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NATIONAL DIGESTIVE DISEASES AND NUTRITION ACT

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HEARING
BEFORE THE
SUBCOMMITTEE ON HEALTH
OF THE
COMMITTEE ON
LABOR AND PUBLIC WELFARE
UNITED STATES SENATE

NINETY-FIRST CONGRESS

SECOND SESSION

ON

S. 3063

TO AMEND THE PUBLIC HEALTH SERVICE ACT TO SUPPORT RESEARCH AND TRAINING IN DISEASES OF THE DIGESTIVE TRACT, INCLUDING THE LIVER AND PANCREAS, AND DISEASES OF NUTRITION, AND AID THE STATES IN THE DEVELOPMENT OF COMMUNITY PROGRAMS, FOR THE CONTROL OF THESE DISEASES, AND FOR OTHER PURPOSES

AUGUST 31, 1970

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



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NATIONAL DIGESTIVE DISEASES AND NUTRITION ACT

MONDAY, AUGUST 31, 1970

U.S. SENATE,
SUBCOMMITTEE ON HEALTH OF THE
COMMITTEE ON LABOR AND PUBLIC WELFARE,
Washington, D.C.

The subcommittee met at 10:35 a.m., pursuant to call, in room 4232 New Senate Office Building, Senator Ralph W. Yarborough (chairman of the subcommittee) presiding.

Present: Senators Yarborough (presiding) and Dominick.

Committee staff present: Lee Goldman, professional staff member; and Jay B. Cutler, minority counsel.

The CHAIRMAN. The Senate Subcommittee on Health will come to order.

This morning the Health Subcommittee on Labor and Public Welfare Committee begins public hearings on S. 3063. If enacted, it would create a separate Institute of Digestive Diseases and Nutrition at the National Institutes of Health.

Digestive diseases are a national problem of major proportions. More than 12 million Americans suffer from digestive diseases. One hospital admission in six is attributable to digestive diseases. More than 200,000 Americans die each year from digestive diseases or complications which arise therefrom. The cost of these diseases amounts to more than \$8 billion annually.

However, in the face of this great problem little is being done. For example, there is no national effort to encourage young physicians to specialize in digestive diseases. Most medical schools have given short shrift to the training of these needed specialists. In addition to the meager support for these programs from the public sector, there is virtually no support from either private industry or philanthropic organizations.

In order to overcome this obvious need, it is necessary to create a separate, special focus for the support of research into digestive diseases. S. 3063 would provide this focus within the National Institutes of Health. The NIH has a track record of proven success and accomplishment. The Institute to be established by this bill would become a part of that successful enterprise.

In cooperation with volunteer and professional health efforts, this Institute will do much to broaden our understanding of the causes of digestive diseases. That understanding can then form the base upon which it will be possible to mount effective treatment programs.

In other words, this bill is additive to the substantial effort which this committee has made over the years to effectively deal with this country's health care crisis. We cannot solve this problem by burying our heads in the sand. We cannot solve it by hoping it will disappear while we "study the problem." We cannot solve it by shedding crocodile tears over Federal expenditures. We can only solve it by understanding its dimensions, and then affirmatively doing what needs to be done.

This bill represents one of those affirmative actions which we can and should take.

Since 9 o'clock this morning, we have been checking on additional data. I had been told in the past that more man days of work were lost in industry from digestive illnesses than any other disease. I have ascertained that 300 million man days of work are lost each year from illnesses due to digestive disease. I wondered why digestive diseases had not received greater attention at the national level, and I have come to the conclusion that it is because so many people have it.

Unlike certain other disabling diseases, like stroke, which are apt to turn a patient into a bedridden patient in a few seconds, digestive diseases are something that many, many millions of Americans work with, and with treatment they get up and go to work even though they have these diseases. Perhaps that is one reason why digestive diseases have not received the national attention in the past. So, I think it is time to act.

(The text of S. 3063 and departmental reports follow :)

91ST CONGRESS
1ST SESSION

S. 3063

IN THE SENATE OF THE UNITED STATES

OCTOBER 22, 1969

MR. YARBOROUGH introduced the following bill; which was read twice and referred to the Committee on Labor and Public Welfare

A BILL

To amend the Public Health Service Act to support research and training in diseases of the digestive tract, including the liver and pancreas, and diseases of nutrition, and aid the States in the development of community programs for the control of these diseases, and for other purposes.

- 1 *Be it enacted by the Senate and House of Representa-*
2 *tives of the United States of America in Congress assembled,*
3 That this Act may be cited as the "National Digestive
4 Diseases and Nutrition Act".

1 and Nutrition (hereafter in this part referred to as the
2 Institute').

3 "DIGESTIVE AND NUTRITIONAL DISEASE RESEARCH AND
4 TRAINING

5 "SEC. 452. In carrying out the purposes of section 301
6 with respect to digestive diseases and nutrition, the Secretary,
7 through the Institute and in cooperation with the National
8 Advisory Digestive Diseases and Nutrition Council (here-
9 after in this part referred to as the 'Council') shall—

10 " (a) conduct, assist, and foster researches, investi-
11 gations, experiments, and demonstrations relating to the
12 cause, prevention, and methods of diagnosis and treat-
13 ment of digestive diseases and nutrition;

14 " (b) promote the coordination of research and con-
15 trol programs conducted by the Institute, and similar
16 programs conducted by other agencies, organizations and
17 individuals;

18 " (c) make available research facilities of the Serv-
19 ice to appropriate public authorities, and to health offi-
20 cials and scientists engaged in special studies related to
21 the purposes of this part;

22 " (d) make grants-in-aid to universities, hospitals,
23 laboratories, and other public and private agencies and
24 institutions, and to individuals for such research projects

1 relating to digestive diseases and nutrition as are rec-
2 ommended by the Council, including grants to such
3 agencies and institutions for the construction, acquisition,
4 leasing, equipment, and maintenance of such hospital,
5 clinic, laboratory, and related facilities, and for the care
6 of such patients therein, as are necessary for such re-
7 search;

8 “(e) establish an information center on research,
9 prevention, diagnosis, and treatment of digestive diseases
10 and nutrition, and collect and make available, through
11 publications and other appropriate means, information
12 as to, and the particular application of, research and
13 other activities carried on pursuant to this part;

14 “(f) secure from time to time, and for such periods
15 as he deems advisable, the assistance and advice of
16 persons from the United States or abroad who are
17 experts in the field of digestive diseases and nutrition;
18 and

19 “(g) in accordance with regulations and from funds
20 appropriated or donated for the purpose (1) establish
21 and maintain research fellowships in the Institute and
22 elsewhere with such stipends and allowances (including
23 travel and subsistence expenses) as he may deem neces-
24 sary to train research workers and procure the assistance
25 of the most brilliant and promising research fellows

1 from the United States and abroad, and, in addition,
2 provide for such fellowships through grants, upon rec-
3 ommendation of the Council to public and other nonprofit
4 institutions; and (2) provide training and instruction
5 and establish and maintain traineeships, in the Institute
6 and elsewhere in matters relating to the diagnosis, pre-
7 vention, and treatment of digestive diseases with such
8 stipends and allowances (including travel and subsistence
9 expenses) for trainees as he may deem necessary, the
10 number of persons receiving such training and instruc-
11 tion, and the number of persons holding such trainee-
12 ships, to be fixed by the Council, and, in addition, provide
13 for such training, instruction, and traineeships through
14 grants, upon recommendation of the Council, to public
15 and other nonprofit institutions.

16 "ADMINISTRATION

17 "SEC. 453. (a) In carrying out the provisions of section
18 452 all appropriate provisions of section 301 shall be ap-
19 plicable to the authority of the Secretary, and grants-in-aid
20 for digestive diseases and nutritional research and training
21 projects shall be made only after review and recommendation
22 of the Council made pursuant to section 454.

23 "(b) The Secretary is authorized to accept conditional
24 gifts, pursuant to section 501, for study, investigation, or re-
25 search into the cause, prevention, or methods of diagnosis or

1 treatment of digestive diseases and nutrition, or for the acqui-
2 sition of grounds or for the erection, equipment, or mainte-
3 nance of premises, buildings, or equipment of the Institute.
4 Donations of \$50,000 or over for carrying out the purposes
5 of this part may be acknowledged by the establishment
6 within the Institution of suitable memorials to the donors.

7 "FUNCTIONS OF THE COUNCIL

8 "SEC. 454. The Council is authorized to—

9 " (a) review research projects or programs submit-
10 ted to or initiated by it relating to the study of the
11 cause, prevention, or methods of diagnosis or treatment
12 of digestive diseases, and certify approval to the Secre-
13 tary, for prosecution under section 452, any such proj-
14 ects which it believes show promise of making valuable
15 contributions to human knowledge with respect to the
16 cause, prevention, or methods of diagnosis or treatment of
17 digestive diseases and nutrition;

18 " (b) review applications from any university, hos-
19 pital, laboratory, or other institution or agency, whether
20 public or private, or from individuals, for grants-in-aid
21 for research projects relating to digestive diseases and
22 nutrition, and certify to the Secretary its approval of
23 grants-in-aid in the cases of such projects which show
24 promise of making valuable contributions to human
25 knowledge with respect to the cause, prevention, or

1 methods of diagnosis or treatment of digestive diseases
2 and nutrition;

3 “(c) review applications from any public or other
4 nonprofit institution for grants-in-aid for training, in-
5 struction, and traineeships in matters relating to the
6 diagnosis, prevention, and treatment of digestive diseases
7 and nutrition, and certify to the Secretary its approval
8 of such applications for grants-in-aid as it determines
9 will best carry out the purposes of this Act;

10 “(d) collect information as to studies which are
11 being carried on in the United States or any other coun-
12 try as to the cause, prevention, or methods of diagnosis
13 or treatment of digestive diseases and nutrition, by cor-
14 respondence or by personal investigation of such studies,
15 and with the approval of the Secretary make available
16 such information through appropriate publications for
17 the benefit of health and welfare agencies and organiza-
18 tions (public or private), physicians, or any other sci-
19 entists, and for the information of the general public;

20 “(e) recommend to the Secretary for acceptance
21 conditional gifts pursuant to section 501 for carrying
22 out the purposes of this part; and

23 “(f) advise, consult with, and make recommenda-
24 tions to the Secretary with respect to carrying out the
25 provisions of this part.

1 "OTHER AUTHORITY WITH RESPECT TO DIGESTIVE DIS-
2 EASES AND NUTRITION

3 "SEC. 455. This part shall not be construed as super-
4 seding or limiting—

5 "(a) the functions or authority of the Secretary
6 or the Service, or of any other officer or agency of the
7 United States, relating to the study of the causes, pre-
8 vention, or methods of diagnosis or treatment of di-
9 gestive diseases and nutrition; or

10 "(b) the expenditure of money therefor."

11 NATIONAL ADVISORY DIGESTIVE DISEASES AND NUTRITION
12 COUNCIL

13 SEC. 4. (a) Section 217 of the Public Health Service
14 Act is amended by adding at the end thereof the follow-
15 ing new subsection:

16 "(d) The National Advisory Digestive Diseases and
17 Nutrition Council shall consist of the Secretary or his repre-
18 sentative, the chief medical officer of the Veterans' Admin-
19 istration or his representative, the Surgeon General of the
20 Army or his representative, the Surgeon General of the
21 Navy or his representative, who shall be ex officio members,
22 and twelve members appointed without regard to the civil
23 service laws by the Secretary. The twelve appointed mem-
24 bers shall be leaders in the fields of fundamental sciences,
25 medical sciences, education, or public affairs, and six of such

1 twelve shall be selected from leading medical or scientific
2 authorities who are outstanding in the study, diagnosis, or
3 treatment of digestive diseases and nutrition. Each appointed
4 member of the Council shall hold office for a term of four
5 years, except that any member appointed to fill a vacancy
6 occurring prior to the expiration of the term for which his
7 predecessor was appointed shall be appointed for the remain-
8 der of such term, and except that, of the members first
9 appointed, three shall hold office for a term of three years,
10 three shall hold office for a term of two years, and three shall
11 hold office for a term of one year, as designated by the Secre-
12 tary at the time of appointment. None of such twelve mem-
13 bers shall be eligible for reappointment until a year has
14 elapsed since the end of his preceding term. Every two years
15 the Council shall elect one member to act as Chairman for
16 the succeeding two-year period."

17 (b) The second sentence of section 217 (b) of such Act
18 is amended by inserting "digestive diseases and nutrition,"
19 immediately after "blindness,".

20 (c) Paragraph (d) of section 301 of such Act is
21 amended by inserting "or, with respect to digestive diseases
22 and nutrition, as recommended by the National Advisory
23 Digestive Diseases and Nutrition Council," immediately after
24 "National Advisory Heart Council,".

1 (d) Section 301 (i) of such Act is amended by insert-
2 ing "or, with respect to digestive diseases and nutrition, upon
3 recommendation of the National Advisory Digestive Diseases
4 and Nutrition Council," immediately after "National Ad-
5 visory Dental Research Council,".

6 CONTROL GRANTS

7 SEC. 5. Title III of such Act is amended by inserting
8 after section 315 the following new section:

9 "GRANTS FOR COMMUNITY PROGRAMS OF DIGESTIVE
10 DISEASES AND NUTRITION CONTROL

11 "SEC. 316. (a) To enable the Secretary to carry out
12 the purposes of part F of title IV and to assist, through
13 grants, States, counties, health districts, and other political
14 subdivisions of the State, and public and nonprofit agencies,
15 institutions, and other organizations, in establishing and main-
16 taining organized community programs of digestive diseases
17 and nutrition control, including grants for demonstrations and
18 the training of personnel, there are hereby authorized to be
19 appropriated for each fiscal year such sums as may be neces-
20 sary for such purposes. For each fiscal year, the Secretary
21 shall determine the total sum from the appropriation under
22 this subsection which shall be available for allotment among
23 the several States, and shall, in accordance with regulations,
24 from time to time make allotments from such sums to the sev-
25 eral States on the basis of (1) the population, and (2) the

1 financial need of the respective States. Upon making such
2 allotments, the Secretary shall notify the Secretary of the
3 Treasury of the amounts thereof.

4 “(b) The Secretary shall from time to time determine
5 the amounts to be paid to each State under this section from
6 the allotments to such State, and shall certify to the Sec-
7 retary of the Treasury, the amounts so determined, reduced
8 or increased, as the case may be, by the amounts by which
9 he finds that estimates of required expenditures with respect
10 to any prior period were greater or less than the actual ex-
11 penditures for such period: *Provided*, That the Secretary
12 may determine and certify to the Secretary of the Treasury
13 amounts to be paid to a county, health district, other political
14 subdivision of the State or to any public or nonprofit agency,
15 institution, or other organization in the State, if he finds that
16 payment to such subdivision or other organization has been
17 recommended by the State health authority of the States, and
18 (1) that the State health authority has not, prior to August 1
19 of the fiscal year for which the allotment is made, presented
20 and had approved a plan in accordance with subsection (c),
21 or (2) that the State health authority is not authorized by
22 law to make payments to such other organization.

23 “(c) The moneys so paid to any State or to any political
24 subdivision or other organization, shall be expended solely
25 in carrying out the purposes specified in subsection (a) and

1 in accordance with plans, approved by the Secretary, which
2 have been presented by the health authority of such State, or,
3 under the circumstances specified in subsection (b) (1), by
4 the political subdivision, or the agency, institution or other
5 organization to whom the payment is made, and, to the ex-
6 tent that any such plan contains provisions relating to mental
7 health, by the mental health authority of such State.

8 “(d) Money so paid from allotments under subsection
9 (a) shall be paid upon the condition that there shall be spent
10 in such State for the same general purpose from funds of such
11 State and its political subdivisions (or in the case of pay-
12 ments to a political subdivision or to an agency, institution or
13 other organization under circumstances specified in subsection
14 (b) (1), from funds of such political subdivision or organiza-
15 tion), an amount determined in accordance with regulations.

16 “(e) Whenever the Secretary, after reasonable notice
17 and opportunity for hearing to the health authority of the
18 States (or, in the case of payments to any political subdivi-
19 sion or any agency, institution, or other organization under
20 the circumstances specified in subsection (b) (1), such sub-
21 division or organization) finds that, with respect to money
22 paid to the State, subdivision, or organization out of appro-
23 priations under subsection (a), there is a failure to comply
24 substantially with either—

25 “(1) the provisions of this section;

1 end of paragraph (p) and inserting in lieu thereof “; and”,
2 and by inserting after paragraph (p) the following new
3 paragraph:

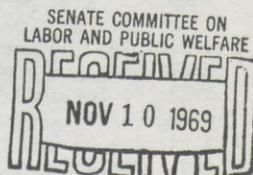
4 “(q) The term ‘digestive diseases’ means diseases of
5 the digestive tract, including liver and pancreas.”



COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON, D.C. 20548

B-74254

November 7, 1969



Dear Mr. Chairman:

This is in reference to your letter of October 24, 1969, requesting our comments on S. 3063, a bill to amend the Public Health Service Act to support research and training in diseases of the digestive tract, including the liver and pancreas, and diseases of nutrition, and aid the States in the development of community programs for the control of these diseases. The proposed law would be known as the "National Digestive Diseases and Nutrition Act."

