient nor likelihood of providing new scientific information."<sup>30</sup> Thus there developed at the NIH a

clear consciousness that there wasn't an adequate scientific base for that action, that it was entirely experimental in character and that there was the growing need to make certain that all the implications of that act . . . had been clearly examined and that there was a valid basis for proceeding with that kind of experimentation in terms of the scientific objectives to be achieved and the protection and condition of the experimental subject involved.<sup>31</sup>

Similar problems also arose in the intramural program.

It became apparent from reading the protocols from the various Institutes that too frequently the statement was made that this is a safe procedure because it has been utilized on a patient with a particular type of disease. So it seemed that certain nontherapeutic procedures were being utilized in patients with disease quite properly to obtain specific types of information relative to the nature of the disease or its effect on certain systems. But at the same time these were nonstandard procedures and did not receive the careful review that the same procedures would have received in a normal individual.<sup>32</sup>

The Clinical Center guidelines written in 1953 were, of course, very flexible with respect to treatment involving a doctor and his patient, which was dealt with in terms of the long-standing doctor-patient relationship. However, after reviewing some of the Institute protocols, Shannon began to inquire, on an Institute-by-Institute basis, about the types of programs of an experimental nature that were being conducted on diseased patients. "We found that much nonstandard diagnostic and

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<sup>30</sup>Interview with James A. Shannon.

<sup>31</sup>Interview with Joseph S. Murtaugh.

<sup>32</sup>Interview with James A. Shannon.

therapeutic devices were being used."<sup>33</sup> It soon became evident to NIH officials that

the absence of any written guidelines on the . . . employment of investigative drugs or procedures with respect to the sick patient was no longer a tolerable situation and that something in the way of a set of basic guidelines to govern this area of activity had to be developed. The pressure internally was growing by virtue of the same advances in medical and surgical capability that was being reflected as well in the Clinical Center as it was throughout the teaching hospitals of the nation.<sup>34</sup>

Another issue integrally linked to the expansion of the extramural program was "what kind of responsibility did the granting agency, the NIH, bear in respect to the circumstances and conditions in which investigative activity was carried out?"<sup>35</sup>

In addition to this internal perception of the problem by key NIH officials, the medical community was reminded of the issues pertaining to human experimentation by a 1959 book called Experimentation in Man. Author Henry K. Beecher wrote,

Ethical and moral implications and problems surround every facet of experimentation in man. The central conclusion is that it is unethical and immoral to carry out potentially dangerous experiments without the subject's knowledge and permission. It also requires . . . profound thought and consideration on the part of the physician, for the complexities of medicine are in some cases so great, it is not reasonable to expect that the patient can be adequately informed as to the full implications of what his consent means.<sup>36</sup>

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<sup>33</sup>Idem.

<sup>34</sup>Interview with Joseph S. Murtaugh.

<sup>35</sup>Idem.

<sup>36</sup>Beecher, op. cit., p. 43.

Recognition of this myriad of problems prompted the NIH in January 1960 to award a three-year grant to the Boston University Law-Medicine Research Institute to conduct a study of actual practices in clinical research in the United States with regard to the legal, moral and ethical issues involved. Of the study's<sup>37</sup> findings, of special significance were the results of a 1962 survey which was sent to 86 departments of medicine and which produced 52 responses. The replies did not indicate any trend toward establishing guidelines or procedures concerning clinical research. Only nine institutions replied that they had a procedural document; an additional five indicated either that they were in the process of developing such a document or that they favored one for their institution. However, upon close examination of those documents, only two of the nine were guidelines generally applicable to all clinical research. The departments were also asked if they used special consent forms for research; only 16 answered positively.

As a result of their recognition of the problems related to human experimentation, it is not surprising that NIH officials began at this time to search for a mechanism to assure that experiments for which public money was being used would receive public screening. According to former Surgeon General Luther L. Terry, "the granting authorities in the Public Health Service were concerned about the Government's responsibility in the absence of such a policy."<sup>38</sup> The

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<sup>37</sup>Irving Ladimer and Donald B. Kennedy, Clinical Investigation in Medicine: Legal, Ethical and Moral Aspects (Boston University Law-Medicine Research Institute, 1963).

<sup>38</sup>Luther L. Terry, in a letter to this author, February 23, 1971.

obvious problem was to develop a reasonable basis for judging the experimental activities of clinical investigators.

#### The Policy-Making Environment

During this period of time another federal agency was involved with a similar problem. Congressional hearings concerning the use and control of drugs were begun by Senator Estes Kefauver's Subcommittee on Antitrust and Monopoly in December 1958. As a result of the hearings, Congress passed the Drug Amendments of 1962,<sup>39</sup> which were explicit in requiring the Secretary of the Department of Health Education and Welfare, through the Food and Drug Administration (FDA), to issue regulations governing the testing of new drugs. Included in the amendments was a provision that made mandatory the consent of a subject before he became part of a procedure involving an experimental drug. The Congressional debate surrounding the introduction and use of experimental drugs had its effect on NIH policy-makers. It made clear to them "the inadequacy of the (PHS) Guidelines with respect to the physician-patient relationship" and also brought into focus the "question of what constituted consent."<sup>40</sup>

In the latter part of 1963, persons from the Office of the Surgeon General and officials from the NIH began more in-depth discussions of the subject of human research. As a result of some preliminary

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<sup>39</sup>P.L. 87-781, 21 U.S.C. 355.

<sup>40</sup>Interview with Joseph S. Murtaugh.

discussions, Shannon asked the Division of Research Facilities and Resources (DRFR),\* which at that time supported the establishment of general clinical research centers, to investigate clearance procedures of current investigation in terms of the conventions that existed at that time and in terms of what they would recommend as a suitable set of controls. Selected to head this study was Dr. Robert B. Livingston, then Associate Chief for Program Development, DRFR. In a memorandum to Shannon, Livingston outlined the steps that he would follow in proceeding with his investigation:

Stage one would aim to define the scope of the study, outline the essential issues, identify the ethically responsible relationships, and specify procedures for carrying out the main study if such is to be undertaken. Stage one would naturally involve a careful assessment of the wisdom of a Government agency undertaking an examination of those problems.

The second stage would undertake an examination of the range and tenor of present professional practices and the nature of the educational, informational, and intellectual guidance processes involved in providing patterns of practice in this delicate area. These considerations would be essential to any recommendations which might be transmitted to you and the Surgeon General.<sup>41</sup>

In replying to Livingston's memorandum, Shannon generally agreed with the scope and plan that Livingston had outlined and emphasized his concern about the end results of such a study.

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\*Due to a NIH reorganization, this division is now the Division of Research Resources (DRR).

<sup>41</sup>Robert B. Livingston, Memorandum to Director, NIH, "Moral and Ethical Aspects of Clinical Investigation," February 20, 1964.

I think it is important to emphasize that our end objective in this matter is to clarify our responsibility as a supporting agency and to identify the courses of action that our responsibility imposes upon us.<sup>42</sup>

Livingston, with assistance from NIH's Office of Program Planning, completed the study and submitted his report on November 4, 1964.<sup>43</sup> Concerning the background of the problem, the report made the following points:

Historically progressive changes in the kinds of clinical research possible to undertake are changing the nature of risks and values relating to clinical research.

There is no generally accepted professional code relating to the conduct of clinical research.

The legal status of clinical research is ambiguous.

The NIH supports clinical research in a wide variety of research institutions and hospitals. There exist conspicuous differences in institutional attitudes toward acceptable professional conduct of clinical research.

As the number of investigators, subjects and institutions engaged in clinical research increases and as the nature of the risks ventured changes according to the extension of research into new areas, a mounting concern is expressed over the possible repercussions of untoward events which are increasingly likely to occur and which may occur in an unfavorable pattern of context. Highly consequential risks are being taken by individuals and institutions as well as the NIH as a direct result of the complexity and ambiguity associated with research on man.<sup>44</sup>

The report also referred to the wide publicity then being given

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<sup>42</sup>James A. Shannon, Memorandum to Dr. Robert B. Livingston, "Review of the Ethical Aspects of Clinical Investigation," March 5, 1964 (Hereinafter referred to as "Memorandum to Livingston").

<sup>43</sup>Robert B. Livingston, Memorandum to Director, NIH, "Progress Report on Survey of Moral and Ethical Aspects of Clinical Investigation," November 4, 1964 (Hereinafter referred to as "Livingston Report").