We have no special information on the desirability of the proposed legislation and have no recommendations as to its merits. However, we offer the following comments for the consideration of the committee.

The bill assigns part F and sections 451 through 455 of title IV to the creation of the National Institute of Digestive Diseases and Nutrition; however, part F and sections 451, 452, and 453 of title IV have already been assigned to the act by Pub. L. 90-489, approved August 16, 1968, which established a National Eye Institute. Accordingly, the bill should assign a different part and different section numbers to the National Institute of Digestive Diseases and Nutrition.

Section 452(d), as proposed by the bill would authorize the Secretary, with the approval of the National Advisory Digestive Diseases and Nutrition Council, to make grants for the construction, acquisition, leasing, equipment, and maintenance of such hospital, clinic, laboratory, and related facilities, and for the care of such patients therein, as are necessary for such research. This language is identical with that used in section 412(d), title IV of the Public Health Service Act (42 U.S.C. 287a) setting forth the functions of the National Heart Institute which is currently the only one of the several institutes established under title IV that contains such language. We were informed by the National Heart Institute that, although the language of section 412(d) appears to authorize the making of grants for the construction of facilities without the requirement of matching non-Federal funds, this authority is not being exercised. The National Heart Institute believes that it cannot exercise such 100 percent construction grant authority because, subsequent to the establishment of the Institute, section 706(a) of title VIII of the Public Health Service Act (42 U.S.C. 292e), which relates to grant payments for the construction of health research facilities, was enacted and provides that the amount of any grant made shall in no event exceed 50 percent of the necessary cost of the construction of such facility as determined by the Surgeon General.

In view of the provision now included in section 706(a) of the act requiring a 50 percent matching of grant funds by the grantee for the construction of research facilities, and the fact that the National Heart Institute does not exercise its construction grant authority, consideration should be given to deleting the proposed section 452(d). However, if it is intended to provide 100 percent construction grant funds for research facilities to be used in conducting research on diseases of the digestive tract and nutrition, we suggest that the bill should make clear the legislative intent in this regard and that section 706(a) of title VII will not apply to this particular research program.

In the event the specific construction grant authority is retained in the bill, we further suggest that consideration be given to including language in the bill, similar to that now provided in legislation applicable to other construction grant programs now authorized by the Public Health Service Act, for example, section 707, title VII (42 U.S.C. 292f), to provide for the return to the Federal Government of all or a portion of Federal grant assistance for the construction or the purchase of facilities or equipment in the event such facilities or equipment cease to be used for the purposes for which constructed or purchased, within a specified number of years after completion of such construction or purchase.

Section 5 of the bill proposes an amendment to title III of the Public Health Service Act, to authorize a separate appropriation to the Secretary of Health, Education, and Welfare for making grants to the States and its political subdivisions for establishing and maintaining organized community programs of digestive diseases and nutrition control.

It is questionable whether such separate appropriation authority is in consonance with the system of grants for comprehensive public health services to the States which was introduced by the Comprehensive Health Planning and Public Health Service Amendments of 1966, Pub. L. 89-749, 80 Stat. 1180, and subsequent amendments. These amendments were intended to replace the system of categorical grants to the States for a variety of specified health services, and instead provide Federal support on the basis of comprehensive State health plans and permit desirable flexibility in rendering health services by the States and local communities.

The committee may wish to consider the desirability of not providing a separate appropriation authority for this new health control program but providing instead that the annual State health plans include adequate community programs of digestive diseases and nutrition control so that the States will receive needed Federal assistance as part of the grants for comprehensive public health services.

In the event a separate appropriation authority for this new health program is considered appropriate, the committee may wish to consider including language in the bill that would specifically set forth the computation of the Federal share and the amount of matching non-Federal funds, similar to the requirements for grants for comprehensive public health services (section 314(d)(5) and (6)). As presently provided in the bill, the matching amount to be spent by the States or otherwise from local funds is not specified by law but shall be determined in accordance with regulations prescribed by the Secretary.

No provision is made in S. 3063, nor in legislation applicable to other grant programs now authorized by title IV of the Public Health Service Act, as amended, to require a grantee to keep adequate cost records of the projects to which the Federal Government makes financial contributions, or specifically authorizing the Secretary of Health, Education, and Welfare or the Comptroller General to have access to the grantee's records for purposes of audit and examination. In view of the increase in grant programs over the last several years, we feel that in order to determine whether grant funds have been expended for the purpose for which the grant was made, the grantee should be required by law to keep records which fully disclose the disposition of such funds. We also feel that the agency as well as the General Accounting Office should be permitted to have access to the grantee's records for the purpose of audit and examination. We therefore suggest that consideration be given to amending the bill to include such requirements with respect to the proposed new grant program, or preferably to an amendment to cover all grant programs authorized by title IV. The latter could be accomplished by the following language:

"Records and Audit

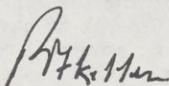
"(a) Each recipient of a grant under this title shall keep such records as the Secretary of Health, Education, and Welfare shall prescribe, including records which fully disclose the amount and disposition by such recipient of the proceeds of such grants, the total cost of the project or undertaking in connection with which such funds are given or used, and the amount of that portion of the cost of the project or undertaking supplied by other sources, and such other records as will facilitate an effective audit.

"(b) The Secretary of Health, Education, and Welfare and the Comptroller General of the United States, or any of their duly authorized representatives, shall have

access for the purpose of audit and examination to any books, documents, papers, and records of the recipients that are pertinent to the grants received under this title."

Language similar to that suggest above is contained in section 11 of the Clean Air Act, approved December 17, 1963, Pub. L. 88-206, 77 Stat. 401, the act of May 31, 1962, Pub. L. 87-460, 76 Stat. 83, in section 25 of the Area Redevelopment Act approved May 1, 1961, Pub. L. 87-27, 75 Stat. 63, 42 U.S.C. 2522, and section 399b of the Public Health Service Act as amended by Pub. L. 89-291, October 22, 1965, 79 Stat. 1066, 42 U.S.C. 280b-11(Supp. II).

Sincerely yours,



Acting Comptroller General
of the United States

The Honorable Ralph Yarborough, Chairman
Committee on Labor and Public Welfare
United States Senate

EXECUTIVE OFFICE OF THE PRESIDENT

BUREAU OF THE BUDGET
WASHINGTON, D.C. 20503

JUN 17 1970

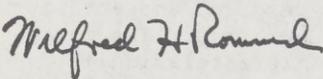
Honorable Ralph Yarborough
Chairman, Committee on
Labor and Public Welfare
United States Senate
4230 New Senate Office Building
Washington, D. C. 20510

Dear Mr. Chairman:

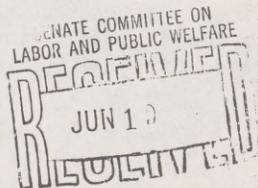
This is in response to your request for the views of the Bureau of the Budget on S. 3063, a bill "To amend the Public Health Service Act to support research and training in diseases of the digestive tract, including the liver and pancreas, and diseases of nutrition, and aid the States in the development of community programs for the control of these diseases, and for other purposes."

In a report being furnished to your Committee, the Department of Health, Education, and Welfare states its reasons for recommending against the enactment of this bill. We concur in the views expressed by the Department, and, accordingly, recommend that your Committee not give favorable consideration to S. 3063.

Sincerely,



Wilfred H. Rommel
Assistant Director for
Legislative Reference



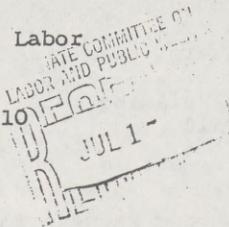


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VETERANS ADMINISTRATION
OFFICE OF THE ADMINISTRATOR OF VETERANS AFFAIRS
WASHINGTON, D.C. 20420

June 25, 1970

The Honorable
Ralph Yarborough
Chairman, Committee on Labor
and Public Welfare
United States Senate
Washington, D. C. 20510



Dear Mr. Chairman:

We are pleased to furnish the following comments in response to your request for a report by the Veterans Administration on S. 3063, 91st Congress, to be cited as the "National Digestive Diseases and Nutrition Act".

The general purpose of the bill is to establish a National Institute of Digestive Diseases and Nutrition in the Public Health Service. This would be an institute for the conduct of research, investigations, experiments, and demonstrations relating to the cause, prevention, and methods of diagnosis and treatment of diseases of the digestive tract, including the liver and pancreas, and diseases of nutrition. It would assist and foster such research and other activity by public and private agencies and promote co-ordination of all such research and activity and the useful application of results obtained. The institute would also provide training in matters relating to digestive diseases and nutrition, including refresher courses for physicians. It would additionally develop and assist States and other agencies in the use of the most effective methods in the promotion and maintenance of health and of prevention, diagnosis, and treatment of digestive diseases and nutrition.

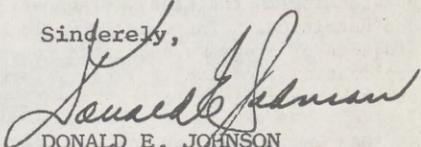
Provisions are made for the establishment of a National Advisory Digestive Diseases and Nutrition Council, which would consist of twelve appointed members having certain qualifications and who are leaders in their fields. The Chief Medical Director of the Veterans Administration and the Surgeons General of the Army and Navy would be ex officio members. The Council would advise, recommend, and certify approval to the Secretary of Health, Education, and Welfare on projects and requests for grants-in-aid for research projects which show promise of valuable contributions to human knowledge in the indicated areas.

The bill does not appear to impose additional administrative responsibilities upon the Veterans Administration, though its broad effects would be of professional interest to this agency in connection with its medical programs. Some 20 percent of our hospitalized veterans evidence diseases of the digestive tract and 17 percent of admissions to our hospitals are attributable to digestive diseases.

While we appreciate the general purpose of S. 3063 to augment knowledge in this important field in which authorities recognize a need, we defer to the views of the Department of Health, Education, and Welfare, which would have overall administrative responsibility, as to whether the approach employed in this bill would be the most effective method of achieving its aims. However, it should be noted that in general the factors responsible for these diseases are more generic disease entities, such as cancer. As progress is made in pursuing these more basic causes, there will be a resulting impact on diseases affecting the digestive organs.

We are advised by the Bureau of the Budget that there is no objection to the presentation of this report from the standpoint of the Administration's program.

Sincerely,



DONALD E. JOHNSON
Administrator



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Honorable Ralph Yarborough
 Chairman, Committee on
 Labor and Public Welfare
 United States Senate
 Washington, D.C. 20510

JUN. 29 1970
 STATE COMMITTEE ON
 LABOR AND PUBLIC WELFARE
 DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
 JUL 1 -
 NEW YORK, N.Y.

Dear Mr. Chairman:

This letter is in response to your request of October 24, 1969, for a report on S. 3063.

The bill would provide for the establishment within the Public Health Service of a National Institute of Digestive Diseases and Nutrition. The Institute would be charged to "conduct, assist, and foster researches, investigations, experiments, and demonstrations relating to the cause, prevention, and methods of diagnosis and treatment of digestive diseases and nutrition," to promote the coordination of research and control programs conducted by the Institute and similar programs conducted elsewhere, to provide grants-in-aid for related research projects, to establish and maintain research fellowship and training programs, and to establish an information center.

The bill would also authorize the establishment of a National Advisory Digestive Diseases and Nutrition Council. The Council would consist of four ex-officio members--the Secretary, the chief medical officer of the Veterans Administration, the Surgeon General of the Army, and the Surgeon General of the Navy or their representatives--and twelve appointed members. The appointed members would be leaders in the fields of fundamental sciences, medical sciences, education or public affairs, six of these to be "leading medical or scientific authorities who are outstanding in the study, diagnosis, or treatment of digestive diseases and nutrition." The Council would be authorized to review research projects or programs submitted to or initiated by it, review grant applications, collect related information, and advise and make appropriate recommendations to the Secretary.

S. 3063 would also establish a categorical grant program for community programs of digestive diseases and nutrition control, including demonstration programs and training grants.

The Department is in sympathy with the objectives of the proposed legislation--to promote research and training in the fields of digestive diseases and nutrition. We feel, however, that this goal is already being approached effectively under present arrangements. Nutrition is not a discrete discipline, but rather has deep roots within medicine, public health, sociological and cultural aspects of life, and the whole spectrum of human development. It is not possible to separate nutrition from these other disciplines without destroying in part both the basis of nutrition science and the achievement of goals in these other specialties. From a medical scientific point of view, nutrition, unlike the heart or the eye, has few unique or highly localized attributes. Nutritional considerations may be of importance in relationship to etiology, treatment, and prevention of many diseases, such as heart disease, kidney disease, diabetes, and anemias; however, it is extremely difficult to separate the nutritional problem from more fundamental metabolic factors concerned in the disease process.

While disorders of the digestive tract do represent a sizable public health problem, with few exceptions, for example, peptic ulcer, the genesis of these disorders is being investigated in the context of already existing programs. For example, cancer of the colon is most properly the responsibility of a national program on cancer, and the psychological aspects of peptic ulcer should be pursued as a behavioral problem.

We would agree that a visible focus for a disease area may have beneficial effects on the area in terms of enhanced scientific and public interest. However, we do not consider that there is a necessary cause and effect relationship between Institute status and improved funding. It should be recognized that no mere change in organizational form will cause a research area to flourish. We would add that these organizational changes involve significant additional administrative costs, which might be met only at the price of diminished support for some other equally important health problem.

The Department is also against proliferation of categorical grant programs such as the proposed categorical program of grants for community programs of digestive diseases and nutrition control.

We therefore recommend against enactment of S. 3063.

We are advised by the Bureau of the Budget that there is no objection to the presentation of this report from the standpoint of the Administration's program.

Sincerely,



Secretary

STATEMENT OF JESSE L. STEINFELD, M.D., SURGEON GENERAL,
 U.S. PUBLIC HEALTH SERVICE DEPUTY ASSISTANT SECRETARY
 FOR HEALTH AND SCIENTIFIC AFFAIRS, DEPARTMENT OF
 HEALTH, EDUCATION, AND WELFARE; ACCOMPANIED BY DR.
 JOHN F. SHERMAN, DEPUTY DIRECTOR, NIH; AND DR. G. DONALD
 WHEDON, DIRECTOR, NATIONAL INSTITUTE OF ARTHRITIS AND
 METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH

Dr. STEINFELD. Accompanying me this morning, Mr. Chairman, on my left, is the Deputy Director of the National Institutes of Health, Dr. John F. Sherman, and, on my right is Dr. G. Donald Whedon, Director, National Institute of Arthritis and Metabolic Diseases.

The CHAIRMAN. We welcome you here. This has been very short notice, but we had to have this short notice if we were to have an opportunity to move at all this year. We appreciate your being here.

You may proceed.

Dr. STEINFELD. Mr. Chairman, Senator Dominick, I am pleased to appear before you this morning to present the views of the Department of Health, Education, and Welfare on S. 3063, a bill "to amend the Public Health Service Act to support research and training in diseases of the digestive tract, including the liver and pancreas, and diseases of nutrition, and aid the States in the development of community programs for the control of these diseases, and for other purposes."

S. 3063 would authorize the establishment in the Department of Health, Education, and Welfare of a National Institute of Digestive Diseases and Nutrition. In implementing this authority, the Secretary of Health, Education, and Welfare would be directed to (1) establish a National Advisory Council for the new institute, and (2) carry out the purposes of the act, through the new National Institute of Digestive Diseases and Nutrition, including the conduct and support of research in digestive diseases and nutrition, provision of relevant training through traineeships and fellowships, provision of grants for the construction, acquisition, and maintenance of facilities and for the care of patients related to such research, and establishment of an information center on digestive diseases and nutrition. In addition, the bill would provide for grants for community service programs related to the control of digestive diseases and nutritional disorders which could include grants for demonstration and training of personnel.

The Department is in complete sympathy with the basic objectives of S. 3063, which are to (1) promote research into the problems of diagnosis, prevention and treatment of digestive diseases and nutritional disorders, (2) to provide for specialized training in the diverse, relevant scientific disciplines related to these conditions, and (3) to assure appropriate community service and demonstration programs. Not only is the Department in full sympathy with these objectives, it has been actively supporting them for many years. It is our view that this bill would only put a "new face" on an important, but already viable and long-active endeavor.

Adequate legislative authority now exists under the Public Health Service Act for all of the functions envisioned for the proposed institute. In fact, all these functions, and more, are now being competently discharged. The National Institutes of Health (NIH) is already supporting an extensive research and training effort pertaining to digestive diseases and nutrition, both intramurally, in the laboratories and clinics of several of the Institutes at Bethesda, and extramurally, through the support of research at numerous medical centers throughout the country, and abroad. Furthermore, the focus for these important efforts is already present in the National Institutes of Health, in the National Institute of Arthritis and Metabolic Diseases.

With regard to digestive diseases: The National Institute of Arthritis and Metabolic Diseases (NIAMD) of the Institute at the NIH charged with responsibility for diseases of the digestive tract and related organs, including the liver and pancreas—and relevant scientific disciplines related to gastroenterology. In addition to its direct research activities carried out in its laboratories and clinics in Bethesda, the NIAMD supports a very substantial program of extramural research in research centers and medical institutions throughout the United States. In addition, the NIAMD finances and administers a substantial and comprehensive program providing research training grants in digestive diseases.

Specifically, the NIAMD has as one of its six intramural clinical investigative programs in the Clinical Center in Bethesda, a branch particularly devoted to highly sophisticated, fundamental research on digestive diseases. Since 1957, the NIAMD has had a Gastroenterology and Nutrition Training Grants Committee; and since its earliest years, the NIAMD has had representatives of the specialty of gastroenterology on its National Advisory Council. This year's president of the American Gastroenterological Association is currently a member of the National Advisory Council.

With regard to nutrition: The National Institute of Arthritis and Metabolic Diseases is also the Institute at the National Institutes of Health (NIH) charged with responsibility for most nutrition and nutrition-related program activities. These activities cover the full spectrum of nutrition from fundamental studies concerning the metabolic and physiologic actions of the various nutrients and their requirements in man, to practical, applied work aimed at alleviation of malnutrition and nutrition deficiency diseases both in the United States and abroad. In addition, the NIAMD finances and administers a substantial and comprehensive program providing research fellowships and research training grants in nutrition. The NIAMD supports about one-half of the extensive nutrition-related activities of the National Institutes of Health.

Mr. Chairman, from a medical and scientific viewpoint, the field of nutrition and nutritional disorders is not a discrete, naturally homogenous entity; aspects of nutrition impinge on a very wide range of health problems. Therefore, beyond the general support provided by the NIAMD, other Institutes at the NIH carry out extensive research and research support in facets of nutrition related to their specific missions.

For example, investigations into the relationship of nutrition and specific nutrients to dental health fall within the purview of the National Institute of Dental Research; the specialized aspects of prenatal nutrition, infant nutrition, and the relationship of nutrition to growth and development are pursued by the National Institute of Child Health and Human Development; and the specialized aspects of the relationship of diet and nutrition to blood vessel disorders and heart disease are pursued by the National Heart and Lung Institute. Additional and substantial nutrition-related research support is provided by the National Institute of General Medical Sciences, the National Cancer Institute, and the National Institute for Neurological Diseases and Stroke.

In the conduct of the very extensive digestive diseases and nutrition programs of the NIH, and specifically of the NIAMD, the advice and assistance of many experts in these fields are obtained continuously from the scientific staff of the National Institutes of Health and, on a consultative basis, from a broad range of outside experts.

Special reports on progress in digestive diseases and gastroenterology have been part of the annual budget presentations to the Congress. These reports, which we are supplying for the record, show a steady development of broad intramural and extramural research programs in this area, and the studies undertaken cover the entire profile of digestive diseases ranging through the full spectrum of their highly diversified causes.

(The information referred to follows:)

SPECIAL REPORT:
NUTRITION

The National Institute of Arthritis and Metabolic Diseases (NIAMD) is responsible for approximately two-thirds of the nutrition research supported by the National Institutes of Health and about three-fifths of all medically oriented nutrition research supported by the Federal Government. In addition to direct research activities in the laboratories and clinics in Bethesda, NIH supports a wide variety of research projects through grants to research centers and medical institutions throughout the United States and abroad. These activities cover the full spectrum of nutrition research from fundamental metabolic and physiologic studies and investigations of dietary requirements of the various nutrients to programs designed to determine how best to alleviate malnutrition and nutritional deficiency diseases both in the United States and abroad.

Scope of the Grants Program

The grants program may be divided into two groupings, physiology of normal nutrition and nutritional disorders. Projects in the physiologic processes of normal nutrition involve such entities as body composition, digestion and absorption of nutrients in the gastrointestinal tract; appetite regulation and food intake; the biochemistry and physiologic role of nutrients; their fate in the body; quantitative requirements of proteins and amino acids, carbohydrates, fats and fatty acids, minerals, trace elements, vitamins, and fluids and electrolytes; interrelationships between different nutrients and between nutrients and hormones, and nutrients and enzymes; nutrition in infancy; nutrition in old age; and the relationship of the intestinal flora to nutrition.

Research in abnormal nutrition involves discovery and definition of deficiency states, nutrient toxicity, obesity, malabsorption of specific nutrients, and the relationship of diet to specific disease entities (such as the role of saturated versus unsaturated fatty acids in the possible genesis of atherosclerosis and coronary heart disease). Another major subdivision of these research grants relates to nutrition in specific diseases or stress states, such as in diabetes, bone and joint disease, liver disease, gastrointestinal disease, infectious disease, disorders of immunity, anemia, endocrine disorders, gallbladder disease, inborn errors of metabolism, skin disorders, kidney disease and urolithiasis, stress (including surgery, trauma, wound healing and environmental extremes), and reproduction and pregnancy.

In addition to this broad research grants program, the NIAMD finances and administers a substantial and comprehensive program providing research fellowships and graduate research training grants in nutrition.

Prepared January 1969 by the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare in connection with 1970 appropriation hearings.

Special Nutrition Studies Abroad

A report on nutrition-related activities of the NIAMD would be incomplete without mentioning the malnutrition/nutrition portion of NIH's U.S.-Japan Cooperative Medical Sciences Program which is financed by a separate appropriation, carried in the budget of the National Institute of Allergy and Infectious Diseases, but which is administered for programmatic reasons by the NIAMD. The mission of this Program is to support research aimed at practical solutions to nutrition and nutrition-related problems of countries in Southeast Asia. This substantial grant and contract Program supports research in the following areas: relationship between malnutrition and mental development, and between malnutrition and infection, nutritional anemias, requirements for essential nutrients, biochemical adaptation to malnutrition, methods for evaluation of nutritional status, development of low-cost protein-rich foods (including the enrichment of staple cereals with amino acids and other essential nutrients, the genetic improvement of protein concentration and composition in rice), and investigations into the occurrence and nature of toxic substances in foods.

Another portion of Institute supported nutrition research overseas is carried out in India, Pakistan, and Egypt with U.S.-owned local currencies under Public Law 480. These studies are concerned with the causes, prevention and treatment of malnutrition and are located in underdeveloped countries because of the ease with which large populations with nutritional deficiencies can be found there. Discovery of pockets of malnutrition among our own population make those studies of special importance to the welfare of our Nation.

Diet Therapy in Chronic Kidney Failure

Another important aspect of nutrition-related studies supported by the NIAMD is pursued in the Institute's Artificial Kidney - Chronic Uremia Program. This program is a special research and development contract effort aimed at the development of improved and more effective dialysis hardware and methodologies and of methods for optimal rehabilitation of patients in chronic renal failure. A substantial effort is made through this program to develop and expand the use of special diets which permit effective rehabilitation and continued moderate to long-term survival of certain patients otherwise doomed to a rapid demise, without resort to artificial kidneys or kidney transplantation. These diets, originally developed in Italy, are based on the principle of internal re-utilization of pathologically accumulating urea (in patients with renal failure) for the daily internal synthesis of new protein. Such diets are particularly useful in patients with chronic irreversible kidney failure who are unable to obtain treatment with artificial kidneys or kidney transplantation.

Research AccomplishmentsNew Vitamin D Metabolite

Recent findings by Institute grantees at the University of Wisconsin have changed some old concepts of vitamin metabolism. Cholecalciferol (Vitamin D₃), for example, has long been considered the active form of Vitamin D. It is ingested in small amounts in food or formed from a precursor substance in the skin when the latter is exposed to ultraviolet light or sunlight. Now a new and significantly more active molecule, 25-hydroxycholecalciferol, has been isolated. This compound has already been shown effective in disorders of calcium metabolism which had not responded to the Vitamin D preparations previously available. This suggests in such conditions an inability to convert ingested Vitamin D to its active form. Apparent inability of the body to use Vitamin D in the amounts required by normal individuals is a feature of several well-known disorders: hypoparathyroidism, malabsorption, celiac disease, and chronic renal diseases. Some cases of rickets, the classical Vitamin D deficiency disease, also do not respond to cholecalciferol in large doses. The new-found compound may provide answers to many basic questions of calcium absorption and physiology, and of bone formation; it may also lead to more effective treatment of disorders previously characterized by an apparent Vitamin D resistance.

Diet, Alcohol and Liver Damage

Institute-supported studies have indicated in the past that excessive consumption of alcohol can lead to development of fatty liver - forerunner of cirrhosis - in man despite a concurrent, well-balanced dietary intake, a finding contrary to the conventional hypothesis that a poor diet is the cause of alcoholic liver damage in alcoholic individuals. Institute grantees at Mt. Sinai School of Medicine and at Cornell Medical Division of Bellevue Hospital in New York City now find that, in persons who drink only occasionally, acute exposure to alcohol may lead rapidly (after only two days) to fat accumulation in the liver and intracellular microscopic structural changes, regardless of nutritional factors. After two days this damage is reversible, but it becomes permanent and cumulative after more prolonged exposures.

According to the investigators, it is clear that alcohol can rapidly produce liver injury when taken in amounts equivalent to those consumed not only by recognized alcoholic persons but by many "social" drinkers as well. The blood alcohol level determinations during the experiments showed that a person need never have been intoxicated to sustain alcohol-induced liver injury.

These findings are significant because they provide insight into the pathogenesis of the alcoholic fatty liver and indicate that, regardless of the high quality of the concurrent diet, alcohol per se in even moderate amounts can lead to the production of a fatty liver.

Malabsorption of Vitamin B₁₂ in Pernicious Anemia

Primary pernicious anemia, an ultimately fatal disease unless proper treatment with Vitamin B₁₂ is instituted, is attributed largely to failure of the gastric mucosa to secrete "intrinsic factor," a substance which facilitates normal intestinal absorption of dietary Vitamin B₁₂. Secondary intestinal malabsorption of Vitamin B₁₂ (and of other substances) has now been described by Institute grantees and is believed to be rather common in pernicious anemia. Deficiency of the vitamin causes generalized damage of the intestinal mucosa which then further aggravates vitamin malabsorption even in the presence of therapeutic intrinsic factor, creating a spiraling deterioration of the condition.

Using electron microscopic studies with radioactive Vitamin B₁₂, grantees have shown that the vitamin enters the mucosal cells only at certain sites near the tips of the villi (finger-like projections which increase contact area of the intestinal lining). These areas are abnormally flattened in the Vitamin B₁₂ malabsorption syndrome. The investigators postulate that the growth of the surfact cells of these structures is too slow when Vitamin B₁₂ cannot be absorbed because of the lack of intrinsic factor. Rapid catabolic processes of the cells therefore continue unchecked, predominate over synthetic processes, and deterioration of the mucosal structures takes place. The vitamin is required in all body cells for the formation of nucleoproteins which form the building blocks of the cell nuclei. Areas where rapid cell turnover is necessary for normal function, such as in secretory membranes, the lining of the intestinal tract and sites of erythropoiesis (red blood cell formation) may be the first to react to deficiency of the vitamin, since these areas are constantly producing new cells and, therefore, need adequate amounts of nucleoprotein, which are not formed in the absence of Vitamin B₁₂.

Milk Intolerance and Lactase Deficiency

During the past three years, Institute-supported researchers have traced the cause of milk intolerance in certain otherwise normal adults and in patients with inflammatory bowel disease to a deficiency in an intestinal enzyme, lactase.

This enzyme, which converts lactose or "milk sugar" into its simple sugar components, glucose and galactose, is essential to digestion and subsequent absorption of lactose. Subsequently, increasing evidence has been found that intolerance to milk is a relatively common syndrome in adults.

Last year Institute grantees at Johns Hopkins University School of Medicine, Baltimore, demonstrated that milk intolerance based on lactase deficiency is much more common in Negro adults (70 percent in Baltimore and 72 percent in Uganda) than in the adult white population (5-10 percent), suggesting that intestinal lactase activity may be genetically controlled. It was also found that lactose-induced symptoms in Negro children and adults increased in frequency with advancing age, suggesting a gradual decrease in lactase activity after weaning. This was not as common in the white subjects studied.

Similar studies also have been carried out by Institute grantees at the University of Oklahoma Medical Center, Norman, Oklahoma. Both the Johns Hopkins and the Oklahoma studies indicate that there is a distinct racial difference in lactase activity, and that a genetically determined intestinal lactase deficiency is responsible for the majority of instances of milk intolerance found in adults.

The same Johns Hopkins investigators now have shown that milk intolerance, presumably due to lactase deficiency, is also very common among adults of Oriental ancestry. Thus, a large part of the world's non-white population may have a genetically determined intolerance to milk, a situation which would require re-evaluation of the importance of milk as a source of nutrition and protein among non-white adult populations.

These studies have considerable diagnostic and therapeutic significance, particularly for Negro and Oriental patients presenting a variety of gastrointestinal symptoms, such as diarrhea, nausea, and abdominal pains, which do not appear to be related to any specifically manifest pathologic lesion. In view of these findings, it becomes necessary to rule out, in such patients, the presence of milk intolerance or lactase deficiency (a presently uncommon diagnosis in adults). Once this diagnosis is confirmed, dietary restriction of milk, milk products, and foods containing milk sugar (lactose) usually leads to cessation of the distressing symptoms.

Deficiency of Other Sugar-Splitting Enzymes

Malabsorption of other sugars has been traced to other enzyme deficiencies. Maltose and isomaltose, the major disaccharide end-products of starch and glycogen digestion by pancreatic secretions, must be broken down by the enzymes maltase and isomaltase. Sucrose (another disaccharide), which is consumed in large quantities in natural as well as combined foods, is broken down by the enzyme invertase. Many cases of deficiency of these enzymes have been found in association with intestinal disorders and malabsorption. Some of these deficiencies are hereditary and others acquired.

Basic findings by several Institute grantees evolving from these enzyme deficiency studies have given new direction to our knowledge of digestion and absorption. Once it was held that disaccharide digestive enzymes are elaborated into the lumen of the intestine from the lining of the digestive tract. Some of them have now been found to exist and act inside the outer "brush border" membranes of the intestinal epithelial cells. Thus, disaccharide sugars (including sucrose), which have long been known to be unabsorbable from the intestine until digested into monosaccharides, do pass into the cells before being hydrolyzed. When the intestinal mucosa is damaged as it is in enteritis, celiac disease, colitis and other intestinal ailments, disaccharide malabsorption symptoms may arise to aggravate the initial condition. Because sugars are active osmotically they serve to increase the amount of fluid in the intestinal lumen and this increase in bulk may irritate the tissue and speed food elimination before adequate absorption can take place. Another concomitant complication is the overgrowth of certain enteric bacteria which normally are a minority population of the gut flora but, because of their ability to metabolize sugars, grow in abnormal quantities in such conditions. Formation of gas and other irritating by-products of their flourishing growth adds further insult to the intestinal tract.

Management of Fat Malabsorption

Dietary supplementation with a semisynthetic fat preparation, medium chain triglycerides, or MCT, has proved its value in managing fat malabsorption disorders of various origins, according to researchers at St. Luke's Hospital Center, New York. MCT has been used to provide additional nutrition both in disorders for which specific therapy exists and in those disorders for which no specific therapy is currently available.

Among the former are included gluten induced sprue, an intestinal sensitivity to the protein fraction gluten (found in wheat, rye, oats and barley), pancreatic and biliary insufficiency, and Whipple's disease; among the latter are included malabsorption following gastrectomy (removal of part of the stomach) and massive resection of the small bowel.

The efficient absorption of MCT in fat malabsorption states has been explained by the finding that medium chain triglycerides are more rapidly hydrolyzed to fatty acids than are most dietary fats, which are composed of long chain triglycerides. In addition, the studies demonstrated that the presence of bile and pancreatic lipase in the intestine is not necessary for the normal absorption of MCT,

explaining its importance in hepatobiliary diseases and in pancreatic insufficiency. Further, MCT may be of particular value in therapeutic diet in infancy and childhood, when malabsorptive disorders take more severe forms and tend to impair normal growth.

Sugar Induced Calcuria and Kidney Stone Formation

Many patients who develop calcium-containing kidney stones have none of the usual predisposing factors such as high serum calcium levels, urinary obstruction or urinary infection. Although some patients do have definitely high calcium excretion (hypercalcuria), others appear to have normal excretion. Institute-supported investigators have shown that both urinary calcium concentration and total calcium excretion rise sharply above normal in calcium stone-formers and in relatives of stone-formers following ingestion of high-sugar foods.

Renal clearance was studied in 15 stone-formers and several relatives after ingestion of 100 grams of glucose or sucrose. All of the subjects responded with hypercalcuria and below-normal urinary volume with resulting higher concentrations of calcium in the urine.

The effect of the sugar load was attributed to a decrease in calcium reabsorption in the kidney and diminished urine flow in the kidney tubules, both of which would favor calcium salt precipitation. If the present findings are substantiated by further study, stone-formers may be advised to avoid high sugar intakes, particularly during exertion or in climates favoring dehydration.