<sup>44</sup>Ibid., pp. 2-3.

to earlier experiments at the Jewish Chronic Disease Hospital in Brooklyn, New York, which had resulted in charges of unethical conduct against Dr. Chester M. Southam and Dr. Emanuel E. Mandel. This research project had been funded by grants from the PHS and the American Cancer Society. It is important to examine some of the details of the incident because it probably "stimulated a greater attention to the problems"<sup>45</sup> associated with research in humans.

Dr. Southam was a physician acting as an employee of the Sloan-Kettering Institute in New York and was conducting cancer research. Dr. Mandel was the Director of Medicine and Director of Medical Education at the Jewish Chronic Disease Hospital. Both doctors were found guilty, censured, and placed on probation for their "conduct in the planning and execution of a research project at the Jewish Chronic Disease Hospital . . . prior to and on or about and after July 16, 1963."<sup>46</sup> The two doctors were found "guilty of fraud or deceit and unprofessional conduct for injecting cancer cells into patients."<sup>47</sup> The doctors informed the patients that they were going to do something to them of an experimental nature, but they "did not tell the patients that they were receiving cancer cell injections, and . . . [the patients] were not asked for written consent."<sup>48</sup> This episode focused attention upon the

<sup>45</sup>Interview with Edward J. Rourke.

<sup>46</sup>Regents Committee on Discipline, University of the State of New York, Report on the Matter of Southam and Mandel, Nos. 158, 159 (undated).

<sup>47</sup>"Two Physicians Put on Year's Probation," New York Times, December 15, 1965, p. 58.

<sup>48</sup>Elinor Langer, "Human Experimentation: Cancer Studies at Sloan-Kettering Stir Public Debate on Medical Ethics," Science, vol. 143, February 7, 1964, p. 552.

actual and potential risk that humans could carelessly be used to achieve the objectives of clinical investigators whose ultimate goals may have been very commendable, but who were exercising unacceptable judgment in achieving those goals. Since NIH officials had been concerned with such problems prior to this incident, its impact upon them is not surprising.

It made all of us aware of the inadequacy of our guidelines and procedures and it clearly brought to the fore the basic issue that in the setting in which the patient is involved in an experimental effort, the judgment of the investigator is not sufficient as a basis for reaching a conclusion concerning the ethical and moral set of questions in that relationship.<sup>49</sup>

The case also brought into focus the legal issues in which the PHS could become involved and dramatized the PHS responsibilities as a public agency. One participant at the National Advisory Health Council (NAHC) meeting on September 28, 1965, clearly expressed this concern when he stated that "if the Southam-Mandel case were to come to court, I think we [the PHS] would look pretty bad by not having any system or any procedure whereby we could be even aware of whether there was a problem of this kind being created by the use of our funds."<sup>50</sup> A related case, Fink v. Jewish Chronic Disease Hospital, did eventually reach a state court in New York. The defendant hospital demanded that the PHS, as one of the sponsors of the research, hold the hospital innocent and take over the defense of the action. The PHS rejected this demand and denied legal

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<sup>49</sup> Interview with Joseph S. Murtaugh.

<sup>50</sup> Stenographic Transcript, National Advisory Health Council meeting in Washington, D.C., September 28, 1965 (Hereinafter referred to as "Transcript, NAHC meeting").

responsibility. The case was settled out of court; the plaintiff reportedly received a large sum of money. While no precedent was established in the area of a grantor's legal responsibility, government official were clearly aware of the possible implications. One legal advisor, Edward J. Rourke, suggested at the time that "the greater need for the PHS is to define to what extent it has responsibility" with respect to its status as a granting agency.<sup>51</sup>

In his report, Livingston also directed his attention to the problem of NIH control.

NIH is not in a position to shape the educational foundations of medical ethics . . . More than that, whatever the NIH might do by way of designing a code or stipulating standards for acceptable clinical research would be likely to inhibit, delay, or distort the carrying out of clinical research . . . it would be advantageous to the national health research program if any general guidelines or code of clinical research behavior were developed by a nonfederal body . . . In our view, it would add to existing insecurities if the NIH were to assume an exclusive or authoritarian position concerning the definition of ethical boundaries or conditions mandatory for clinical research.<sup>52</sup>

One of the participants in the Livingston group recalls the reluctance on the part of the group to suggest any action by the NIH. "It was very difficult to get that small group that was convened to agree on the necessity for any action on the part of the NIH. There was strong resistance on attempting to set forth any guidelines or restraints or policies in this area."<sup>53</sup> It was this particular part of the report,

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<sup>51</sup>Edward J. Rourke, Memorandum to the Surgeon General, "Clinical Research," October 26, 1965, p. 3.

<sup>52</sup>Livingston Report, pp. 7-8.

<sup>53</sup>Interview with Joseph S. Murtaugh.

regarding the responsibility of the NIH, that Shannon found "wholly unsatisfactory, because what it said basically was that what a scientist does within his own institution is of no concern to the PHS and therefore there is no reason for you as Director of the NIH to be concerned with what was going on."<sup>54</sup> For Shannon this was an unsatisfactory resolution of a significant problem; it was his conviction that "we did have as an institutional responsibility the decision to assure that an institution had a mechanism that would have to be used to review the experimental work for suitability."<sup>55</sup>

In July 1964, as part of the process of developing its report, the Livingston group held an informal, ad hoc meeting with a small number of NIH advisors knowledgeable about problems relating to clinical research and experienced in a variety of research institutions and professional societies. This ad hoc committee made four recommendations; they were included in Livingston's report.<sup>56</sup> These recommendations may be summarized as follows:

1. That an appropriate professional group be encouraged to formulate a statement of principles relating to the moral and ethical aspects of clinical investigation.
2. That there was a need for more factual information regarding actual research practices.
3. That the NIH should consider providing advice, at the request of grantees, concerning the ethical problems and risk-reducing practices appropriate for the development of clinical research.

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<sup>54</sup>Interview with James A. Shannon.

<sup>55</sup>Idem.

<sup>56</sup>Livingston Report, pp. 9-11.

4. That research grant documentation relating to clinical investigation using human subjects should be identified for special consideration throughout the NIH-PHS review process.

In his letter of transmittal to the Surgeon General, Shannon agreed in principle with all four recommendations, and urged "that the highest priority be given [to] the rapid accomplishment of the objectives" of the first and fourth recommendations.<sup>57</sup> However, he gave evidence of his belief that the first recommendation "did not constitute a means for executive action,"<sup>58</sup> and suggested an alternative course of action.

We are in full agreement with the advisory group that there is a need for a widely acceptable statement of principles relating to the moral and ethical aspects of clinical investigation. The problem is to conceive of a manner by which the statement of principles will be assured of endorsement as a consensus position which can serve as a positive guide to the conduct of clinical research. The advisors recommend that this statement of principles be developed by an appropriate professional group. We are inclined to think a broader approach may be necessary.

To win general acceptance within not only the medical research community but also our society at large, the final statement of principles should probably emerge from a group which includes representatives of the whole ethical, moral and legal interests of society. The nature of this group and the manner of its convening remains the critical question in acting upon recommendation number one. This question needs further discussion.<sup>59</sup>

During 1965 Shannon continued discussion of this particular point with members of his own staff, with the hope of deriving a method by which to

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<sup>57</sup>James A. Shannon, letter of transmittal to the Surgeon General, "Moral and Ethical Aspects of Clinical Investigation," January 7, 1965 (Hereinafter referred to as "letter of transmittal").

<sup>58</sup>Interview with James A. Shannon.

<sup>59</sup>Shannon, letter of transmittal.

establish such a statement of principles. In the meantime, the issues surrounding experimental research on man were receiving world-wide attention. The World Medical Association issued its "Declaration of Helsinki," which permitted experimentation, with the patient's consent, if the experiment could be justified on therapeutic grounds.<sup>60</sup> The Medical Research Council of Great Britain declared that experimentation was permissible as long as "the true consent of the subject is explicitly obtained," at least in those cases where there is "no direct benefit to the individual and that, in consequence, if he is to submit to it he must volunteer in the full sense of the word."<sup>61</sup> A decision was subsequently made by Shannon and Surgeon General Terry to bring the matter before the National Advisory Health Council (NAHC) at its September 1965 meeting. The Council, which had members representing both the medical and scientific professions, was designed to take up issues within the health field which had very broad policy implications.