Special Diet Therapy Beneficial in Chronic Kidney Failure

During the past year, the Institute's Artificial Kidney Program has striven to encourage clinical studies in the United States of a special diet, and modifications thereof, which has shown in trials in Italy and England that it permits moderate-term survival, cessation of symptoms, and rehabilitation in certain types of patients with chronic renal failure who are otherwise faced with the need for chronic dialysis or kidney transplantation. During a 21-month study period, Institute supported scientists in Los Angeles have indeed demonstrated that a 20 gram, balanced, low-protein diet limited largely to essential amino acids, but unlimited in carbohydrates and fats can ameliorate uremic symptoms in patients with minimal, residual renal function while maintaining a satisfactory body nitrogen balance. The results of dietary treatment, as measured by amount of relief from previous uremic symptoms and total duration of remission, were significant in all patients with an ability to excrete urea greater than about 2% of normal. Of 27 patients who followed the diet, relief of loss of appetite, nausea, vomiting, weakness,

fatigue and lethargy was obtained in 23. The results of therapy were felt to be good to excellent in ten patients, with remission of symptoms persisting for 8.3 months in one patient. Serum urea nitrogen decreased in all patients. The resulting remission depends on prevention of acute deterioration of renal function and rigid adherence to the diet by the patient. The Program has recently activated investigations to study the efficacy of a maintenance regimen which combines the use of this diet with infrequently administered peritoneal dialysis or hemodialysis.

Similar encouraging results were obtained by another contractor at New York Medical College who has already progressed to maintenance of patients with a combination of this diet and infrequently applied hemodialysis (once every two weeks rather than the conventional three times per week).

Feasibility of Utilization of New Types of Protein Sources

In the face of a world-wide shortage of dietary protein, there have been many suggestions concerning large scale development of food proteins from algae, yeasts and from bacteria grown on relatively inexpensive petroleum wastes. An Institute grantee has been studying the nutritional consequences to be expected from large scale dietary use of proteins derived from algae and other microorganisms. One of the imbalances of nutrients found in one-celled organisms is their high content of nucleic acids which are metabolized to urate and uric acid, the metabolites which are abnormally increased in gout. Using a purine-free basal diet varying in protein quantity up to 75 grams and varying in yeast ribonucleic acid up to 8 grams, investigators followed the uric acid levels in urine and plasma in healthy male volunteers. When 75 grams of protein was consumed, uric acid levels in the plasma were higher than when protein-free diets were taken and levels in the urine were lower. When nucleic acids were fed, the uric acid levels in both plasma and urine rose proportionately in four of five subjects.

The investigators concluded that for practical dietary supplementation of protein-deficient diets, nucleic acid content of microorganisms should not bar their use. These low protein diets, with 10 to 20 grams daily of microbial protein food added could be advantageous and are probably not hazardous with respect to their nucleic acid content. Addition of crude microorganisms to diets containing large amounts of muscle and organ meats however, should be approached with caution since they might precipitate an attack of gout.

Nutritional Status of Migratory Farmers

In a study among migratory agricultural workers in the state of New York, biochemical tests of nutritional status were performed on blood

and urine of 104 persons. One-third of the group proved to be deficient in riboflavin and thiamine. Smaller percentages, particularly among the men, were deficient in ascorbic acid (vitamin C). The diet, prepared in a central camp kitchen, was found to consist almost entirely of beans, rice, luncheon meat sandwiches and potato chips. Wine was consumed with meals to substitute for impalatable high-mineral water, and constituted the largest single food expenditure. Alcoholism was not a problem among the workers, however, and the diet provided important quantities of iron. Fruits and vegetables which were being harvested were not being used in cooking, although amounts which may have been consumed in the field were not recorded. Recommendations were proposed for educating camp leaders of these groups in proper balance of foods.

Nutrition Among American Indians

Phase I of a nutrition study directed by the Institute's Epidemiology and Field Studies Branch is now near completion. In this part of the new inquiry into disease patterns among the Pima Indians of Arizona, associations were sought between dietary practices and incidence of diabetes, gallstones, and rheumatic disease. Such knowledge would be expected to contribute significantly to an understanding of the cause of these prevalent ailments. Data from these studies has not yet been evaluated. In previous Institute studies, the Pima Indians have been found to have a prevalence of diabetes 10-15 times higher than the average population and a very high prevalence of gallbladder disease.

Nutrition Research Overseas

The Institute has traditionally conducted nutrition research in underdeveloped countries overseas because of the ease with which large populations afflicted with nutritional deficiency diseases can be found and studied there. Foremost among such research activities are studies in India, Pakistan, Egypt and South Africa with particular emphasis on the cause, prevention, and treatment of malnutrition. Considerable contributions to our knowledge of normal nutrition and nutritional deficiencies have resulted from this work which has also yielded concrete benefits to the nutritional status of the local population. The recent pinpointing of pockets of malnutrition and nutritional deficiencies within our own population indicates strongly that these studies are not merely altruistic research exercises, but investigations of utmost importance to the welfare of the United States.

Protein Malnutrition Studies in India

Illustrative of such comprehensive studies, which also include developmental efforts to increase the world food potential are two interrelated research and development projects administered by the Institute in South India, and funded through PL-480 U. S. surplus commodity funds. One is located at the Central Food Technological Research Institute (CFTRI) in Mysore, and the other at the Christian

Medical College (CMC), in Vellore. Both projects interdigitate closely in their ultimate aim. They are part of an intensive and comprehensive program to find a practical answer to the problem of protein malnutrition in a typical underdeveloped-country setting, while simultaneously studying intermediary metabolism and selected metabolic disturbances in patients hospitalized for kwashiorkor (protein malnutrition). The Mysore project is concerned primarily with the laboratory development of protein-rich food supplements based on indigenous protein sources which are intended to prevent the widespread endemic kwashiorkor prevalent among preschool-age children in India; secondarily, this project involves animal testing and evaluation of such protein supplements, and studies of intermediary metabolism in kwashiorkor. In addition, the Mysore project has become strongly involved in the problem of aflatoxin, a highly toxic substance produced by mold growth in a wide range of foodstuffs all over the world. Aflatoxin is implicated in liver damage and carcinogenesis in animals and man.

The Vellore project encompasses clinical trials of the value of experimental protein blends developed in Mysore in the treatment of patients hospitalized for kwashiorkor, and large scale feeding tests in controlled institutional and village populations of the prophylactic value of these food supplements in the diet of weaning and school age children. In addition, selected metabolic disturbances associated with kwashiorkor are studied in hospitalized patients.

In view of the fact that the scope of the work undertaken is extremely broad and a very large number of individual projects are undertaken, only a very brief summary of recent progress is given in this report.

1. The CFTRI has succeeded in developing a series of protein concentrates and isolates from widely available indigenous plant sources. These include protein concentrates from peanuts, Bengal gram, soy, coconut, sesame and cotton seed. In addition, plain flours (some microatomized) of the above raw materials have been developed as well as solvent-extracted, defatted, and non-defatted fish flours. The preparation of these materials has posed a considerable series of technical difficulties which were overcome in the course of lengthy technological and chemical experimentation.

2. During each of these operations, determinations were made of original vitamin and amino acid content of the raw material and of the resulting refined product. The respective nutritive losses which result from the use of alternate choices of processing methods have been determined, and optimal technology has been developed for preparation of each product. Protein efficiency ratios (PER) and net

protein utilization (NPU) were established of the various fractions obtained, and technological choices were made primarily on nutritional considerations. Where PER and NPU values of individual products appeared borderline or low, mixed or amino acid-fortified products were developed.

3. After a large series of animal tests and subsequent formulation of feasible protein food blends for human consumption, feeding experiments were carried out in controlled populations of children in Mysore. These involved many different blends based on the raw materials enumerated above. Significant increases in height, weight, red cell count and hemoglobin levels were noted in children receiving daily supplements to their usual marginal diet with some of these blends, as compared with control groups receiving isocaloric cereal supplements.

4. A series of feeding trials has established minimal requirements for supplementation of typical, poor, rice diets with lysine, methionine (or dl-methionine hydroxy analogue) and threonine to obtain optimal biological value and net protein utilization in children.

5. A weaning food for infants based primarily on a nutritious mixture of inexpensive vegetable proteins has been developed and has now been accepted for commercial production by the largest Indian manufacturer of infant foods. The product has already seen small-scale animal and clinical testing in Mysore.

6. A Mysore-pioneered mixture of wheat (65%), peanut flour (25%), and Bengal gram (10%) under the brand name of Balahar is presently made by five different food manufacturers for use in the famine in the state of Bihar. The commercial price is 2.5 rupees per kilogram - and thus suitable for prevailing economic conditions in India.

7. Small-scale experiments in Mysore, involving twenty-four 6- to 9-year-old children, have shown that lysine supplementation of a typical marginal sorghum diet can result in a distinct increase in growth and nitrogen retention. Similar experiments are being continued involving other types of local marginal diets.

8. The most important advance in Mysore is the development of a process which destroys aflatoxin in peanut flour. Almost all of the high protein supplements developed in Mysore and tested in Vellore in an effort to provide inexpensive, indigenous protein nutriture to preschool children as a prophylaxis against kwashiorkor are based on peanut flour. Unfortunately, because of the vagaries of the peanut harvest, and the lax methods of harvesting and storage used in India, much of the peanut stores is infested with aspergillus mold and consequently contain the highly toxic factor aflatoxin. Unless a commercially

feasible method is found to destroy or remove aflatoxin from peanut flour in India, work with this promising base for any type of local, inexpensive high-protein supplement remains a theoretical exercise. The new process developed in Mysore which is now in the pilot plant stage is capable of destroying aflatoxin without inflicting organoleptic or nutritional damage on the basic raw material. Cost of detoxification is presently reported at one and one-half to two cents per kilogram, which makes it economically feasible and not prohibitive for a food supplement to be bought by the poorest strata of the population. Animal studies carried out thus far seem to show that the process does not affect the protein efficiency ratio of the peanut protein.

9. A new method has also been developed for the spectrophotometric quantitative determination of aflatoxin. Preliminary results seem to demonstrate that the new method gives faster and more accurate results than the presently used biological tests.

10. In Vellore, a series of clinical trials involved children with kwashiorkor who were fed a variety of fish protein concentrates during convalescence (after recovery had been initiated with feeding of skim milk protein). One of these preparations from CFTRI in Mysore was found satisfactory with respect to clinical progress, nitrogen retention as judged by nitrogen balances, and regeneration of serum albumin. Another showed equivocal results, and suggestions for nutritive improvement of the product were proposed.

11. A very important finding was made during extensive studies on vitamin A metabolism in undernourished preschool children. Contrary to current practice and to previously published reports the group in Vellore has demonstrated unequivocally that the prophylactic injection of a single large dose of vitamin A in oil in children on marginal diets does not have prophylactic value with respect to eventual vitamin A deficiency and its clinical sequelae (which may include xerophthalmia and blindness). On the other hand, the feeding of one ounce per day of mixed green vegetables during a six month period protects such children from an excessive fall in serum vitamin A levels during the subsequent six months on a marginal diet devoid of greens. The Vellore group has now shown quite convincingly that injectable vitamin A in oil is prophylactically inactive in children with frank kwashiorkor. In contrast, the water soluble injectable vitamin A is highly effective. It has also been shown in Vellore that orally administered vitamin A in oil will not improve vitamin A serum levels (or liver storage) in children with kwashiorkor, but will be readily absorbed and will result in improved vitamin A levels once the children have recovered from the acute phase of kwashiorkor. In view of the well controlled observations concerning the prophylactic failure of the injection of vitamin A in oil, efforts will be made to communicate these findings as broadly as possible, since in many quarters the injection of vitamin A in oil is relied on as a prophylactic measure in threatened child populations. The scientific staff of one of the manufacturers of this material in the United States has been apprised of the lack of efficacy of this material.

A new facet has recently been added to the Vellore project - studies on the fortification of wheat with lysine. Like many vegetable proteins, wheat protein is not of high enough biological quality to support rapid growth in children and to serve as the main source of protein in the human diet. Proteins of high biological value (usually from animal sources, such as milk, eggs, meat and fish) have a qualitatively and quantitatively more complete complement of amino acid components. The first, most limiting amino acid in the incomplete wheat protein is lysine. There are indications that the addition of inexpensive synthetic lysine to wheat from the United States, which is used for control of under-nutrition in India and other underdeveloped countries, might improve the biologic quality of wheat considerably - to the point where lesser quantities of the expensive and unobtainable animal proteins would be needed to attain satisfactory nutrition in the population. Because of the excellent clinical and field testing facilities already operating in Vellore, a new program of experimental enrichment of wheat (as it is used in its various forms in the local diet) has been started, coupled with laboratory, clinical and field testing of the nutritive efficacy of lysine fortification.

Benefits to U. S. From Overseas Nutrition Research

The Mysore-developed protein rich products which are evaluated in Vellore and the Vellore-initiated lysine fortification of wheat serve as prototypes for similar efforts in other underdeveloped regions of the world wherever agricultural necessities and economic and social factors preclude large scale inclusion of animal proteins in the diet.

The scientific findings emanating from this work are enriching the fund of scientific knowledge in the United States. Of particular importance are the contributions concerning intermediary metabolism during protein deprivation and vitamin deficiency which could not have been carried out in the United States adequately because of lack of sufficient patient material concentrated in any one particular locality. Since the majority of these findings are published in American scientific journals they are disseminated to the rest of the world through the medium of the American scientific literature and are thus enhancing the standing and image of American science. These particular studies are also an example of effective and beneficial use of PL-480 funds in biomedical studies and demonstrate the value of continued Congressional support of this funding mechanism.

These efforts also contribute specifically to the technological knowhow of the United States food industry. Of particular importance are the contributions to our knowledge concerning aflatoxin. Traces of aflatoxin have been found in U. S.-made peanut butter. There is considerable importation of peanuts (which may be contaminated with aflatoxin) to the United States from abroad, and little is known

concerning the presence of aflatoxin in many feeds used in the United States and the potential economic importance of such contamination. The laboratory techniques and technologic achievements in aflatoxin destruction developed in Mysore are of considerable importance in the United States both from the public health standpoint and that of agricultural and food economics.

Projects like those, in addition to the scientific aspects beneficial to the United States, are aimed at helping an underdeveloped country help itself. Rather than letting the host country rely on gifts of expensive protein-rich foods (such as powdered milk) from the United States which this country cannot afford forever, it gives the underdeveloped country the scientific wherewithall to utilize effectively inexpensive proteins which it can produce by itself and with the aid of which it can cope successfully with the problem of protein malnutrition among its children.

Guide to Nutrition Terminology

Under the terms of a contract with Vanderbilt University awarded jointly by this Institute and the National Institute of Child Health and Human Development, A Guide to the Classification of Nutrition Terminology for Indexing and Retrieval is being developed. A broadening awareness of the relationships between diet and total health, combined with the rapid increase in world population which demands the most efficient nutritional technology, have created an urgent need for coordinated resources for nutrition data. The guide should help to make such data more readily available and definitive to researchers in the future.

OUTLOOK

Despite the wide reduction of frank nutritional deficiency diseases in this country, the margin of safety is not large. Improved methods of determining nutritional status and revised criteria for normal nutritional status have contributed to a new emphasis on the definition and diagnosis of malnutrition. Through application of new principles and laboratory techniques learned in recent years from studies of intermediary metabolism, many supported by this Institute, the evaluation of nutritional status in the absence of overt disease is no longer dependent on ill-defined lesions and symptoms or the subjective judgment of physicians. These advances in knowledge now form the basis for exacting nutrition surveys needed to pinpoint pockets of malnutrition in vulnerable population groups in the United States. They will also be necessary in many developing countries to cope with the world-wide famine and malnutrition predicted for the near future if the runaway disproportion between population increase and agricultural selfsufficiency is not drastically reversed in the near future.

In relation to specific diseases, the discovery of the chemical nature of hereditary molecular diseases and of many physiological consequences of other lesser known diseases of uncertain etiology have contributed effectively to our understanding of the probable roles of required nutrients. Scientists now appear to be near to describing the nutritional participation of individual amino acids and fatty acids as well. The relationship of nutrients to ultramicroscopic physical structures is simultaneously evolving. Of greatest importance, among currently ongoing studies, is elucidation of the role which dietary adjustments in lipid intake may play in large scale prophylaxis of atherosclerotic heart disease in the United States.

Once again, the study of nutrition has taken on the vigor which provided its first big advances with the discovery of vitamins fifty years ago. With continued research, investigators in the field of nutrition expect rewards in the near future to be fully as extensive.

SPECIAL REPORT:
NUTRITION

When the National Institute of Arthritis and Metabolic Diseases (NIAMD), one of the National Institutes of Health (NIH), was established it acquired the laboratories of the Experimental Biology and Medicine Institute (EBMI), which had been a "general" Division of NIH. Through these laboratories, the Institute can trace its origins back some 80 years. Thus, its tradition of nutrition research stems from the classic work on pellagra as a vitamin deficiency disease by Dr. Joseph Goldberger (assigned to this problem by the Public Health Service in 1914) and by his student, Dr. W. H. Sebrell, who later served as Director of the EBMI, as the first Director of the Institute, and subsequently, as Director of the NIH until 1955.