The feeling was that we ought to have this kind of public concurrence for the procedural actions that we were going to take. That is why it was submitted to the Council. The report of the ad hoc committee was never considered a sufficient basis of action without some kind of broader concurrence. The National Advisory Health Council provided that mechanism.<sup>62</sup>

Prior to that September meeting, however, another important policy development occurred within the NIH. In March 1965, the National

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<sup>60</sup>World Medical Association, "Declaration of Helsinki," Helsinki, Finland, 1964.

<sup>61</sup>Medical Research Council of Great Britain, "Responsibility in Investigations on Human Subjects," British Medical Journal, vol. 2, July 18, 1964, pp. 178-79.

<sup>62</sup>Interview with Joseph S. Murtaugh.

Advisory Heart Council adopted for the National Heart Institute a special procedure relating to cases involving hazardous clinical research proposals. The procedure stated that

it is the responsibility of the applicant or grantee institution to furnish the Institute with a statement of acceptance of its responsibility in the use of the procedure or procedures in question. The Institute has the responsibility for deciding whether to issue a statement of grant award and whether to release grant funds with or without first having obtained such a statement.<sup>63</sup>

Recognizing the problems faced by the NIH with respect to its responsibilities in the area of moral and ethical aspects of clinical investigation, Dr. John Sherman, then NIH Associate Director for Extramural Programs, urged that "each Institute adopt in principle the sense of the document as an interim measure until such time as it is superseded by a definite PHS policy."<sup>64</sup> At the July 1, 1965, meeting of the NIH Executive Committee for Extramural Affairs a motion to adopt the basic principles of the Heart Institute procedure was passed.

In a letter dated September 13, 1965, Congressman Cornelius E. Gallagher (N.J.), who was Chairman, Special Inquiry of the House Committee on Government Operations, notified Surgeon General Terry that he was conducting an investigation regarding the problem of the invasion of privacy as it was related to certain investigative activities of the Federal Government. Gallagher wrote that

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<sup>63</sup>"National Heart Institute Extramural Procedure In Case Of Hazardous Research Proposals," March 15, 1965.

<sup>64</sup>John Sherman, Meeting of the NIH Executive Committee for Extramural Affairs, July 1, 1965.

One of our primary concerns has been the use of personality tests, inventories and questionnaires in research projects financed by grants and contracts under the Federal Government. It is our belief that the sponsoring agencies should adopt effective policies and guidelines to make certain that the protection of individual privacy is a matter of paramount concern and that the testing is without compulsion.<sup>65</sup>

Terry referred this letter to Dr. Philip R. Lee, then Assistant Secretary for Health and Scientific Affairs, Department of Health, Education and Welfare, since the issues involved related not only to the activities supported by the PHS, but also to those of the Children's Bureau of the Welfare Administration and of the Vocational Rehabilitation Administration. In his reply, Lee wrote that "I do not believe that there is any disagreement on the principles involved. In my view, the main question is how to implement the principles and protect the individual against an invasion of privacy. We believe that this can best be done by a voluntary cooperative effort."<sup>66</sup> It is readily apparent, then, that throughout all levels of Government concerned with health affairs--NIH, PHS, and the upper levels of the Department of Health, Education and Welfare (DHEW)--there was, by 1965, a manifest concern with respect to the potential problems of experimenting with human beings and to the proposition that any proposal regarding the restraint of such activity should involve a minimum of federal intervention.

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<sup>65</sup> Representative Cornelius E. Gallagher (N.J.), letter to Luther L. Terry, September 13, 1965.

<sup>66</sup> Philip R. Lee, letter to Representative Cornelius E. Gallagher, November 22, 1965.

The Government's Response

The general question of the ethical, moral and legal aspects of clinical investigation was discussed with the NAHC at its meeting on September 28, 1965. Shannon reviewed the issues that had been discussed by his ad hoc advisory committee and his staff for the Council. His remarks emphasized the following points:<sup>67</sup> There was a general awareness on the part of people engaged in clinical research activity that the present guidelines under which they operated were inadequate. The problems stemmed from the change in the nature of clinical investigation. In the past, such investigation was more in the line of observation and stemmed from the normal physician-patient relationship in an attempt to find a more accepted treatment. However, observation was being replaced by manipulation in not only the diseased individual but also in normal individuals. Shannon stressed that

we have the feeling that since such investigation departs from the conventional patient-physician relationship, where the patient's good has been substituted for by the need to develop new knowledge, that the physician is no longer in the same relationship that he is in the conventional medical setting and indeed may not be in a position to develop a purely or a wholly objective assessment of the moral nature or the ethical nature of the act which he proposes to perform. We would think that if indeed this is the case, that investigative procedures that depart from those which are purely therapeutic in nature perhaps might be the subject of discussion before the fact with the investigator's peers, so that the environment within which he resides could reach a sound judgment as to the worthwhileness and to the validity of the things that he chose to do.<sup>68</sup>

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<sup>67</sup>This information has been taken from the Stenographic Transcript of the National Advisory Health Council Meeting, September 28, 1965 (Hereinafter referred to as "Transcript, NAHC Meeting").

<sup>68</sup>Ibid.

Shannon told the Council that, while there had been various attempts to develop codes and declarations, in his opinion they had been produced to fit the need of very specific circumstances and did not apply generally. Shannon concluded that he felt that the PHS had

a dual responsibility. One is a minor one of keeping the Government out of trouble . . . but really the major one is through these programs to try to encourage the development of terms and conditions that will encourage the flourishing of sound clinical investigation rather than discouraging it. I am searching for some way of creating a more profound sense of an institutional awareness of the importance of this aspect of the problem without tying them down and immobilizing them in their capabilities.<sup>69</sup>

Shannon and his associates hoped that their efforts would help to develop an institutional framework of review that would become "an integral part of the working process of biomedical research" and that "all investigative activity involving a human subject, regardless of the support, would be reviewed . . . as a part of the normal workings of a good scientific establishment."<sup>70</sup> Shannon also proposed for consideration by the NAHC a draft resolution which expressed the view that, in research involving human subjects,

the judgment of the investigator must be subject to review by his peers to assure an independent determination of the risk-benefit of the scientific work involved and maximum protection of the rights and welfare of the individual or individuals involved.

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<sup>69</sup> Ibid.

<sup>70</sup> Joseph S. Murtaugh, in a letter to this author, October 4, 1971

An arrangement to provide for this review by peers of proposed clinical investigation should be clearly provided for in every institution where such work is conducted.<sup>71</sup>

The Council expressed its concern with these issues and agreed that a restrictive code was not possible or warranted. It expressed a desire to study carefully the proposed resolution and to discuss it within the institutional environments of its members with the intent of taking a definitive stand on the issue in the Council's next meeting in December 1965.

Dr. Dael Wolfle, now Professor of Public Affairs at the University of Washington and a past member of the NAHC, explains the attitude of the Council toward the issues before it.

If rules were to be written that would apply generally over the country they would be either vague enough to require a good deal of interpretation or so specific as to try to cover a great variety of conditions. Neither alternative seemed desirable, in view of the fact that Federally supported research involving human subjects ranges over such a wide variety of conditions with respect to the kind of information to be secured from the subject, the methods of treatment, and possible harm.

Accordingly, we agreed that we should put the burden of responsibility on the experimenter and his professional colleagues. We thought the Government should have more protection than the mere statement by the principal investigator that his methods were sound and appropriate.<sup>72</sup>

On December 3, 1965, the NAHC adopted a resolution reflecting much of the earlier work done by Shannon with his advisors and staff. The

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<sup>71</sup>Draft Proposal for Discussion, "Resolution of the National Advisory Health Council on the Exercise of Ethical and Moral Judgment in the Conduct of Clinical Investigation," September 28, 1965.

<sup>72</sup>Dael Wolfle, in a letter to this author, April 7, 1971.

Council resolved that the

Public Health Service support of clinical research and investigation involving human beings should be provided only if the judgment of the investigator is subject to prior review by his institutional associates to assure an independent determination of the protection of the rights and welfare of the individual or individuals involved, of the appropriateness of the methods used to secure informed consent, and of the risk and potential medical benefits of the investigation.

The recommendations of the NAHC were accepted by Surgeon General Stewart; on February 8, 1966, he issued the first official Policy and Procedure Order (PPO No. 129) outlining the position to be taken by the PHS regarding clinical research using human subjects.