The Institute is now responsible for the largest single portion of the nutrition research supported by the Institutes of the National Institutes of Health and for about one-half of all medically oriented nutrition research supported by the Federal Government. In addition to direct research activities in the laboratories and clinics in Bethesda, NIH supports a wide variety of research projects through grants to research centers and medical institutions throughout the United States and abroad. These activities cover the full spectrum of nutrition research from fundamental metabolic and physiologic studies of dietary requirements of the various nutrients, to programs designed to determine how best to alleviate malnutrition and nutritional deficiency diseases both in the United States and abroad.

Scope of the Grants Program

The grants program is divided into two groupings: physiology of normal nutrition and nutritional disorders. Projects in the physiologic processes of normal nutrition involve body composition, digestion and absorption of nutrients in the gastrointestinal tract; appetite regulation and food intake; the biochemistry and physiologic role of nutrients; and their fate in the body; quantitative requirements of proteins and amino acids, carbohydrates, fats and fatty acids, minerals, trace elements, vitamins, and fluids and electrolytes; interrelationships between different nutrients and between nutrients and hormones, and nutrients and enzymes; and the relationship of the intestinal flora to nutrition.

Research in abnormal nutrition involves discovery and definition of deficiency states, nutrient toxicity, obesity, malabsorption of specific nutrients, and the relationship of diet to specific disease entities, such as celiac disease and others. Another major subdivision of these research grants relates to nutrition in specific diseases or stress states, such as in diabetes, bone and joint disease, liver disease, gastrointestinal disease,

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infectious diseases, disorders of immunity, anemia, endocrine disorders, gall-bladder disease, inborn errors of metabolism, skin disorders, kidney disease and urolithiasis, and stress (including surgery, trauma, wound healing and environmental extremes).

In addition to this broad research grants program, the NIAMD finances and administers a substantial and comprehensive program providing research fellowships and graduate research training grants in nutrition.

Special Nutrition Research Studies

Two unique areas of continuing research include design and assessment of diets for kidney failure patients and conduct of malnutrition research abroad.

The first of these is pursued in the Institutes' Artificial Kidney-Chronic Uremia Program. This Program is a special research and development contract effort aimed at developing more effective dialysis hardware and methodologies, as well as methods for optimal rehabilitation of patients in chronic renal failure through use of particular diets, without utilizing the artificial kidney or organ transplantation.

Specific research projects are carried out abroad among populations with nutritional deficiency diseases to find solutions to complex malnutrition problems. These projects are funded through the U.S.-Japan Cooperative Medical Sciences program in Southeastern Asia, and through PL-480 "Counterpart Funds", U.S. owned local currencies in developing countries derived from the sale of surplus agricultural commodities.

RESEARCH ACCOMPLISHMENTS

The findings reported do not indicate the Institutes' total effort, but rather illustrate the variety of problems associated with nutrition research, as well as the broad coverage of the research supported. The past year has seen the development of numerous significant research findings contributed by both NIAMD scientists and Institute-supported investigators. Foremost among these include studies that clarify the liver as the major site of vitamin D activation, the pathogenesis of cirrhosis of the liver, the relationship of the enzyme lactase and the milk intolerance syndrome, as well as methods of diminishing calcium loss in immobilized patients--the nearest simulation to weightlessness encountered in space flight.

Vitamin D Conversion

Old concepts of vitamin metabolism are being refuted by Institute grantees at the University of Wisconsin. Cholecalciferol (vitamin D₃) for example, has long been considered the active form of vitamin D. This vitamin, necessary for intestinal calcium absorption and maintenance of normal bone metabolism, is ingested in small amounts in food or formed from a precursor substance in skin exposed to ultraviolet light or sunlight.

Last year a new and significantly more active molecule, 25-hydroxycholecalciferol (25-HCC) was isolated. This compound had been shown effective in disorders of calcium metabolism which did not respond to the vitamin D preparations previously available, suggesting an inability, perhaps a missing enzyme, to convert ingested vitamin D to its active form. Apparent inability of the body to use vitamin D in the amounts required by normal individuals is a feature of some disorders, such as chronic renal disease. The latter, unlike ordinary rickets, and so-called "vitamin D resistant rickets", the classical vitamin D deficiency disease characterized by faulty bone formation, does not respond to cholecalciferol except in very large doses. The new-found compound may provide answers to many basic questions of calcium absorption and physiology, and of bone formation; it may also lead to more effective treatment of disorders previously characterized by an apparent vitamin D resistance.

These same scientists now have shown that the liver is the major, if not the only, physiological site of vitamin D conversion into its metabolically active form. This work suggests that bone dystrophies and higher vitamin D requirements observed in patients with severe liver diseases may be due to the liver's inability to transform vitamin D into 25-HCC. The researchers currently are attempting to isolate and identify the enzyme that converts vitamin D into its biologically active form.

Vitamin D and Calcium-Binding Protein Relationship

The manner in which vitamin D affects a specific calcium-binding protein elaborated by the mucosa of the small intestine and how the protein in turn, appears to aid calcium absorption and transport processes has been clarified in Cornell University studies by grant-supported scientists of the National Institute of Arthritis and Metabolic Diseases and the National Institute of Dental Research.

Previous studies showed that the calcium binding protein was not found in vitamin D-deprived animals with rickets; however, after vitamin D was given, the protein appeared and the intestine again absorbed calcium. Another study in these animals showed that vitamin D treatment increased the rate of calcium uptake and release across the mucosal border of intestinal cells concomitant with the appearance of the protein.

Now the Cornell group has reported that the calcium-binding protein has been isolated in high purity and has been found throughout the intestinal lining, in kidneys and in avian shell glands (all regions where calcium is actively transported), but not in liver, muscle, pancreas, blood or bone. This protein was identified in rats, dogs, calves, sheep, and monkeys, as well as in chickens, and as expected, there was more of it in young than old animals.

Further studies showed that the protein is concentrated in epithelial goblet cells and in the brush-border region of intestinal absorptive cells, where vitamin D manifests a primary effect. Other physiological studies showed that the protein always appeared after the vitamin is taken, and that calcium absorption appeared to coincide with the appearance of the protein.

Moreover, the concentration of the protein increases when the body calcium requirement is greater. The researchers now believe that the binding substances may act by altering cell membranes to make calcium diffusion easier, or that an as yet unknown cellular calcium-pump mechanism may exist, and that this protein may only serve to move calcium faster through the protoplasm after it has already entered the cell.

Alcohol and Liver Damage

Institute-supported studies have indicated in the past that excessive consumption of alcohol can lead to development of fatty liver, forerunner of cirrhosis, in man despite a concurrent, well-balanced dietary intake, a finding contrary to the conventional hypothesis that a poor diet is the cause of alcoholic liver damage in alcoholic individuals. Last year Institute grantees at Mt. Sinai School of Medicine and at Cornell Medical College in New York City provided further insight into the pathogenesis of the alcoholic fatty liver. They found that, in persons who drink only occasionally, acute exposure of alcohol may lead rapidly (after only two days) to fat accumulation in the liver and to intracellular microscopic structural changes, regardless of nutritional factors. After two days this damage is reversible, but it becomes permanent and cumulative after more prolonged exposures.

These findings are significant because it is now clear that alcohol can rapidly produce liver injury when taken in amounts equivalent to those consumed not only by recognized alcoholic persons but by many "social" drinkers as well. The blood alcohol level determinations during the experiments showed that a person need never have been intoxicated to sustain temporary alcohol-induced liver injury.

A University of North Carolina grantee has evaluated the effects of the drug prednisolone on alcoholic hepatitis and reported a better survival rate and increased caloric intake in severely ill patients who had been on such a drug regimen. Prednisolone did not affect the rate of clinical, biochemical or histological improvement in mild cases of alcoholic hepatitis, and supportive care alone, a high-protein diet and vitamins, resulted in survival in all mild and moderately ill patients. These clinical results do suggest a possible role for prednisolone treatment in severely ill patients, and studies are continuing.

The role of alcoholic hepatitis in the development of cirrhosis was evaluated also, but remains unclear. Alcoholic hepatitis may heal with the clear development of cirrhosis, but apparently is reversible. Repeated overt episodes of alcoholic hepatitis possibly may result in progression of cirrhosis in the alcoholic, but other determining factors at present are unknown.

New Findings in Milk Intolerance and Lactase Deficiency

During the past four years, Institute-supported researchers have traced the cause of milk intolerance in certain otherwise normal adults and in patients with inflammatory bowel disease to a deficiency in an intestinal enzyme, lactase. This enzyme, which converts lactose or "milk sugar" into its simple sugar components, glucose and galactose, is essential to digestion and subsequent absorption of lactose. Increasing evidence has been found recently to indicate that intolerance to milk due to deficiency or lack of intestinal lactase is a relatively common syndrome in adults.

Institute grantees at Johns Hopkins University School of Medicine, Baltimore, two years ago, demonstrated that milk intolerance based on lactase deficiency is much more common in Negro adults (70 percent in Baltimore and 72 percent in Uganda) than in the adult white population (5-10 percent), suggesting that intestinal lactase activity may be genetically controlled. In a later study adults of oriental ancestry also were found to be commonly afflicted with this disorder. It was then found that lactose-induced symptoms in Negro children and adults increased in frequency with advancing age, suggesting a gradual decrease in lactase activity after weaning. This was not as common in the white subjects studied.

Similar studies carried out by Institute grantees at the University of Oklahoma Medical Center, Norman, have indicated that there is a distinct racial difference in lactase activity, and that a genetically determined intestinal lactase deficiency is responsible for the majority of instances of milk intolerance found in adults. Thus, a large part of the world's non-white population may have a genetically determined intolerance to milk, a situation which would require re-evaluation of the importance of milk (particularly when used as an imported nutritional aid in under-developed countries) as a source of nutrition and protein among non-white adult populations.

In another lactase intolerance study, Institute grantees at Johns Hopkins University School of Medicine last year studied six school-age children, three white and three Negro, aged 6-13, who complained of recurrent abdominal pain for six months. They concluded that lactase intolerance was the cause of abdominal pain, and that milk intolerance be considered in evaluating recurrent gastrointestinal symptoms in school age children, as well as in planning nutritional aid programs.

These studies have considerable diagnostic and therapeutic significance, particularly for Negro and Oriental patients presenting themselves with a variety of gastrointestinal symptoms, such as diarrhea, nausea, and abdominal pains, which do not appear to be related to any specifically manifest pathologic lesion. In view of these findings, it becomes necessary to rule out, in such patients, the presence of milk or lactose intolerance due to lactase deficiency (a presently uncommon diagnosis in adults). Once this diagnosis is confirmed, dietary restriction of milk, milk products, and foods containing milk sugar (lactose) usually leads to cessation of the distressing symptoms.

Calcium Loss in Immobilization, Weightlessness

Previous research on effects of weightlessness on mineral metabolism-based mainly on ground immobilization studies (as the nearest simulation to weightlessness) clearly predicted that derangements in bone mineral metabolism might be associated with weightlessness encountered in space flight. In patients immobilized for long periods as a result of illness, complications from the bed rest itself often develop: loss of bone mineral manifested by hypercalciuria, negative calcium balance, and ultimately, demonstrable osteoporosis. These effects of immobilization on calcium metabolism appear to be due mainly to decreased physical stress on the skeleton and increased rate of bone resorption without a compensatory increase in bone mineral deposition.

NIAMD collaborative studies with Cornell and Baylor Universities and the NASA Manned Spacecraft Center, Houston, now have provided the first comprehensive metabolic data in man during space flight. The results, probably reflective of co-existing multiple influences, indicated that the Gemini astronauts lost a substantial amount of calcium during their 14-day mission. (This Gemini VII flight was the longest in the series.)

In related work a Harvard Medical School grantee obtained evidence to suggest that oral phosphate supplements can prevent or ameliorate hypercalciuria and negative calcium balance associated with prolonged immobilization. Additional studies are continuing to assess further the effects of such therapy during longer periods of immobilization, for it is reasonable to expect that disuse osteoporosis could be at least partially prevented in immobilized patients by phosphate supplementation.

Goiter Studies

Endemic goiter (abnormal thyroid gland enlargement due to low iodine content of the normal local diet) continues to be a significant health problem in many areas of the world, including certain remote sections of Ecuador and Peru, where iodized salt is unknown or difficult to introduce into the diet of the native population. Spurred by earlier successful field trials by other scientists in New Guinea, a pilot program using iodized poppy seed oil has been instituted in several rural communities in both Ecuador and Peru.

Institute grantees at the Massachusetts Institute of Technology, have demonstrated, after a two-year study, the feasibility and effectiveness of a prophylactic program consisting of parenteral administration of iodized oil, in lieu of ingestion of iodized salt in the treatment and prevention of endemic goiter in isolated population groups.

The study was conducted in two Ecuadorian and three Peruvian villages with known chronic iodine deficiencies, where endemic goiter is severe and cretinism is commonplace. Cretinism is characterized by a lack of thyroid hormone secretion since birth (beginning with deficient or absent maternal thyroid hormone secretion during fetal development, resulting in retarded physical and mental development. Various populations were given a single intramuscular injection of iodized poppy seed oil, or were left untreated. Epidemiological surveys for goiter prevalence, incidence and associated defects were conducted thereafter at 6 to 25 month intervals.

Results indicated a sharp reduction in the incidence of goiter, and associated cretinism did not appear among progeny of treated populations. The data obtained were consistent with, and suggestive of a dramatic effect on the prevention of cretinism. Such a procedure is technically simple, free of serious risk, and is recommended for endemic goiter regions where salt-iodization programs have not yet been implemented. Several more years of observation, however, are needed to assess the full impact of this type of prophylactic treatment.

In another goiter research study at Vanderbilt University, Institute grantees have identified a goiter-producing substance which apparently occurs naturally in the water supply in a region of Columbia prone to endemic goiter. Endemic goiter in the area could not be attributed to dietary iodine deficiency, which is felt to be the usual cause of the disease. It could, however, be correlated with the source of drinking water. Children supplied by one well had a 23 percent goiter incidence, while those supplied by a second well had only an 11 percent incidence. When water from these wells was combined into a central system, goiter incidence in the previously low area rose to 31 percent, while that of the previously high area remained about the same.

Laboratory rats maintained on suspected goitrogenic water for two months developed significantly larger thyroid glands and demonstrated lower thyroidal iodine uptake and iodine concentrations than did rats maintained on water from the second well. When the suspect water was distilled the goitrogen appeared in the distillate, indicating that the goitrogen was a relatively volatile substance, and only rats imbibing the distillate developed abnormal thyroid glands, while those consuming the residual boiled water were unaffected.

Attempts to isolate and identify the active agent revealed a specific group of compounds similar to some of those isolated in the past from certain goitrogenic foods. Definitive identification of the active agent, elucidation of its natural origin, and its elimination as a health hazard are the investigators' current objective.

Obesity

One of the most important nutritional problems in the U. S. today is not underconsumption of nutrients, but overconsumption of calories. Nearly 20 percent of all adults are overweight to a degree that impairs their health and longevity. Diet and obesity appear to be extremely significant factors in causing, preventing and treating disorders such as atherosclerosis and hypertension, diabetes, and gallbladder disease.

In a study of adolescent girls, Institute-supported scientists at the Harvard School of Public Health found that as a group, the girls underestimated calories in meat portions and overestimated them in starchy foods. This bias in calorie estimation may be widespread and may be keeping fat girls, as well as boys, from losing weight.

Evidence has been accumulating that indicate lean tissue, as well as fat, is lost when the weight of an obese individual is reduced by means of drastic calorie restriction especially when the subject is placed on a complete hunger regimen. Other observations have suggested that exercise might protect against the loss of lean tissue occurring when an individual is in a negative calorie balance. In a recent study, an Institute grantee at Washington University School of Medicine, St. Louis, has compared effects on body composition of weight reduction in obese rats brought about by exercise alone and by calorie restriction alone.

Although the weight loss of the exercising and sedentary calorie restricted animals was comparable, the exercisers lost significantly more fat and less than one half as much lean tissue muscle (protein) as did the food restricted rats. The finding that the exercising animals were leaner than the sedentary controls of the same weight points to a fat mobilizing and protein-conserving effect of exercise. These findings may be of some clinical interest when viewed in the context of studies showing that prolonged exercise, under some circumstances, can be effectively incorporated into weight reducing programs of obese patients.

Institute grantees at the University of California, Berkeley, have cautioned against carbohydrate-free diets in obese persons on a reducing diet because of the problems involved in the body's compensatory utilization of its own protein as a source of needed calories, in addition to the desirable "burning up" of fat depots. They found that a minimal level of carbohydrates was necessary in the diet to cause protein sparing and to avoid the resultant ketosis due to protein breakdown. It was noted also that the carbohydrates promoted adequate clearance of uric acid when endogenous fat became the chief source of energy. Exogenous protein can fulfill part of this clearance function but the protein is less effective than carbohydrates at equivalently low calorie intakes.

Malnutrition and Disease

The effect of malnutrition on brain function currently is being studied by an Institute grantee at St. Joseph Hospital, Lancaster, Pennsylvania, to determine the correlation between nutritional status, central nervous system activity, and results of psychological testing for clinical ability and performance. Electroencephalograph testing and computer analysis revealed statistically significant differences between subjects and controls, with evidence of delays in normal electrophysical maturation in the undernourished.

Another grantee study, at Vanderbilt University School of Medicine, has revealed that deficiencies in iron, folic acid, thiamine, and vitamin A occur in a higher proportion than previously suspected in economically disadvantaged children. Further, twenty percent of these children studied tested below the 10th percentile in height, and 39 percent showed evidence of periodontal disease.

Determination of Folate Absorption

Until recently, there was no way of determining how much folate in ingested food was available for absorption (to supply the essential vitamin "folic acid") because only a fourth of folate material naturally occurring in foods in the free form is known to be biologically active in man. The rest occurs as polyglutamates of folic acid which give contradictory results in tests for their biological activity. These polyglutamates are folic acid precursors found most plentifully in foods such as green leafy vegetables, yeast and liver.

Now a team lead by an Alabama grantee at the Birmingham Medical College has found a way to track each of the polyglutamates on its way through the body by synthesizing the glutamate chains and radioactively tagging them. They found that polyglutamates are much more easily absorbed than nutritionists had formerly believed; between 37 percent and 67 percent of ingested polyglutamates were retained in the body.

The investigators reasoned that extra glutamates in food folates were split off by digestive enzymes early in the absorption process and were oxidized, leaving free folic acid to be absorbed. This means that in planning a diet with enough foods necessary to supply an adequate amount of folic acid, both the free form and about one half of the polyglutamate form of folates present in the food must be taken into account.

Nutrition Research Abroad

The Institute has traditionally conducted nutrition research in developing countries overseas because large populations afflicted with nutritional deficiency diseases can only be found and studied there. Considerable contributions to our knowledge of normal nutrition and nutritional deficiencies have resulted from this work which also has yielded concrete benefits to the nutritional status of the local population. The recent discovery of pockets of malnutrition and nutritional deficiencies within our own population indicates strongly that these studies are not merely altruistic research exercises, but investigations of utmost importance to the welfare of the United States.

Southeastern Asia

The nutrition portion of NIH's U.S. - Japan Cooperative Medical Sciences Program, financed by a separate appropriation carried in the budget of the National Institute of Allergy and Infectious Diseases, is administered for programmatic reasons by the NIAMD. The mission of this Program is to support research aimed at practical solutions to nutrition and nutrition-related problems of countries in Southeast Asia. This substantial grant and contract Program supports research in the following areas: relationship between malnutrition and mental development, infection, and nutritional anemias; requirement for essential nutrients; biochemical adaptation to malnutrition; methods for evaluation of nutritional status; investigations into the occurrence and nature of toxic substances in foods; and development of low-cost protein-rich foods, including the genetic improvement of protein concentration and composition in rice.

Rice is the principal food of 60 percent of mankind; however, ordinary commercial rice does not contain enough protein to support normal growth and development of infants and children maintained on a predominant rice diet, and does not protect the adult population from serious protein under-nutrition. If the present protein level of rice (approximately 7-1/2 percent) could be elevated by several percentage points, an automatic and sweeping nutritional improvement would take place in all the populations for whom this one crop represents the nutritional mainstay. Such development concomitantly would relieve the current burden of the United States which supplies hundreds of millions of dollars' worth of supplementary foods to developing rice-eating countries. The potential nutritional improvement among Southeast Asian populations and developing rice-eating countries throughout the world is an important aim of the U. S. - Japan Program and of the applied nutrition program of the Institute.

Major findings have emerged from an ongoing research project aimed at improving the protein level of rice. The first year's work on this contract at the International Rice Research Institute, Manila, has identified about 100 rice varieties among the many thousands tested which contain between 13-1/2 to 17-1/2 percent protein. Actual growing experiments are now continuing under Southeast Asian climatic conditions to identify the specific rare high protein varieties (from among these 100 varieties) which would be agriculturally and commercially feasible in a Southeast Asian setting. Thus far, six high protein strains of rice have been crossbred successfully with a new rice variety (IR₈) which had been developed previously at the Institute. These strains possess near-ideal plant characteristics including disease resistance, a high yield per acre, and a strong response to fertilization. In the face of encouraging progress, further crossbreeding of the resulting hybrids in larger plots is now being carried out.

Highlights of other current research projects which further advance the objectives of the U.S. - Japan Cooperative Medical Sciences Program include: observations that Chinese male students have lower protein requirements per kilogram body weight than their Caucasian counterparts, perhaps reflecting Asian adaptation to meager protein supplies; findings that bladder stones in children, a serious medical problem in Northeast Thailand, are due to low phosphate intake in combination with urinary hydroxyproline excretion and can be prevented or reversed by phosphate administration; and revelation of an unexpectedly high frequency of mold toxins in food materials consumed in Thailand, Malaysia and Hong Kong, and the possibility, subject to further investigation, that there might be a relationship between such chronically ingested toxins and Reyes Syndrome, an acute and usually fatal disease common in children in Southeast Asian countries, or to liver malignancy.

Protein Malnutrition Studies in India

Illustrative of such studies are two interrelated research and development projects administered by the Institute in South India, and funded through PL-480 U. S. surplus commodity funds. One is located at the Central Food Technological Research Institute (CFTRI) in Mysore, and the other at the Christian Medical College (CMC), in Vellore. Both projects are part of an intensive and comprehensive program to find a practical answer to the problem of protein malnutrition in a typical underdeveloped-country setting, while simultaneously studying intermediary metabolism and selected metabolic disturbances in patients hospitalized for kwashiorkor (protein malnutrition). The Mysore project primarily is concerned with the laboratory development of protein-rich food supplements based on indigenous protein sources intended to prevent the widespread endemic kwashiorkor prevalent among preschool-age children in India. Secondly, this project involves animal testing and evaluation of such protein supplements, and studies of intermediary metabolism in kwashiorkor. In addition, the Mysore project has become involved in the problem of aflatoxin, a highly toxic substance produced by mold growth in a wide range of foodstuffs all over the world. Aflatoxin is implicated in liver damage and carcinogenesis in animals and man.

The Vellore project encompasses clinical trials of the value of experimental protein blends developed in Mysore in the treatment of patients hospitalized for kwashiorkor, and large scale feeding tests in controlled institutional and village populations of the prophylactic value of these food supplements in the diet of weaning and school age children. In addition, selected metabolic disturbances associated with kwashiorkor are studied in hospitalized patients.

The reader is referred to last year's Special Report on Nutrition by the National Institute of Arthritis and Metabolic Diseases (1969) for a detailed account of the numerous and substantial accomplishments of these projects to date. The most recent achievements deal with the fortification of wheat with lysine. Like many vegetable proteins, wheat protein is not of high enough biological quality to support rapid growth in children and to serve as the main source of protein in the human diet. Proteins of high biological value (usually from animal sources, such as milk, eggs, meat and fish) have a qualitatively and quantitatively more complete complement of amino acid components. The first, most limiting amino acid in the incomplete wheat protein is lysine. There are indications that the addition of inexpensive synthetic lysine to wheat from the United States, which is used for control of under-nutrition in India and other underdeveloped countries, might improve the biologic quality of wheat considerably - to the point where lesser quantities of the expensive and unobtainable animal proteins would be needed to attain satisfactory nutrition in the population. The recently concluded investigations on lysine fortification of wheat protein are particularly gratifying since they represent the first conclusive study of this kind in humans which has shown that the addition of lysine to dietary wheat can significantly improve the growth of preschool children. Children, aged two to five years residing in an orphanage, had been maintained on a diet providing two grams of vegetable protein and 100 calories per kilogram body weight per day for a preliminary control period of three months. At the start of the feeding trial, the children were divided into two groups matched for height, weight, age, and rate of growth during the preceding three months. The only difference in the diet of the two groups during a subsequent six-month experimental period was that lysine was added to the wheat in the diet of the experimental group. The cereal consumed by the control group provided a daily lysine intake of 0.68g., while the experimental cereal provided an additional 0.37 g/day of lysine (total 1.05g). Wheat flour used in the experimental diet was enriched through homogeneous admixture of finely powdered lysine. Where the dietary items called for whole wheat grain or broken wheat kernels, the experimental wheat grain was enriched through the admixture of specially prepared wheat kernels, containing 10 percent by weight of lysine. During the six-month experimental period the children on the lysine supplemented wheat diet grew significantly in height compared to the children in the control group.

Lysine-supplementation of wheat is logistically feasible primarily for those population groups residing in cities, or to those consuming centrally processed cereal products. An expanded program, however, might reach large numbers of non-urban peoples as well. The importance of the study lies in the fact that it has conclusively demonstrated the potential benefit of what may become an inexpensive, yet effective method of improving protein nutrition in many developing countries which is not dependent on education or orientation of individuals toward better nutrition (a slow procedure at best) or on major changes in the dietary habits of local populations.

Benefits to U. S. From Overseas Nutrition Research

The Mysore-developed protein rich products evaluated in Vellore, together with the Vellore-initiated lysine fortification of wheat, serve as prototypes for similar efforts in other developing regions of the world wherever agricultural necessities and economic and social factors preclude large scale inclusion of animal proteins in the diet.

The scientific findings emanating from this work are enriching the fund of scientific knowledge in the United States. Of particular importance are the contributions concerning intermediary metabolism during protein deprivation and vitamin deficiency which could not have been carried out adequately in the United States because of a lack of sufficient patient material concentrated in any one particular locality. Since the majority of these findings are disseminated to the rest of the world through the medium of the American scientific literature they are enhancing the standing and image of American science. These particular studies are also an example of effective and beneficial use of U.S. - owned counterpart funds ("PL-480 funds") in biomedical studies, demonstrating the value of this funding mechanism which demands no current expenditure of U.S. funds.

These efforts also contribute specifically to the technological knowhow of the United States food industry, particularly to our knowledge concerning naturally occurring mold toxins in foods, such as aflatoxin. Traces of aflatoxin have been found in U.S.-made peanut butter. There is considerable importation of peanuts (which may be contaminated with aflatoxin) to the United States from abroad, and little is known concerning the presence of aflatoxin in many U. S. feeds or the potential economic importance of such contamination. Laboratory techniques and technologic achievements in aflatoxin destruction developed in the Institute's Mysore project are of considerable importance in the United States from the standpoint of both public health and agricultural and food economics.

Projects like these, in addition to the scientific aspects beneficial to the United States, are aimed at helping a developing country help itself. Rather than letting the host country rely on gifts of expensive protein-rich foods (such as powdered milk) from the United States which this country cannot afford forever, it gives the developing country the scientific knowhow to utilize effectively inexpensive proteins which it can produce by itself. Thus, the country can cope more successfully with the problem of protein malnutrition among its children.

OUTLOOK

Once again, the study of nutrition has taken on the vigor which provided its first big advances with the discovery of vitamins and of specific nutrition deficiency diseases fifty years ago. Despite the wide reduction of frank nutritional deficiency diseases in this country, the margin of safety is not large. Improved methods of determining nutritional status and revised criteria

for normal nutritional status have contributed to a new emphasis on the definition and diagnosis of malnutrition. Through application of new principles and laboratory techniques learned in recent years from studies of intermediary metabolism, mostly supported by this Institute, the evaluation of nutritional status in the absence of overt disease is no longer dependent on ill-defined lesions and symptoms or on the subjective judgment of physicians. These advances in knowledge now form the basis for more exacting nutrition surveys used to pinpoint pockets of malnutrition in vulnerable population groups in the United States. They will also be necessary in many developing countries to cope with the world-wide famine and malnutrition predicted for the near future if the runaway disproportion between population increase and agricultural selfsufficiency is not drastically reversed. Although this past year has proven highly productive in adding to our understanding of human nutrition in health and disease, the Institute confidently expects even more significant advances in this complex research endeavor in the future.

SPECIAL REPORT
GASTROENTEROLOGY

The field of gastroenterology continues to prove one of the more challenging and fascinating for both scientists and practicing physicians. The diversity and magnitude of gastrointestinal disorders combine to place these diseases in a prominent position among the chronic afflictions occurring in man.

The impact of gastroenterology is vast not only from the standpoint of the number of individuals afflicted but also because of the extensive number of diseases encompassed. Included among these are the better-known disorders of the gastrointestinal tract, such as peptic ulcer, ileitis, and ulcerative colitis; in addition, there exist the equally debilitating diseases affecting organs such as the liver, gallbladder, and pancreas.

It is estimated that approximately 14 million Americans, or over 7 percent of the entire U. S. population, now have or have had an ulcer of the stomach or duodenum. Each day an estimated 4,000 more individuals develop ulcers, and every year about 10,000 persons die of peptic ulcer complications. The cost in terms of lost man hours and direct medical expenses due to peptic ulcer alone is estimated at \$500 million annually. In one recent year direct expenditures for diseases of the digestive tract in the U. S. amounted to \$4.2 billion.

The National Institute of Arthritis and Metabolic Diseases (NIAMD) bears the responsibility for the Government's program of research in this field, and presently a broad array of ailments of the digestive tract is undergoing investigation. Due to the highly complex interaction of a variety of factors in gastroenterological diseases, research progress has been achieved only after the most intensive and comprehensive laboratory experiments and clinical trials. The past year, however, has seen the development of numerous important research findings, several of far-reaching significance, contributed by both NIAMD scientists and Institute-supported investigators. Foremost among these are improved diagnostic techniques for celiac disease and Hirschsprung's disease, new information on the Zollinger-Ellison Syndrome, milk intolerance, bile blockage and bile salt malabsorption, as well as elucidation of the control mechanism in sterol metabolism and of the pathogenesis of the alcoholic fatty liver.

Gastrin Synthesis

Several years ago Institute grantees at the University of Liverpool in England elucidated the chemical nature and structure of gastrin, the hormone which stimulates secretion of gastric juices. The hormone, a peptide consisting

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of 17 amino acids, was subsequently synthesized by them. This synthesis of gastrin provides an important research tool for studying peptic ulcer, a condition in which an excess of acid digestive juices is usually secreted. The mechanisms which control such secretion under normal and abnormal conditions have remained quite obscure, in spite of considerable research effort. Now, however, a potent secretory stimulant is available for assessing gastric secretory function.

Gastrin and Peptic Ulcer Study

The availability of a chemically pure gastrin has opened new avenues of approach to old problems. For example, by using immunochemical techniques an Institute grantee at Washington University School of Medicine, St. Louis, recently demonstrated that blood levels of gastrin are ten times higher than normal in patients with the Zollinger-Ellison Syndrome, which is characterized by very severe and unmanageable peptic ulceration in the upper gastrointestinal tract, extreme gastric hyperacidity and certain pancreatic cell tumors.

This study confirms the prevalent theory that gastrin is the agent which stimulates the excessive gastric hydrochloric acid secretion and the resulting peptic ulcer disease characteristically observed in this syndrome. Measurement of serum levels of the hormone by immunochemical techniques now should afford a direct and accurate method of diagnosing this disorder.

Many other studies, such as those dealing with the possible identification of native anti-gastrins, and with the artificial creation of such substances, are under way. Extensive tests are necessary now to determine if and how gastrin function differs from normal in the peptic ulcer patient.

Intracellular Localization of Gastrin

The same scientist, working at Washington University, now has used immunofluorescent techniques to locate and describe the specific cells in human and porcine antral gastric mucosa which contain and, presumably, synthesize and secrete gastrin. The hormone was found to reside in or on granules contained within the cytoplasm of certain differentiated mucosal epithelial cells of antral pyloric glands.

This finding should shed light on the pathogenesis of gastrointestinal diseases such as peptic ulcer. Further studies will be required to determine whether gastrin is actually synthesized by the gastrin-containing cells identified in this study.

Milk Intolerance and Lactase Deficiency

During the past three years, Institute-supported researchers have traced the cause of milk intolerance in certain otherwise normal adults and in patients with inflammatory bowel disease to a deficiency in an intestinal enzyme, lactase.

This enzyme, which converts lactose or "milk sugar" into its simple sugar components, glucose and galactose, is essential to digestion and subsequent absorption of lactose. Subsequently, increasing evidence has been found that intolerance to milk is a relatively common syndrome in adults.

Last year Institute grantees at Johns Hopkins University School of Medicine, Baltimore, demonstrated that milk intolerance based on lactase deficiency is much more common in Negro adults (70 percent in Baltimore and 72 percent in Uganda) than in the adult white population (5-10 percent), suggesting that intestinal lactase activity may be genetically controlled. It was also found that lactose-induced symptoms in Negro children and adults increased in frequency with advancing age, suggesting a gradual decrease in lactase activity after weaning. This was not as common in the white subjects studied.

Similar studies also have been carried out by Institute grantees at the University of Oklahoma Medical Center, Norman, Oklahoma. Both the Johns Hopkins and the Oklahoma studies indicate that there is a distinct racial difference in lactase activity, and that a genetically determined intestinal lactase deficiency is responsible for the majority of instances of milk intolerance found in adults.