The PPO maintained that

No new, renewal, or continuation research or research training grant in support of clinical research and investigation involving human beings shall be awarded by the Public Health Service unless the grantee has indicated in the application the manner in which the grantee institution will provide prior review of the judgment of the principal investigator or program director by a committee of his institutional associates. This review should assure an independent determination: (1) of the rights and welfare of the individual or individuals involved, (2) of the appropriateness of the methods used to secure informed consent, and (3) of the risks and potential medical benefits of the investigation. A description of the committee of associates who will provide the review shall be included in the application.

The statement also indicated that the policy applied to "all PHS research and research training grant regulations and research and research training policy statements." In addition, assurances of compliance with the PHS policy were required with each separate grant application.

The general reaction of the research community toward the policy statement was favorable. "Opposition to the guidelines was

minimal. There was no doubt that American science was ready for this type of regulation."<sup>73</sup> Some opposition both of a procedural and of a substantive nature did develop.

There were behavioral scientists who felt that this would interfere with their research. They said how can we possibly find out about people if we don't ask them these very personal questions. There is a whole class of studies in social psychology that depend on deception of the subjects. This was one issue. Another issue was that the individual investigator felt that he was being tied up with more red tape.<sup>74</sup>

This opposition had little impact upon the policy-makers and their decision that such guidelines were required.

Once it was realized that the policy was necessary it was issued because we felt that we were going to the Congress to obtain money for certain types of investigation and we had a responsibility to see that amenities relative to the protection of individuals were not placed in jeopardy.<sup>75</sup>

Experience with administering the policy, however, led by July 1, 1966, to a major revision. A memorandum from Dr. Mordecai Gordon of the Division of Research Grants to the Assistant General Counsel, DHEW, describes the major administrative problem. "The most frequent apparent misunderstanding is reflected in the submission of an assurance for an insitution as a whole instead of for each application."<sup>76</sup> As a result of

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<sup>73</sup>Interview with James A. Shannon.

<sup>74</sup>Interview with Mordecai Gordon, former Special Assistant to the Director, Division of Research Grants, National Institutes of Health, Bethesda, Maryland, April 27, 1971.

<sup>75</sup>Interview with James A. Shannon.

<sup>76</sup>Mordecai Gordon, Memorandum to Assistant General Counsel, Department of Health, Education and Welfare, "Clinical Research and Investigation Involving Human Beings," April 18, 1966.

this feedback, PPO No. 129, Revised Policy, eliminated the requirement of individual assurances of compliance with each grant application and provided instead for an institution-wide assurance to cover all subsequent grant proposals. The assurances were to include (1) agreement with the principles of the policy; (2) a description of the method of review; (3) the competencies represented in the review committee; (4) the administrative mechanism for surveillance and advice; and (5) the manner in which the institution would assure itself that the advice of the committee would be followed. In addition to resolving significant administrative problems, the single institution-wide assurance had another purpose. In their attempt to develop an institutional framework of review which would encompass all investigative activity involving human subjects, NIH officials "hoped that the use of a single but institutionally oriented assurance would, in most, if not in all situations, stimulate consideration also of reviews by a similar process of projects not supported by PHS grants."<sup>77</sup> The revision also extended the necessity for peer group review of research using human subjects to all PHS grants and required the institutions to report any changes in policy, procedures, or in the composition of review committees.

In the month prior to the issuance of the revised PPO No. 129, Dr. Henry K. Beecher published an article in which he cited 22 examples of experiments using human subjects which involved serious ethical problems. Beecher wrote that

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<sup>77</sup>John F. Sherman, Deputy Director, NIH, in a letter to this author, November 5, 1971.

Evidence is at hand that many of the patients in the examples to follow never had the risk satisfactorily explained to them, and it seems obvious that further hundreds have not known that they were the subject of an experiment although grave consequences have been suffered as a direct result of experiments described here.<sup>78</sup>

While the article created quite an uproar in the medical research community, there is little doubt that the momentum to prevent such ethical errors was already strong within the PHS. If any problem did exist it was to find, to repeat an earlier statement by Shannon, "some way of creating a more profound sense of an institutional awareness of the importance" of the ethical and moral aspects of experimenting with man. The PHS Guidelines were an attempt to attain that objective.

On December 12, 1966, the Surgeon General, in order to clarify past statements as they related to the behavioral and social sciences, issued another policy statement. As indicated earlier, some investigators had complained that fully informed consent was impossible in much research, particularly in those cases involving psychological factors. The December clarification made it clear that the Guidelines applied to experiments of a behavioral or sociological nature, but PHS officials "tried to introduce into the clarification a little common sense. We tried to leave some leeway for judgments by both the investigators and the review committees."<sup>79</sup>

The clarifying statement also noted that there were some studies in the behavioral sciences that "did not require the fully informed

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<sup>78</sup>Henry K. Beecher, "Ethics and Clinical Research," The New England Journal of Medicine, vol. 274, June 16, 1966, p. 1354.

<sup>79</sup>Interview with Mordecai Gordon.

consent of the subject or even his knowledgeable participation." The clarification made clear the responsibility of the grantee institution to assure that experiments were "in accordance with the laws of the community in which the investigations are conducted and for giving due consideration to pertinent ethical issues." It also stressed concern for the protection of the subject as "most critical when the subject is not of age or competence to make an adequate judgment in his own behalf."

On January 24, 1967, the Surgeon General issued a further revision<sup>80</sup> of the July 1, 1966 statement. The primary purpose of this revision was to enunciate clearly the responsibility of the PHS:

Nothing in this institution-wide assurance should inhibit the PHS staff, advisory groups, or consultants from (1) identifying concern for the welfare of human subjects, and communicating this concern to the grantee institution, or (2) recommending disapproval of the application if the gravity of the hazards and risks so indicate.

The final major policy revision to be discussed in this paper was issued on May 1, 1969. The primary reason for this revision was the perceived need both to strengthen previous policy statements and to assure a greater consistency in interpreting and implementing their provisions.

It was on the basis of our experience with administering the policy that, for one thing, PPO No. 129 originally saw the light of day in February 1966, and over a period of months after that was revised and supplemented and pieced and patched together so many times that it became almost incoherent. So there was a need to put all of the policy in one pot, so to speak.<sup>81</sup>

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<sup>80</sup>PPO No. 129, Revised Supplement No. 3, January 24, 1967.

<sup>81</sup>Interview with Mark H. Conner, Institutional Relations Office, Division of Research Grants, Bethesda, Maryland, February 16, 1971.

On July 24, 1968, Dr. Philip Lee appointed a Task Force of various PHS-NIH officials to review and revise the guidelines for the protection of the individual as a research subject. The initial meeting of the Task Force was held on October 28, 1968. Eighteen months later, in a letter to the heads of institutions receiving PHS grants, the chairman of the Task Force summarized the group's findings. "The review confirmed the utility of the policy, but recommended changes in the policy statement to provide better understanding of the requirements."<sup>82</sup>

The changes were more procedural than substantive. The revised policy statement, Protection Of The Individual As A Research Subject, once again emphasized that protecting the rights and welfare of human subjects was a responsibility of the grantee institution. Specifically, the policy required that a review committee within each institution be concerned primarily with: (1) the rights and welfare of the individual, (2) the appropriateness and adequacy of methods used to obtain informed consent from the subject, and (3) the risks and potential benefits of the investigation. It was made clear that the Guidelines applied to all research involving human subjects, whether concerned with medical or behavioral studies. The most significant change from the criterion enumerated in prior policy statements was in criterion (3),

which recognized that direct benefits to subjects could be other than medical, and that the importance of the knowledge to be gained might justify a committee in permitting an informed subject to accept risks in the interests to humanity, even though there was no direct benefit to him.<sup>83</sup>

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<sup>82</sup>Eugene A. Confrey, Former Director, Division of Research Grants, National Institutes of Health, letter to Heads of Institutions Receiving PHS Grants, May 1, 1969.

<sup>83</sup>Donald T. Chalkley, letter to Mrs. Lindsey Miller Lerman, Center for Criminal Justice, Harvard Law School, January 25, 1971.