The same Johns Hopkins investigators now have shown that milk intolerance, presumably due to a lactase deficiency, is also very common among adults of Oriental ancestry. Thus, a large part of the world's non-white population may have a genetically determined intolerance to milk, a situation which would require re-evaluation of the importance of milk as a source of nutrition and protein among non-white adult populations.

These studies have considerable diagnostic and therapeutic significance, particularly for Negro and Oriental patients presenting a variety of gastrointestinal symptoms, such as diarrhea, nausea, and abdominal pains, which do not appear to be related to any specifically manifest pathologic lesion. In view of these findings, it becomes necessary to rule out, in such patients, the presence of milk intolerance or lactase deficiency (a presently uncommon diagnosis in adults). Once this diagnosis is confirmed, dietary restriction of milk, milk products, and foods containing milk sugar (lactose) usually leads to cessation of the distressing symptoms.

LIVER DISEASES

The liver performs a multitude of complex chemical tasks without which life cannot exist. The liver functions, for example, as a filter and clearing station for purification and detoxification of blood, as a chemical factory

for interconversion of carbohydrates, fats, and proteins, as a storage house for certain nutrients (particularly sugars and certain vitamins), as a site of production of blood proteins and of antibodies, and as a secretory gland which aids both digestion and the removal of wastes.

It is not surprising, then, that an organ of such complexity is also subject to a broad range of injuries and diseases, including disorders of infectious, parasitic, nutritional, metabolic, obstructive, toxic, and malignant origin. Prominent among liver diseases is cirrhosis, the end-stage of a progressive destructive process often resulting from chronic alcoholism or infection.

Fatty Livers

Institute-supported studies have indicated in the past that excessive consumption of alcohol can lead to development of fatty liver - forerunner of cirrhosis - in man despite a concurrent, well-balanced dietary intake, a finding contrary to the conventional hypothesis that a poor diet is the cause of alcoholic liver damage in alcoholic individuals. Institute grantees at Mt. Sinai School of Medicine and at Cornell Medical Division of Bellevue Hospital in New York City now find that, in persons who drink only occasionally, acute exposure to alcohol may lead rapidly (after only two days) to fat accumulation in the liver and intracellular microscopic structural changes, regardless of nutritional factors. After two days this damage is reversible, but it becomes permanent and cumulative after more prolonged exposures.

According to the investigators, it is clear that alcohol can rapidly produce liver injury when taken in amounts equivalent to those consumed not only by recognized alcoholic persons but by many "social" drinkers as well. The blood alcohol level determinations during the experiments showed that a person need never have been intoxicated to sustain alcohol-induced liver injury.

These findings are significant because they provide insight into the pathogenesis of the alcoholic fatty liver and indicate that, regardless of the high quality of the concurrent diet, alcohol per se in even moderate amounts can lead to the production of a fatty liver.

Liver Enzyme Detects Bile Blockage

Determination of the changes in concentration of different liver enzymes in the serum has been an accepted practice in diagnosing hepatobiliary disease. This method is imperfect, however, for specific diagnosis of liver disease in individual patients because none of the indices used to date differentiate between intrahepatic and extrahepatic biliary obstruction.

At St. Luke's Hospital Center, New York, Institute grantees have evaluated the potential clinical application of determining serum alcohol dehydrogenase levels in the diagnosis of liver disease. Alcohol dehydrogenase is an enzyme found principally in hepatic tissue cells. They determined that elevated serum levels of alcohol dehydrogenase reflect in the serum the extent of necrosis

of liver cells and may serve to differentiate between extrahepatic biliary obstruction and intrahepatic cholestasis (suppression of bile excretion). Measurement of the levels of this enzyme in the serum will probably be of greatest clinical value in the diagnosis of patients with prolonged obstructive jaundice of unknown cause.

Estrogens and Altered Liver Functions

Another grantee at Cornell University Medical College has duplicated the symptoms of itching, jaundice, and cholestasis which complicate some pregnancies by administering a synthetic estrogen to patients post-partum. In each instance clinical and biochemical abnormalities associated with impaired hepatic excretory function, similar to those recorded during pregnancy, were exhibited.

Although several investigations have pointed to a hormonal basis for this disorder, no direct evidence of such a relationship had been demonstrated heretofore. Estrogens, it is now suggested, may play an important role in the pathogenesis of these symptoms and, perhaps, in that of the associated alterations in liver function. These findings are of particular interest in view of recent reports that estrogen-containing hormones given to suppress ovulation may occasionally cause hepatic dysfunction.

Bile Acid Absorption

In absorption studies on bile acids, grant-supported investigators at Long Island Jewish Hospital-Queens Hospital Center Affiliation, Jamaica, New York; The Long Island Jewish Hospital; and the Public Health Research Institute of New York City have established the previously unproved concept that significant absorption of bile acids takes place from the large bowel of man. The cecum, ascending colon, hepatic flexure, and transverse colon may all be reabsorption sites. Their data suggested that 5-20 percent of the bile acid pool is exposed daily to the effects of bacteria in the large bowel before being reabsorbed into the circulation and eventually, reexcreted into the gallbladder. The presence of bacterial transformation products of primary bile acids in the human gallbladder can be explained on the basis of these data.

MALABSORPTION STUDIES

Bile Salt Malabsorption

In studies relating to bile salt malabsorption, investigators at the University of Colorado Medical Center, Denver, examined this phenomenon in regional ileitis, ileal resection, and in mannitol-induced diarrhea, concluding that ileal resection and ileal disease are major factors, with rapid

intestinal transit a minor factor, in causing excessive fecal bile salt loss. It is therefore clear that the amount of healthy ileal mucosa present is the single most important factor in bile salt absorption.

Malabsorption Management

Dietary supplementation with a semisynthetic fat preparation, medium chain triglycerides, or MCT, has proved its value in managing fat malabsorption disorders of various origins, according to researchers at St. Luke's Hospital Center, New York. MCT has been used to provide additional nutrition both in disorders for which specific therapy exists and in those disorders for which no specific therapy is currently available.

Among the former are included gluten induced sprue, an intestinal sensitivity to the protein fraction gluten (found in wheat, rye, oats and barley), pancreatic and biliary insufficiency, and Whipple's disease; among the latter are included malabsorption following gastrectomy (removal of part of the stomach) and massive resection of the small bowel.

The efficient absorption of MCT in fat malabsorption states has been explained by the finding that medium chain triglycerides are more rapidly hydrolyzed to fatty acids than are most dietary fats, which are composed of long chain triglycerides. In addition, the studies demonstrated that the presence of bile and pancreatic lipase in the intestine is not necessary for the normal absorption of MCT, explaining its importance in hepatobiliary diseases and in pancreatic insufficiency. Further, MCT may be of particular value in therapeutic diet in infancy and childhood, when malabsorptive disorders take more severe forms and tend to impair normal growth.

NEW DIAGNOSTIC METHODS

Hirschsprung's Disease

Hirschsprung's disease is a disorder of the nerve centers (ganglions) that control contractile movements of the colon. Because of the derangement of nervous control in the lower rectum peristaltic action is impaired, defecation is infrequent and incomplete and the upper rectum fills and dilates massively and the abdomen may become quite enlarged.

Presently the only method of diagnosing this disorder is by surgery - a deep-muscle biopsy of the lower rectum to prove the absence of ganglion cells. Because this procedure carries some risk, grantees at Baltimore City Hospitals and at Johns Hopkins University School of Medicine have devised a nonsurgical technique for diagnosing Hirschsprung's disease. The new technique utilizes a manometric device, with separate pressure recordings obtained from internal and external anal sphincters by a double balloon device, and from the rectum by a third balloon.

In addition, since the pathophysiology is incompletely defined, and since the therapy of Hirschsprung's disease is surgical and thus its differentiation from other forms of colonic dilatation is important, these investigators also described more accurately the reflexes of the various intestinal sphincters in this disorder. These reflexes were contrasted with those found in idiopathic megacolon, a condition in which there is massive dilatation of the lower colon, but normal ganglion cells are present throughout the bowel.

They found that in patients with Hirschsprung's disease the external sphincter responses were normal (contracted), but there was contraction instead of relaxation of the internal sphincter. In this disorder there was also a consistent rectal contraction that was both delayed and longer-lasting than normal. In contrast, in 31 patients with idiopathic megacolon, both internal and external sphincter responses were normal, indicating that the abnormal contractile response found in Hirschsprung's disease is characteristic of this disorder, and further, that this response probably contributes to obstructive symptoms in the disease.

Celiac Disease

Celiac disease (nontropical sprue) is characterized by fatty diarrhea, intestinal malabsorption, and dietary deficiency symptoms, all caused by an intestinal sensitivity to a polypeptide fraction (gliadin) of the wheat protein, gluten, in the diet.

Antibodies to gluten fractions are frequently found in the blood of celiac disease patients. Recently, grant-supported scientists at Yale University School of Medicine and the Yale-New Haven Hospital, Connecticut, have suggested that inadequately digested polypeptides of gluten elicit production of antibodies with immunologically competent cells in the intestinal mucosa and that the intestine continues to secrete these antibodies for extended periods even in the absence of foods with a high gluten content, such as wheat, rye, barley and oats.

The investigators succeeded in demonstrating intestinal antibodies to a specific gluten fraction in the stools of three patients with celiac disease. In two patients coproantibodies were present when the disease was diagnosed; in the third, they were found after the patient had been receiving a gluten-free diet for six months and had become asymptomatic. No such antibodies were found in fourteen patients with other, non-celiac diarrheal diseases or in six normal control subjects. The demonstration of these antibodies to a fraction of wheat, the scientists feel, may be a clue to the nature of gluten sensitivity and, with further evaluation, may provide a specific means for diagnosing celiac disease.

EPIDEMIOLOGICAL STUDIESGallbladder Disease in Pima Indians

In a study of an American Indian tribe the prevalence of diagnosed gallbladder disease was found to be six times higher than that in a similar study done among Caucasians in Framingham, Massachusetts. The Pima Indians of the Gila River Reservation were examined by Institute scientists at the Clinical Field Studies Unit in Phoenix, Arizona, and were compared with the Framingham population.

Epidemiological studies, which evaluate relationships of various factors, (such as age, sex, environment) and determine frequencies and distributions of disease states in specific human communities, are necessary to clarify the determinants of gallstone formation.

In both sexes, significantly more gallbladder disease was found in the Pimas than in the people of Framingham; for example, 5.9 percent of Framingham females aged 30-62 had "definite" gallbladder disease, as compared with 36.0 percent among Pima females of the same ages. The study also showed the relationship of the disease to age in each sex. Pima males had little gallbladder disease prior to the age of 55, while Pima females showed a high prevalence of the disease in all decades after the second.

Having documented a high prevalence of gallbladder disease in these Indians, the scientists tried to associate this with possible predisposing conditions. None of the following factors - increased numbers of pregnancies, diabetes, body weight, serum cholesterol, or diet - appeared to be responsible for the excess gallbladder disease in the Pimas.

Further biochemical and physiologic studies to supplement the current epidemiologic investigations are continuing in an effort to find out whether genetic or environmental factors play the stronger role in determining the difference in the frequency of gallbladder disease between these American Indians and Caucasians.

Red-Cell Defect and Chronic Bowel Disease

A simultaneous occurrence of two uncommon diseases in several families originating from a relatively circumscribed geographical region has been the subject of epidemiological investigation for Institute-supported scientists at Boston Floating Hospital of the New England Medical Center Hospitals and at Tufts University School of Medicine, also in Boston.

Erythrocyte glucose-6-phosphate dehydrogenase deficiency (G6PD) and chronic granulomatous bowel disease were the two unusual diseases observed. The G6PD disorder, a red blood cell metabolic defect due to mutations of

enzyme structures, is inherited as a sex-linked characteristic. It is found largely among persons with a Mediterranean or African ancestry and the administration of a number of common drugs (such as the sulfonamides) may lead to hemolysis (destruction of red blood cells) in patients with G6PD deficiency.

Closely related forms of chronic granulomatous bowel disease of unknown origin are regional enteritis and granulomatous colitis (small and/or large bowel inflammation and granulomatous scarring). Previous studies have shown that 10 percent of those affected with regional enteritis have close relatives also afflicted with granulomatous diseases of the bowel, suggesting a genetic link.

In the Boston study, the G6PD deficiency was found in association with either regional enteritis or granulomatous colitis in five unrelated persons of Ashkenazic Jewish origin. In two of these five, four further family members were found to have both diseases. A survey of 53 patients with regional enteritis and granulomatous colitis revealed G6PD disease in 9.6 percent, whereas none of 50 patients with ulcerative colitis, another colon disorder, had a similar red-cell defect.

Several of the agents commonly recommended for treatment of regional enteritis may lead to marked hemolysis in patients with a severe form of red-cell G6PD deficiency. Therefore, all patients with chronic granulomatous diseases of the bowel, especially those with the familial form, should be tested for the red-cell defect before drug therapy is initiated.

Antacids and Gastric Hypersecretion

Rebound gastric hypersecretion induced by some antacids has long been suspected, and recently, investigators at the University of Texas Southwestern Medical School in Dallas reported that a commonly used antacid, calcium carbonate, induces rebound gastric hypersecretion in duodenal ulcer patients in contrast to aluminum-magnesium hydroxide and sodium bicarbonate, two other commonly used antacids.

Extensive investigations in a patient sensitive to calcium carbonate were made to discover the mechanism by which this antacid induces hypersecretion. Apparently, calcium salts provoke gastric hypersecretion through the action of calcium ion within the gastrointestinal tract, an action potentiated by ingestion of food. Although calcium carbonate therapy, in addition to neutralizing gastric acid, also increases serum calcium concentration, the data obtained suggested that hypercalcemia is not the mechanism by which this antacid stimulates gastric secretion. The clinical significance of this finding is clear because calcium carbonate is extensively used in treatment of peptic ulcer, but whether this has a deleterious effect on the long-term course of peptic ulcer is not yet known.

OUTLOOK

The wide-ranging and significant accomplishments of the past year in the treatment or prevention of malabsorptive disorders, regional enteritis, and fatty livers - precursor of cirrhosis of the liver - give renewed hope for improved diagnostic, therapeutic, and surgical techniques.

While some of these advances have found immediate application at the bedside, others, of a more basic nature, are contributing to the broader base of research knowledge from which comes future progress in these disorders. These and other research findings are systematically uncovering promising scientific approaches in the search for improved treatment for the millions of individuals disabled by gastrointestinal diseases.

SPECIAL REPORT:
GASTROENTEROLOGY

Encompassing all the diseases of the digestive tract, which may range from peptic ulcer and ileitis to ulcerative colitis, gastroenterology is an area of medicine perhaps second only to heart disease in the frequency of physician house calls and office visits required. There are numerous diseases of the gastrointestinal tract and its associated organs about which much remains to be learned, such as diseases of the liver, gallbladder and pancreas. The diversity and magnitude of these disorders combine to place these diseases in a high position among the chronic afflictions affecting man.

The National Institute of Arthritis and Metabolic Diseases (NIAMD) bears the responsibility for the Government's program of research in gastroenterology. The increasing research interest in gastrointestinal disorders had led to the establishment during this reporting year of a Digestive and Hereditary Diseases Branch within the Institute. Enhancing the research interest of the former Gastroenterology Section, which it supersedes, the Branch is conducting clinical and laboratory investigations to determine abnormalities in structure and function of the esophagus, stomach, small and large intestines, pancreas and liver, and research on certain hereditary metabolic diseases. Other investigations are seeking to clarify enzyme and metabolic pathways within the tissues of the gastrointestinal tract. Branch scientists are also examining the pathogenesis of digestive diseases and studying improved treatment methods.

Through grants to scientists at research centers across the country, a broad array of ailments of the digestive tract is also undergoing investigation. Research progress has been achieved only through the most intensive and comprehensive laboratory experiments and clinical trials. The past year has seen the development of numerous important research findings, several of far-reaching importance.

Research Developments

Prevention of Gastrointestinal Bleeding

It is well known that large doses of aspirin in tablet form may cause a significant degree of gastrointestinal bleeding in many patients. This is of special interest in the management of patients with rheumatoid arthritis where aspirin, in high doses, is the initial drug of choice because of its anti-inflammatory and analgesic action.

Institute grant-supported scientists at Case Western Reserve University and the State University of New York have shown that aspirin-induced gastrointestinal bleeding may be reduced or prevented by administering the drug in a soluble form in a buffered effervescent solution. The data suggest that the gastrointestinal blood loss associated with administration of aspirin in tablet (solid) form, especially when given in large doses, is a local rather than systemically mediated phenomenon, and that the bleeding potential of available aspirin preparations can be reduced or even eliminated by appropriate pharmaceutical formulation.

Prepared January 1970 as background information for the Director, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Department of Health, Education, and Welfare, in connection with the fiscal year 1971 appropriation hearings.