There were two other important changes. The policy provided a more detailed description of what constituted "consent." It stipulated that for minors or other legally incompetent persons, consent could be obtained from parents, guardians or next of kin. The policy stated that "such consent is valid, however, only if the individual is given a fair explanation of the procedures to be followed, their benefits and attendant hazards and discomforts, and the reasons for pursuing the research and its general objectives." It made clear that the subject "may withdraw his consent at any time." This represented, by far, the greatest amplification of the term "consent" on the part of PHS officials. The other important change was of a procedural nature. It required certification of the review of individual applications. The July 1, 1966 policy revision had required that each application had been or would be reviewed by the institutional review committee. "This requirement was dropped in March 1967, on the insistence of some institutions that this was a bothersome requirement."<sup>84</sup> It was the opinion of the Task Force, however, that in order to prevent any problems from arising concerning the PHS's recognition that the institution was aware that the experiment involved human subjects, such certification should once again be required. "Our intent, therefore, was to provide a device that would enable an awarding unit within the PHS to be certain that the institution had in fact recognized that human subjects were involved in a particular proposal."<sup>85</sup>

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<sup>84</sup>Interview with Donald T. Chalkley.

<sup>85</sup>Idem.

It might be helpful at this juncture to summarize the major provisions of the Guidelines:

1. Broad guidelines, rather than detailed controls, are provided.
2. There are three basic guidelines:
  - a. the protection of the rights and welfare of the individual,
  - b. the judgment of methods used to obtain informed consent,
  - c. the determination of the risks and potential benefits of the investigation.
3. Compliance with these guidelines is accomplished by submitting an institution-wide assurance for all projects funded by the PHS. The institution is not required to adopt a specific set of ethical principles as long as its methods and procedures conform to the relevant principles outlined in the PHS Guidelines.
4. A system of self-regulation is established in the institutions funded by the PHS. This does not imply, however, a passive attitude on the part of the PHS. The Service retains its responsibility for a final overview of all research proposals.
5. Supervision of the Guidelines is vested in a review panel of the peers of the investigator within his own institution. Members of the panel cannot have a vested interest in any project that they review.
6. The committee review is not to be an independent review of the Guidelines for protecting the research subject. Rather it is a review of the judgment of the investigator and his methods for complying with the Guidelines. In this manner, the PHS places the primary responsibility for designing and carrying out the research project on the investigator.
7. The PHS has refrained from rigorously defining such terms as "informed consent," "rights and welfare of human subjects," and "invasion of privacy." However, it has attempted to provide the review committees, particularly in the May 1, 1969 statement, with a frame of reference for reaching a consensus regarding the meaning of such terms.

Rapid advances in biomedical science and the increase in the use of human subjects in research experiments have resulted in enormous benefits to the health of this nation. Such progress, however, has also brought into focus various ethical and social problems related to the

use of human beings as research subjects. Instances such as the Southam-Mandel case and those cited by Beecher provided ample evidence that the problems are real. In response to these developments, the PHS has felt it necessary to review its responsibility in the area of clinical research and to determine the course of action that such responsibility required. There were a variety of interests involved: among them the research subject, the clinical investigator, and the general public. The crucial question was how to balance those interests, weighing both the objectives being sought and the values held by key groups in society. This portion of the study has attempted to trace the evolution of the PHS's answer to that question. Whether well or badly done, government officials did define their responsibility and proceeded on a course of action designed to fulfill that responsibility. To explain why those officials defined their responsibility as they did and why they took a particular course of action may provide valuable insights into the policy-making process used to approach a very complex and sensitive problem.

PART II: THE P.H.S. GUIDELINES:  
AN ANALYSIS OF THE POLICY-MAKING PROCESS

Government exists precisely for the reason that there is a need to have special persons in society charged with the function of promoting and protecting the public interest.<sup>86</sup>

Paul Appleby  
Big Democracy, 1945

The PHS Guidelines are the result of an effort by one agency of the government to protect and promote the public interest and to maintain the delicate balance between the welfare of the research subject and the expansion of medical research. In this specific case there existed a point of tension between these two objectives with respect to medical experimentation on human subjects, since procedures to be used for the benefit of man must first be tested on human beings. There have been instances when investigators, who have justified their action by the need to promote research, have disregarded the welfare of the individual. Clearly, there has been a conflict between two values, both strongly held in American society. The task which confronted government policy-makers, themselves former scientists, was to resolve that conflict without excessively sacrificing either the welfare of the individual or the benefits to be gained from future research. The comments of a past member of the NAHC illustrate the dilemma:

Some of us felt regretful at the necessity of writing an additional rule or regulation . . . for what we were doing was to impose one more "bureaucratic" restriction. However, we thought the "restriction" necessary, both in order to protect subjects against occasional lapses from good practice and also to assure Congress and the public that good practice was always to be insisted upon.<sup>87</sup>

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<sup>86</sup>Paul Appleby, Big Democracy (N.Y.: Alfred A. Knopf, 1945), p. 5.

<sup>87</sup>Dael Wolfle, in a letter to this author.

The purpose of this part of the study is to analyze the policy-making process outlined in Part I. That analysis will be based on an eclectic framework of various concepts of policy-making, drawn primarily from the literature of the social sciences. Within this framework, an attempt will be made to explain why the PHS Guidelines took the form that they did.

On the most basic level the Guidelines which resulted can best be explained in the context of what Amitai Etzioni refers to as a "mixed-scanning strategy." In such a strategy, policy-makers differentiate fundamental decisions from what Etzioni terms "bit decisions." Fundamental decisions

are made through an exploration of the main alternatives seen by the actor in view of his conception of his goals, but . . . details and specifications are omitted so that overviews are feasible. Bit decisions are made "incrementally" but within the contexts set by fundamental decisions.<sup>88</sup>

It is the fundamental decisions, then, that set the basic direction of policy and it is the incremental or bit decisions that are made either to implement those basic decisions or to revise them. Etzioni also suggests that "the cumulative value of the incremental decisions is greatly affected by the underlying fundamental decisions."<sup>89</sup> The decisions by the PHS in the mid-1960's to assume formal responsibility in an area theretofore void of government involvement and to adopt a particular course of action represent such fundamental policy decisions. Actions subsequent to those decisions were for the most part attempts

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<sup>88</sup>Amitai Etzioni, The Active Society (N.Y.: The Free Press, 1968), p. 283.

<sup>89</sup>Ibid.

by policy-makers to implement through bit decisions their initial decisions more effectively.

The most important task confronting the policy-makers in developing the PHS Guidelines was, to use Yehezkel Dror's concept, the "processing of values."<sup>90</sup> According to Dror, "values can be mutually independent, mutually reinforcing, contradictory or anywhere in between. In their 'raw' form, they are not very useful for evaluating problems or formulating goals for public policymaking . . . values should be specified at least enough to point out the main avenues of action and some rough priorities for them, including the basic values that must not be impaired."<sup>91</sup> Prior to the 1960's, there was no formal policy by the PHS regarding research involving human subjects in its extramural program and there was no formal attempt to specify and to order values according to some scale of priorities so that such a policy might be established. That the PHS did not have such a policy by this time is not very surprising. The rationale underlying the lack of an explicit policy included, as this author views it, two major considerations. First, the problem was so complex that caution was generally accepted as the best way to approach the question of federal involvement. One authority felt that

it is not my view that many rules can be laid down to govern experimentation in man. In most cases, these are likely to do harm than good . . . legal development can be helpful and directed toward progress or can be harmfully restrictive. Which it shall be will be determined by the breadth of understanding expended on this 'complex subject.'<sup>92</sup>

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<sup>90</sup>Yehezkel Dror, Public Policymaking Reexamined (Pennsylvania: Chandler Publishing Co., 1968), pp. 164-66 contain a detailed explanation of this phase of policy-making.

<sup>91</sup>Ibid., pp. 164 and 165.

<sup>92</sup>Henry K. Beecher, "Experimentation in Man," Journal of the American Medical Association, vol. 169, January 1959, p. 471.

Hence, if there was to be a fundamental change in policy it would have tended to evolve over a period of time, rather than to appear suddenly. The evolutionary process was well along by the start of the 1960's. The second factor which helped to determine the PHS's aloof stance on the issue of research guidelines was the traditional concept of the purpose of a research grant and of the inherent nature of scientific research.

The traditional grant is essentially string free. This was true in the early days of the National Cancer Institute program which started in 1937. The extramural program . . . has repeatedly emphasized the need of the Federal Government to disengage itself from direct control of the grant in any way. It was the feeling that it would not be in keeping with the traditions of scientific freedom for the government to exert any degree of control over the conduct of the work.<sup>93</sup>

This "was a very strong tradition within the PHS . . . the limited approach in the clinical research field was due largely to this tradition."<sup>94</sup> These two factors--the complexity and uncertainty surrounding the problem and the traditional concept of the research grant--help explain the early attitude of the PHS. However, views and values of policy-makers frequently change as new experiences with a problem or a policy shed light on what is possible and desirable, and such was the case with respect to this policy issue as the 1960's unfolded.

Dror has written that "an intuitive awareness of 'problems' can be consciously cultivated by introspection and by systematically surveying subjectively-felt problems by means of, for instance, brainstorming sessions and panel discussions."<sup>95</sup> Certainly the efforts of Shannon and his staff

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<sup>93</sup>Interview with Donald T. Chalkley.

<sup>94</sup>Interview with Edward J. Rourke.

<sup>95</sup>Dror, op. cit., p. 170.

and the Livingston group represent mechanisms for the introspection and surveying cited by Dror. It was because of the meetings and discussions held by these groups that government officials came to realize in a concrete way that the expansion of the NIH clinical research program and the growth of new and complex medical procedures made the absence of some type of government policy no longer tolerable.

The basic force behind the Guidelines was an internal perception of the problem, arising out of the growing awareness that we had cultivated an investigative capability, particularly in the surgical area, that now presented a whole new set of issues in terms of the extent to which individuals could be submitted to that kind of capability for experimental and research purposes.<sup>96</sup>

As an outgrowth of this recognition, two important considerations became of central importance. First, it became apparent that the judgment of the investigator was "not sufficient as a basis for reaching a conclusion concerning the ethical and moral set of questions in that relationship."<sup>97</sup> Second, it became clear that it was necessary to clarify the responsibility of the NIH "as a supporting agency and to identify the courses of action that that responsibility" imposed.<sup>98</sup> Implicit but inherent in these two interrelated considerations was the fundamental decision to intervene, to whatever degree was found necessary and desirable, in the research programs of institutions whose projects were funded by the PHS. Shannon, with reference to the PHS Guidelines, declares that "as soon as we decided that other institutions were not behaving responsibly as we felt that we should behave then it was inevitable that this development would come."<sup>99</sup> The next

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<sup>96</sup>Interview with Joseph S. Murtaugh.

<sup>97</sup>Idem.

<sup>98</sup>Shannon, Memorandum to Livingston.

<sup>99</sup>Interview with James A. Shannon.

important decision to be made was to determine the direction that such intervention would take. It was in this stage of the policy-making process that the "processing of values" assumed such an important role.

Since this was so it might be useful at this point to discuss the concept of the "processing of values." Values are the principles by which one establishes priorities of importance among needs, demands and goals. The growth of new and complex medical procedures presented a whole new set of issues with respect to securing protection for the research subject without immobilizing the clinical investigator. Policy-makers realized that, as techniques of medical research became more sophisticated, the problems they now experienced would become more complex. The nature and degree of this complexity was unclear to them, nevertheless they believed that their most important task was to determine how the best possible balance between the welfare of the research subject and the requirements of medical research could be assured.

The obvious difficulty for policy-makers in this case was determining "the best possible balance" for all situations at all times in the future. The difficulty was very real, since what may be highly valued in one circumstance might be of only minor concern in another circumstance. Another important variable was that, as man's capability for doing and evaluating medical research increases, his practical information about certain experimental procedures will also increase, resulting in possible changes in the risks/benefits ratio. Thus as more or different factual information is obtained, there will be a greater tendency for a shift in those values viewed as relevant to attacking an explicit problem. Frequently, goals are altered

in light of both a change in available means and of a change in the cost of achieving an objective. Of course, one can also view the decision-making process as beginning first with a shift in values which then affects the design of policies and the role played by certain facts. Even during one particular point in time "we must deal continually with conflicts of value, where one person's gain is another's loss."<sup>100</sup> The ordering of priorities will differ among individuals, with one willing to sacrifice some value at the expense of another while another person remains unwilling to make the same sacrifice. Hence, the crucial problem for decision-makers arises "from multiplicity and fluidity of values and from social disagreement about values."<sup>101</sup> Thus, it is not realistic to expect a precise and permanent ordering of values when a variety of persons and institutions are involved in the decision-making process.

There appear to have been five basic values articulated by the policy-makers which played an important role in the decision-making process. Each of these values were included in what Dror designates as the "basic values that must not be impaired." First, there was the strongly-held belief that no man had the right to risk the health and welfare of another human being without his knowledge and consent. This was apparent from the very beginning of the NIH attempt to assess the environment of clinical research. Shannon, in his request to Livingston to inquire into the existing state of clinical

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<sup>100</sup>Victor A. Thompson, Decision Theory, Pure and Applied (1971 General Learning Corporation), p. 7.

<sup>101</sup>Charles E. Lindblom and David Braybrooke, A Strategy of Decision: Policy Evaluation As A Social Process (London: Collier MacMillan, Ltd., 1963), p. 113.

investigation, expressed the desire for a mechanism that would "serve as some protection for the individual who submitted to these research procedures."<sup>102</sup> Second, there was the belief in the impropriety of excessive government involvement. Dr. Eugene A. Confrey suggests that "surveillance by the Federal Government of research procedures and their ethical implications relating to tens of thousands of grants and contracts is . . . infeasible, to say nothing of its propriety."<sup>103</sup> While although the management of such a task was viewed as impracticable, it was the excessive surveillance by the Federal Government that was presumed to be improper and this was a crucial factor in determining the substance of the policy. This value judgment provided the basis for the next one. The policy-makers valued the importance of cooperation between the PHS, the institution, and the individual investigator. This value judgment was widely supported throughout all levels of the bureaucracy. There were three parties involved in this cooperating effort. Since the investigator designed the research, he was in the best position to evaluate the propriety of his procedures. However, "the investigator is first and foremost a scientist in search of new knowledge, and it would not be in accord with our understanding of human motivation to expect him always to be as vigilant for his subject's welfare as for the productiveness of his own research."<sup>104</sup> Thus, recognition was given to "the institution . . . [as] the proper agent for overseeing research programs involving human subjects."<sup>105</sup>

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<sup>102</sup>Interview with James A. Shannon.

<sup>103</sup>Eugene A. Confrey, "PHS Grant-Supported Research With Human Subjects," U.S. Public Health Reports, vol. 83, February 1968, pp. 127-33.

<sup>104</sup>Office of Science and Technology, Privacy and Behavioral Research (Washington, D.C.: GPO, February 1967), pp. 5-6.

<sup>105</sup>Confrey, "PHS Grant-Supported Research," op. cit.

The third party and spokesman for the public was the sponsoring agency. The agency was responsible for assuring that the investigator and his institution were cognizant of the importance of the ethical aspects of the proposed research and that they had done what was necessary to protect the welfare of the research subject. The fourth value considered by the policy-makers was the conviction that the diversity inherent in scientific research was desirable. They believed that the preservation of such diverse research precluded either a too broad or a too restrictive policy. Dael Wolfle expressed this belief earlier when he wrote that

neither alternative seemed desirable, in view of the fact that Federally supported research involving human subjects ranges over such a wide variety of conditions with respect to the kind of information to be secured from the subject, the methods of treatment, and possible harm.

Hence, there was no attempt on the part of the government to apply common rules to diverse situations. The policy-makers also valued highly the grant-oriented program, which they believed was of a special nature. This fifth value was, in part, held over from earlier years when the need was emphasized for "the Federal Government to disengage itself from direct control of the grant in any way."<sup>106</sup> Policy-makers still found it improper for the Government to constrain the investigator in his search for knowledge.

The agency has not contracted for a tangible product, to be produced under rigorously specified terms and conditions. On the contrary, a grant is interpreted as a form of financial assistance to an institution on behalf of an investigator so that he may pursue a problem in which he is interested and which coincides with an area of biomedical research relating

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<sup>106</sup>Interview with Donald T. Chalkley.

to a national objective. Given this concept, the agency will endeavor to optimize the conditions conducive to the advancement of knowledge, including maximal freedom of inquiry.<sup>107</sup>

These, then, were the five basic values processed by the policy-makers and subsequently incorporated into the resolution promulgated by the NAHC on December 3, 1965. This resolution represents a fundamental decision in Etzioni's terms. The Council gave policy-makers the "broader concurrence"<sup>108</sup> they thought necessary to effectuate their policy aims. The use of such a mechanism reflects what Dror has identified as the "organizational and social distance between the units" involved in policy-making. Such distance is necessary, according to Dror, in order that the units "operate at high quality"<sup>109</sup> so that a policy will have a better opportunity to succeed. The policy-makers agreed that

it was much more important for an external group to make pronouncements that are going to be restrictive on themselves as they appear as professionals within an institution than for us as federal bureaucrats . . . to enunciate a restrictive policy.<sup>110</sup>

The Guidelines which subsequently evolved were a result of an effort by policy-makers to bring form and direction to their basic values in order to achieve their overall goal. That goal was to develop a mechanism that would both protect and promote the interests of the American people, and that would neither sacrifice the welfare of the individual nor deny the nation the benefits which would accrue from future research. In order to

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<sup>107</sup>Confrey, "PHS Grant-Supported Research," op. cit.

<sup>108</sup>Interview with Joseph S. Murtaugh.

<sup>109</sup>Dror, op. cit., p. 211.

<sup>110</sup>Interview with James A. Shannon.

develop a policy that would assure optimum protection of human subjects as well as achieve the goals of research, a consensus developed among policy-makers that a detailed code of ethics that "did not apply generally"<sup>111</sup> was neither practical nor desirable. Restrictions that might be warranted in a particular situation might be unjustified in another. The policy-makers reasoned, therefore, that "such control would be likely to inhibit, delay and distort the carrying out of research."<sup>112</sup> In their attempts to design a workable policy, within the context of their five basic values, the policy-makers were able to decide upon the basic direction that the Guidelines were to take: primary responsibility for executing the policy would reside at the local level. Of course, through the PHS-NIH review process federal officials maintained their responsibility of final judgment of all research proposals. It seems fair to conclude that in the case of this particular policy the five basic values specified by policy-makers formed the framework in which all later fundamental and incremental policy decisions were made. The construction of such a framework was an essential step because of the important role played by values in determining policy objectives, the kinds of implementing mechanisms that could be established to achieve them, and the resulting degree of success. General agreement among policy-makers regarding basic values remained constant throughout this decision-making process, but, as Dror writes, "values can be specified and ordered to

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<sup>111</sup>Shannon, Transcript, NAHC Meeting.

<sup>112</sup>Donald T. Chalkley, "Intent and Experience in the implementation of PHS Regulations Concerning Projects Involving Human Subjects," speech before the American Psychological Association, San Francisco, California, August 31, 1968.

various degrees" and what is required on this continuum "depends very much on the particular policy that has to be made."<sup>113</sup> Since value considerations are intertwined with cognitive considerations and since both considerations may vary with changing conditions, policy-makers often choose to effect new policies through incremental changes. Incremental policy-making "proceeds through a sequence of approximations. A policy is directed at a problem; it is tried, altered, and tried in its altered form, altered again, and so forth."<sup>114</sup> Dael Wolfle indicated in a statement cited earlier that "research involving human subjects ranges over a wide variety of conditions with respect to the kind of information to be secured from the subject, the methods of treatment, and possible harm." It was unreasonable, therefore, to expect an accurate forecast of those myriad of conditions. The incremental approach to decision-making focuses on margins or increments of change so that only small changes from the status quo are evaluated. The approach is "deliberately exploratory. Rather than attempting to foresee all of the consequences of various alternate routes, one route is tried, and the unforeseen consequences are left to be discovered and treated by subsequent increments."<sup>115</sup> Any attempt to go beyond this, suggests Charles E. Lindblom, is usually unrealistic and perhaps unwise; policy-makers possess neither the knowledge to predict future outcomes, nor are they able to reach agreement on the ordering of the various values involved. Thus, by making policy decisions incrementally,

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<sup>113</sup>Dror, op. cit., pp. 164 and 165.

<sup>114</sup>Lindblom and Braybrooke, op. cit., p. 73

<sup>115</sup>Etzioni, op. cit., p. 271.

variations in values and the degree to which they are valued by policy-makers, as well as new factual information, can more easily be incorporated into the decision-making process. As will be shown later, the policy revisions made subsequent to the initial and fundamental policy decisions to intervene and to intervene in a particular fashion reflected only incremental differences in the ranking of priorities rather than any deviation from the commitment to the primary values held by the policy-makers throughout the process under study.

Since the initial policy statement of February 8, 1966, represents the basic form of the Guidelines, it will be useful to examine that statement in light of the original decision made by the policy-makers concerning the direction that the policy would take. For the purposes of this analysis, it is important to see if the initial statement, as well as subsequent statements, reflect Etzioni's contention that "the cumulative value of the incremental decisions is greatly affected by the underlying fundamental decisions." Perhaps the most important substantive point in the initial statement was the requirement that each grantee institution provide for "prior review of the judgment of the principal investigator or program director by a committee of his institutional associates." This requirement was certainly consistent with the second through fifth values held by the policy-makers. It represents an attempt to avoid an unnecessarily restrictive "exercise of federal responsibility"<sup>116</sup> and to create an "institutional awareness"<sup>117</sup>

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<sup>116</sup>Curran, op. cit., p. 439.

<sup>117</sup>Shannon, Transcript. NAHC Meeting.

regarding the responsibility of the institution to promote a favorable environment for clinical research. If the primary responsibility for overseeing experimental procedures was to rest with the individual institutions, their review committees and their investigators, it was necessary for the policy-makers to instill the values underlying the overall policy into those review committees and scientists. This attitude was clearly expressed by one of the policy-makers: "We must use every opportunity in a continuing campaign of education among the grantees that . . . the grantee institution must accept and discharge in a forthright manner its responsibility for both scientific and administrative overview of grant-supported activities by its faculty or staff."<sup>118</sup> Recognizing the diversity involved in clinical research, NIH officials sought to encourage the local review committee to solve their own problems. "We realized that we . . . couldn't possibly ride herd on the multiple situations that would arise. Our responsibility was satisfied if we were convinced that the individual institution within which the research took place had an adequate review mechanism."<sup>119</sup>

The review committees were given the responsibility to determine: (1) the rights and welfare of the individual involved; (2) the appropriateness of the methods used to secure informed consent; and (3) the risks and potential medical benefits of the investigation. Dror asserts that "policy-making must . . . often leave the concrete definitions of the policy to be

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<sup>118</sup>John Sherman, Memorandum to members of the Interbureau Advisory Committee for Extramural Programs, National Institutes of Health, "Statement of Assurance With Respect to Clinical Investigation," January 23, 1966.

<sup>119</sup>Interview with James A. Shannon.

determined when it is applied to discrete issues during its execution."<sup>120</sup> Recognizing the diversity of research and the variety of situations that might arise, the policy-makers chose not to define rigorously these three responsibilities, but instead left their definition to the review committees. A good example of this aspect of the process is the policy-makers' attitude toward the meaning of "informed consent." The requirement that the investigator obtain the consent of his subject prior to initiating the experimental procedure was consistent with the belief that the subject be assured adequate protection. That requirement was equally consistent, however, with the other four principal values. Because of the absence of legal precedent and of the variety of possible interpretations of the meaning of informed consent, government officials refrained from developing a rigorous definition for it. "We had great debates over informed consent. The lawyers repeatedly said that there was very little legal precedent in law and, therefore, no real legal interpretation of informed consent. We did not think it was possible to construct a law. . . on informed consent."<sup>121</sup> For the policy-makers to attempt such a construction might have meant the obstruction of future research and would certainly have violated the philosophy of a grant-operated support program, both important values. At the same time, however, "informed consent" was viewed as an important mechanism for which to strive and was, therefore, to be considered in any decision concerning a research project.

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<sup>120</sup>Dror, *op. cit.*, p. 191.

<sup>121</sup>William H. Stewart, in a letter to this author.

Government officials were then confronted with the decision of how to determine whether or not the grantee institution had such a review mechanism. Once again, consistent with the principles of minimal federal encroachment and maximum local involvement, the decision was to require each institution to submit an assurance of compliance for any research project funded by the PHS. The assurance mechanism was designed to secure policy objectives and was selected within the context of the original fundamental decisions. In a similar fashion, examination of subsequent policy revisions will show that the incremental changes made between February 1966 and May 1969, were consistent with the original set of value premises articulated by the policy-makers. The first major revision was issued on July 1, 1966. Important to note, in light of Etzioni's framework for the analysis of policy-making, is that this revision did not include any substantive changes from the original policy statement. The most significant change was of a procedural nature--the replacement of the grant-by-grant assurances of compliance with an institution-wide assurance to cover all grant proposals. The change was made in order to implement original policy decisions more effectively, not to modify them. Etzioni explains the place of such implementing mechanisms in the policy-making process; he writes that "the decision-making and implementation processes . . . are closely interwoven, with decisions affecting implementations . . . Decision-making is hence not to be viewed as a passive process. There is a continual give-and-take between decision-making and implementation."<sup>122</sup> The give-and-take of which Etzioni writes is made possible by the response of the policy-makers

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<sup>122</sup>Etzioni, *op. cit.*, p. 303.

to feedback received from those executing the policy. Karl Deutsch writes that "in feedback processes . . . the system itself is not isolated from its environment but, on the contrary, depends for its functioning upon a constant stream of information from the environment."<sup>123</sup> The importance of recognizing and reacting to such feedback was realized by the policy-makers. At the conclusion of his policy statement of July 1, 1966, Surgeon General Stewart wrote that he would "be pleased to receive suggestions and information from officials and investigators of grantee institutions to assist the Service in the conduct of its study." That such feedback was heeded by the policy-makers is evident in statements such as that of December 12, 1966, which reflected "the advice of the American Psychological Association and the American Sociological Association."<sup>124</sup> In that policy statement, Surgeon General Stewart made it clear that there were some experiments that "did not require the fully informed consent of the subject or even his knowledgeable participation." However, the statement remained consistent with the basic values held by the policy-makers and their original fundamental policy decisions since it placed the responsibility to assure that experiments were "in accordance" with local laws and reflected consideration of "pertinent ethical issues"<sup>125</sup> on the grantee institution.

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<sup>123</sup>Karl Deutsch, The Nerves of Government (N.Y.: The Free Press, 1966), pp. 186-87.

<sup>124</sup>Ernest M. Allen, former Grants Policy Officer, Office of the Surgeon General, Memorandum to Bureau Chiefs, December 16, 1966.

<sup>125</sup>PPO, 129, Revised Supplement No. 2, December 12, 1966.

The policy revision of January 24, 1967, restated the responsibility of the PHS. Dror writes that "some 'motivation' must be introduced for executing the policy, which includes... 'pushing' the executing."<sup>126</sup> By emphasizing that the PHS was prepared to disapprove of an application "if the gravity of the hazards and risks so indicate,"<sup>127</sup> the policy-makers expressed their intent to assure the implementation of their original policy decisions.

The final major policy revision was issued on May 1, 1969. Once again, the changes were primarily procedural rather than substantive. On the basis of feedback from the individual institutions and their investigators, policy-makers realized the need to "put all of the policy in one pot"<sup>128</sup> in order to remove any confusion that may have arisen. An attempt was also made to amplify the meaning of "informed consent." At the same time, however, the revised policy insisted that primary responsibility for determining whether or not a "fair explanation"<sup>129</sup> had been given to the subject remained with the institutional review committees. One policy-maker explained, "We have never insisted on particulars. We have described in general what our conception of informed consent means. We can only offer suggestions and remind people of their obligations to the people that they experiment on."<sup>130</sup> This revision, like the ones preceding it, was basically an incremental decision designed to implement the initial policy decisions. In all instances of policy-making

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<sup>126</sup>Dror, op. cit., p. 188.

<sup>127</sup>PPO No. 129, Revised Supplement No. 3, January 24, 1967.

<sup>128</sup>Interview with Mark H. Conner.

<sup>129</sup>Protection Of The Individual As A Research Subject, p. 3.

<sup>130</sup>Interview with Mark H. Conner.

subsequent to formulation of the original policy, none of the revisions violated any of the fundamental value premises articulated by the policy-makers. Such incremental revisions were made "within the contexts set by fundamental decisions" and demonstrated the effect on them of those underlying fundamental decisions.

The PHS Guidelines were not a result of hastily-made decisions. The initial policy statement was developed over a period of years, during which time policy-makers set forth their basic values as a framework within which to evolve subsequent decisions. In order to fulfill their responsibility as a public agency as well as their responsibility as the chief supporter of medical research in the United States, NIH policy-makers sought to develop guidelines that would provide adequate protection for the research subject as well as bring into fruition the benefits to be gained from clinical research. The various mechanisms for executing the policy were not immediately clear. Confronted with the task of deciding upon the basic direction that their efforts would take, the policy-makers chose an approach of decentralized regulation, one consistent with their processed values. Subsequent revisions, products of the evaluation of feedback from those primarily responsible for executing the policy, were instituted in order to achieve original policy decisions.

The decision-making process used to develop the Guidelines is a good illustration of Etzioni's "mixed-scanning strategy." After fixing their basic values, the policy-makers proceeded with an "exploration of the main alternatives"--a detailed code or flexible guidelines, local versus national control--omitting details so that an overview of the alternatives was possible. The nature of subsequent policy decisions and the processes employed to make them also gives credibility to Etzioni's contention that

"the cumulative value of the incremental decisions is greatly affected by the underlying fundamental decisions."

The "mixed-scanning strategy," which employs elements of both comprehensive planning and incremental decision-making, must be considered when evaluating public policy-making. While it proposes that decision-makers formulate long-term goals and examine various alternative policies, it also recognizes the inherent limitations of policy-makers. "The likelihood that decisions can accomplish large social changes and, at the same time, be guided by a high level of intellectual comprehension of the problem is slim. Such decisions require prodigious feats of synoptic analysis, beyond human capacities."<sup>131</sup> Each of the two elements in the "mixed-scanning strategy" --fundamental and incremental decision-making--help to neutralize the short-coming of the other. The strategy permits a flexible response to the results of policy decisions, but does so within the context of broader policy considerations. Etzioni contends that

societal decision-making requires two sets of mechanisms: (a) a high-order, fundamental policy-making process which sets basic directions, and (b) an incremental process which prepares for fundamental decisions and revises them after they have been reached.<sup>132</sup>

This case study suggests that, at the federal level, these two mechanisms may be an integral part of the policy-making process.

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<sup>131</sup>Lindblom and Braybrooke, *op. cit.*, p. 65.

<sup>132</sup>Etzioni, *op. cit.*, p. 290.

## AFTERWORD

During the time that this paper was being prepared, the Department of Health, Education and Welfare announced the adoption of a new policy<sup>133</sup> governing research using human subjects. The policy is no longer restricted to the health field, but instead applies to all programs and activities supported by grants or contracts from the Department and in which the subjects may be at risk.

The new department-wide policy closely parallels the PHS Guidelines issued in May 1969. Perhaps the most important divergence in the new policy concerns the requirements for informed consent. The basic elements of informed consent are enumerated fully and clearly in the new policy. Furthermore, the policy requires that the procedure used to obtain informed consent and the basis for committee determinations that the procedures are adequate are to be fully documented. The documentation may follow one of three forms:

(1) The "provision of a written consent document embodying all of the basic elements of informed consent" which must "be signed by the subject or his authorized representative;" (2) the "provision of a 'short' form written consent document indicating that the basic elements of informed consent have been presented orally to the subject." This form is to "be signed by the subject or his authorized representative and an auditor-witness to the oral presentation and to the subject's or his authorized representative's signature;"

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<sup>133</sup>Chapter 1-40, "Protection of Human Subjects," Department of Health, Education and Welfare Grants Administration Manual, April 15, 1971.

(3) the "modification of either of the above two primary procedures" which "must be approved by the [institutional review] committee." While the latter alternative provides much the same freedom of action permitted under earlier versions of the policy, a greater burden is on the review committee to document its agreement to a particular consent procedure. The greater the departure from fully informed prior written consent, the greater the burden on the committee. This procedure is consistent with the PHS policy's emphasis on decentralized regulation, with primary responsibility resting with the research institution. At the same time, however, it represents a larger degree of involvement by the Federal Government. By placing this greater burden on the institutional review committee, the Government, in effect, exerts a new measure of influence that might well play an important part in committee decision-making. Greater care in obtaining informed consent will be of primary concern for all institutional review committees. Aside from this difference, however, the essential elements of the two policies remain quite similar. The PHS policy was clearly the model for the new HEW policy, which will affect a wide range of social research. The understanding of how the PHS policy evolved and the values underlying it is, therefore, an important element in evaluating the broader set of guidelines.

(Whereupon, at 2:40 p.m. the subcommittee recessed, subject to the call of the Chair.)



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