The aspirin solutions were also more rapidly absorbed and, thus, caused higher plasma salicylate concentrations than did the aspirin tablets, lending support to the theory that aspirin-induced gastrointestinal blood loss is a local rather than a systemic effect. Further development may provide a sodium-free agent with just sufficient buffering capacity to prevent such bleeding and to permit side effect-free long-term administration of aspirin in high doses. The possible use of sodium-free buffering agents may further enhance the suitability of such solutions for the long-term administration of aspirin in high doses.

Chest Pain of Unexplained Origin

A definitive etiological diagnosis is often difficult to establish in patients with symptoms of substernal pain, difficulty in swallowing, or both, and such unexplained chest pain may be misinterpreted as being of cardiac origin. A study by Institute-supported scientists at the University of Alabama Medical Center has shown that excessive stomach muscle contractions should be considered as the source of difficulty in such patients, inasmuch as such a diagnosis can easily be established and appropriate and effective treatment is available.

During a two year period, eleven of 381 patients referred for diagnostic testing of the esophagus were found to have excessive contractions at the gastroesophageal junction. The principal characteristic of these patients was the prolonged duration of contraction. Symptomatically, chest pain and difficulty in swallowing were prominent complaints.

The condition of the symptomatic patients usually improved with reassurance, symptomatic treatment, and medical management of hiatal hernia which co-existed. Surgery provided excellent relief of symptoms in two of the latter patients.

New Approaches to Peptic Ulcer Treatment

Several years ago NIAMD-supported investigators at Washington University, St. Louis, successfully produced antibodies in rabbits that were directed against the functional portion of the gastrin molecule. Subsequently, they showed in animal studies that these antibodies inhibit the ability of exogenous gastrin to stimulate the secretion of gastric acid in the stomach.

The same team of scientists, during the past year, has shown in animal studies that the same antibody preparation also inhibits the potent gastric acid stimulatory action of endogenous by-produced gastrin. The degree of antibody inhibition of gastric acid secretion in experimental rats averaged 73 percent.

Inhibition of excessive gastrin-mediated acid secretion might have important clinical application. It is possible that acid secretion rates and, thereby, disease processes associated with excessive secretion of gastric acid, such as peptic ulcer, may be modified by antibody binding of endogenous gastrin molecules.

Unrestricted Diet in Ulcer Treatment

In another important finding, Institute-supported researchers at the Veterans Administration Hospital and the University of Iowa College of Medicine, have found that the traditional ulcer diet ("bland diet") does not affect the outcome in the treatment of patients with duodenal ulcers.

A controlled study alternated a regular hospital diet with a bland diet in patients diagnosed as having active duodenal ulcers after X-ray examination. Both diets were planned to meet fully the nutritional requirements for normal healthy persons. All of the patients remained in the hospital for a minimum of three weeks after diagnosis. Accurate records were kept of food items served, with the reaction to them and the reasons for tray refusals. Clinically and radiographically there was no significant difference in the regular response of patients to the two diets.

These findings are consistent with results of a similar test, recently conducted in England, which also showed that use of a special ulcer diet, or of a regular diet, did not influence healing of peptic ulcers in a large series of patients alternatively assigned to either diet and prohibited the use of coffee, alcohol, and tobacco.

Liver Diseases and Transplantation

Life cannot exist for any duration without the liver. It performs at least 5000 major biochemical reactions that are known, and probably more that are as yet not well defined. The liver is essential for protein, carbohydrate, and fat metabolism, and it is absolutely necessary for the detoxification of a number of toxic products circulating in the blood. The liver also functions as a storage depot for certain nutrients such as sugars, various trace minerals and vitamins.

An organ of such complexity is, not surprisingly, subject to a wide variety of injuries and disease states including disorders of infectious, parasitic, nutritional, metabolic, obstructive, toxic, and malignant origin. Clearly the use of transplanted livers to prolong the lives of patients with hopelessly diseased livers is one of the most intriguing areas of medicine.

Institute-supported investigators have achieved significant advances in the very difficult procedure of liver transplantation in patients with end-stage disease through use of advanced surgical techniques, the judicious use of a serum that modifies rejection mechanisms of the body (antilymphocyte serum), improved organ storage, and meticulous tissue typing. Prognosis for liver transplants is continuing to improve, with a few young recipients surviving up to a year or more. The antilymphocyte serum (ALS), or a more concentrated and purified fraction (antilymphocyte globulin) employed by Institute grantees in liver transplants is commonly used with or instead of immunosuppressive drugs to combat rejection not only of liver and kidney transplants but of other organ transplants as well.

A team headed by an NIH-supported grantee, Dr. Thomas E. Starzl, at the University of Colorado, has now performed approximately half of the world's reported liver transplants, with constantly increasing survival times suggesting that liver transplantation may become a more widely used therapeutic method. In a series of liver grafts begun by the Denver team in July 1967, six of the 18 recipients have survived one year or more. This rate is almost identical to that achieved in cadaveric renal transplantation when the first successful trial with that operation was made during the period from 1962-1964.

Hepatitis

Hepatitis, or inflammation of the liver, is a public health problem of immediate and growing magnitude. Now an Institute scientist, working with scientists from the Division of Biologics Standards, has provided a basis for future development of an anti-hepatitis vaccine.

In recent years, much indirect evidence had been provided to suggest that both infectious and serum hepatitis are of viral etiology. The so-called Australia antigen, first described by a former intramural NIAMD investigator, was originally linked with various leukemias, mongolism, and infectious hepatitis. More recently, evidence was obtained to link this antigen closely with serum hepatitis.

This past year, Institute scientists detected Australia antigen in the blood of 74 percent of patients with serum hepatitis. A lower incidence was found in the blood of patients with infectious hepatitis, but morphologically and immunologically identical antigen-associated virus-like particles were seen in both types of patients. The data suggest that Australia antigen may be hepatitis virus itself, a finding that might lead to development of a vaccine effective against both types of hepatitis.

In related studies, NIH scientists produced a very practical health-saving advance, development of a sensitive test for screening blood donors and blood products to help eliminate the presently ubiquitous risk of transmitting hepatitis by transfusion of blood containing viable hepatitis virus. NIH scientists have shown that complement fixation techniques afford a much more sensitive means of detecting and measuring Australia antigen than agar-gel precipitation, the method currently in use. The newly developed complement fixation techniques provide a valuable diagnostic test for hepatitis as well as usefulness in screening large numbers of blood donors in order to exclude carriers of hepatitis virus.

Diagnosing Liver Disease by Computer

In a significant number of cases, the clinical pattern of liver disease in a jaundiced patient fails to become characteristic of any one disease which may be the cause of jaundice, even after the course has been followed carefully for a month or more. Making the proper diagnosis in these patients is difficult since one of six diseases which can mimic one another closely is usually responsible. These are: non-malignant biliary obstruction, chronic active hepatitis, primary biliary cirrhosis, drug-induced jaundice, malignant extrahepatic obstruction, and viral hepatitis. An Institute grantee at Stanford University School of Medicine has written a computer program evaluating the symptoms present so as to improve the diagnosis of these six diseases and thus make it possible for the physician to distinguish them with greater accuracy. Using 144 diagnostic criteria descriptive of the six pathological conditions, he achieved greater diagnostic accuracy (94-98%) in a large series of jaundiced patients by computer diagnosis than by the use of conventional methods. Improvement upon these encouraging results may provide almost 100 percent accuracy.

Gallstone Formation

Although gallstone disease ranks fifth among the causes of hospitalization in the United States and may lead to serious complications, little is known about how these stones are formed. An Institute grantee, however, now has obtained evidence that glycoprotein mucous substances (proteins containing carbohydrate) in biliary secretions may play an important role in gallstone formation.

Gallstones were induced in rabbits by feeding them dihydrocholesterol (DHC), an established and reliable method of inducing stone formation in this experimental animal. After periodic sacrifice of the animals, their gallbladder mucosa was examined by light and electron microscopy. The hexosamine content in bile, gallbladders, and gallstones, as an index of the quantity of mucous substances, was measured before, during, and after gallstone formation and these data were correlated with the microscopic findings.

Gallstones occurred in rabbits fed DHC for at least nine days. Secretory vesicles appeared in gallbladder epithelial cells of DHC-fed animals after five days, but not in control animals. These cells secreted PAS-positive (characteristic staining in tissue sections) mucous substances in increased amounts before gallstones were formed, and this enhanced secretion continued during the period of gallstone growth.

Hexosamine concentrations in gallbladder tissue were significantly higher in DHC-fed animals than in control rabbits. The gallstones themselves contained hexosamine in all cases, and gallstone formation appeared to parallel increases in hexosamine concentrations.

The stimulus for enhanced secretion of mucous substances by the gallbladder musosa appeared to be contained in bile, because increased secretion did not occur when ligation of the cystic duct prevented pathological bile from entering the gallbladder. The data obtained in this study suggest that mucous substances, by entrapping crystalline particles in the gallbladder, form the nidus of gallstones and the scaffolding upon which further crystalline deposition occurs.

Ulcerative Colitis Activity

Ulcerative colitis is a chronic, progressive, inflammatory disease of the colon or large bowel. It is one of the most common chronic debilitating disorders of the gastrointestinal tract. Even though infectious, allergic and even psychosomatic etiologies have been suspected and investigated in the past, the cause of the disease is still unknown. Severe cramps, bloody diarrhea, weight loss, anemia, and potentially fatal loss of body fluids and minerals are its symptoms. Perforation of the bowel, leading to peritonitis, is a serious complication of the disease. Therapy is aimed primarily at correcting mineral and nutrient loss, controlling diarrhea, preventing secondary infection, and taking care of the patient's psychologic needs.

One problem in ulcerative colitis facing clinicians and scientists involves estimation of the degree of activity of this disease in individual patients. During the past year, research performed by Institute grantees at the Mayo Clinic at Rochester, Minnesota has provided evidence that serum "alpha-one" acid glycoprotein is increased abnormally in active chronic ulcerative colitis, thus suggesting that concentration of this glycoprotein in the patient's serum may serve as an index to the degree of activity of the inflammatory process in ulcerative colitis. It may also provide a future clinical guide to the efficacy of therapeutic procedures for chronic ulcerative colitis.

Celiac Disease

Celiac disease (nontropical sprue) is characterized by intestinal malabsorption, fatty diarrhea, and dietary deficiency symptoms, all caused by an intestinal sensitivity to a polypeptide fraction (gliadin) of the cereal protein, gluten, in the diet. Diagnosis of the disorder is based on intestinal absorption tests and biopsy of the small intestine and the disease can be managed successfully with the aid of a gluten/gliadin-free diet.

Recently, grant-supported researchers at the Yale University School of Medicine in New Haven, Connecticut, have suggested that undiscovered celiac disease may be a cause of iron deficiency anemia. Two female patients were given oral iron to combat iron deficiency anemia. There was no response to the rather prolonged treatment and after thorough work up of the patients it was found that both patients represented unsuspected cases of celiac disease. Their anemia responded to oral iron supplementation once a gluten-free diet was instituted. The scientists feel that in cases where treatment of iron deficiency anemia is unsuccessful, tests of intestinal absorption and biopsy of the small bowel are indicated.

Treatment of Diarrhea Associated with Intestinal Resection

In 1964 Institute-grantees showed that orally administered cholestyramine, a bile acid-sequestering resin, lowers cholesterol levels in patients with excess cholesterol in the blood and controls these levels as long as the resin is given. Other Institute-supported researchers at the Mayo Foundation and the University of Minnesota in Minneapolis, have now shown that the same agent is also of value in treating the diarrhea that characteristically follows surgical resection of the ileum.

Twenty patients, who had undergone resection of 20 to 230 cm of ileum and subsequently developed bile acid malabsorption and diarrhea, were treated with a placebo or with cholestyramine. Ten of 12 patients with less than 100 cm of ileum resected and some remaining ascending colon responded to cholestyramine therapy within 48 hours with significant decrease in fecal frequency, or fecal weight, or both. In every case, cholestyramine withdrawal resulted in a return of diarrhea. By contrast, none of eight patients having a resection of more than 100 cm of ileum responded to cholestyramine.

In addition, the degree of steatorrhea was also of predictive value for therapeutic response. All eight patients with fecal fat excretion of less than 20 gm per day responded to the resin therapy, whereas none of five patients with a greater amount of steatorrhea responded. Thus, it was concluded that cholestyramine may be a useful symptomatic treatment for diarrhea in patients with small ileal resections (less than 100 cm) and mild steatorrhea (less than 20 gm/day).

The findings lend support to the theory that diarrhea in these patients is caused by an impairment in quantitative reabsorption of bile in the shortened ileum leading to increased passage of bile acids into the colon, where they induce secretion of salt and water. Cholestyramine is thought to act by irreversibly binding (and thus inactivating) any left-over bile not reabsorbed in the ileum, thus abolishing bile acid-induced secretion of water and electrolytes into the colon.

Control of Short-Bowel Syndrome

Removal of massive portions of the small bowel because of inflammatory bowel disease or for other reasons can lead to a life-threatening "short-bowel syndrome". In successful attempts to avoid the typical loss in stools of excessive amounts of water and essential electrolytes (such as sodium, potassium, and chloride), Institute grant-assisted investigators at Albany Medical Center, Albany, New York, undertook dietary manipulations in patients with massive intestinal resections. The researchers found that treatment of these patients with medium-chain triglycerides (special man-made fats which contain fatty acid chains considerably shorter than those ordinarily found in natural oils and fats) led to a gradual reduction in the loss of water and electrolytes when substituted for long-chain fats in the diet. A remarkable improvement in patient nutritional status was observed on long-term follow-up.

While the mechanism by which medium-chain triglycerides caused the decrease in fecal fluid and electrolyte loss is as yet unknown, Institute-supported research by scientists at St. Luke's Hospital Center, New York, reported last year, showed that these synthetic medium-chain triglycerides are of substantial value in managing fat malabsorption disorders of various origins.

"Artificial Gut" for Patients with Severe Bowel Disease

Research on artificial kidney methodologies by an Institute grantee at the University of Washington, Seattle, has provided a new and exciting treatment for victims of certain bowel diseases as well as for patients undergoing treatment with artificial kidneys. The grantee, who had originally devised a permanently implanted arteriovenous (AV) shunt for artificial kidney patients, has now converted the shunt to an "artificial gut" system which can provide prolonged nutrition to patients devoid of effective bowel function. The system can be self-operated around the clock and has potential for maintenance of health of patients with chronic bowel disease.

A silicone rubber side arm, which is filled with heparin and capped when not in use, is used to introduce concentrated sterilized nutrients into the plastic shunt in which blood circulates constantly. Thus, dilution of these irritating, sclerosing solutions occurs within the shunt and not in vessels susceptible to damage. Patients with a measure of residual bowel function, who require infusion only at night, need only uncap the side arm and connect it to a gravity-powered infusion system at the bedside. This home system has proved workable, safe and easy to use.

A portable infusion system also has been devised for those patients who require total parenteral nutrition. A battery-operated pulsatile pump delivers sterile nutrient solutions carried in a 500 ml plastic bag. At night the patient disconnects the portable infusion apparatus and attaches the bedside infusion system.

Use of the artificial gut system is foreseen in patients with too little remaining bowel, following massive bowel resection, to maintain nutrition, and in the temporary treatment of ileocolitis, mesenteric thromboembolism, and various bowel diseases in infants.

Outlook

Although this resume of research progress in gastroenterology encompasses but a small portion of the Institute-financed research in this extremely broad field, it demonstrates the diversity and productivity of the many investigations conducted and supported by the National Institute of Arthritis and Metabolic Diseases. These and other research findings are systematically uncovering numerous promising and new scientific leads and approaches in the search for improved methods of treatment and diagnostic techniques for the millions of individuals disabled by and afflicted with gastrointestinal disorders. While some of these advances have found immediate application at the bedside, others, of a more fundamental nature, are contributing to the broader base of research knowledge from which comes future progress in these disorders. Altogether, these findings give renewed hope for improved therapeutic modalities in the field of digestive diseases in the foreseeable future.

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DIVERTICULOSIS AND DIVERTICULITIS

WHAT IS IT?

Diverticulosis is a condition of the digestive tract characterized by tiny mucosal sacs (diverticula) which protrude through the muscular wall of the large intestine. If these sacs become infected, the condition is known as diverticulitis, which means inflammation of the diverticula.

More than 30 percent of persons over 45 years of age and over 80 percent of those over 60, have diverticulosis. Of all cases, more than 25 percent develop the infected form, diverticulitis. The condition is found more often in women than in men.

Diverticulosis usually occurs in the colon, that portion of the large intestine which prepares residual intestinal contents for evacuation by water adsorption and a series of muscular contractions. It occurs predominately in the narrowest part of the colon, the sigmoid region.

WHAT CAUSES IT?

The exact cause of diverticulosis is as yet unknown. In all cases studied, however, a thickening of the muscular wall of the intestine was found. Studies have demonstrated, in addition, that the combined pressure of food and gas on soft spots, usually near

blood vessels in the abnormally thickened intestinal wall, may precipitate development of sacs. Chronic constipation and the ensuing use of high-powered cathartics increase the pressure.

These sacs can become stretched by deposits of small particles of undigested material such as seeds, or by small hard feces retained too long in the lower intestine. Infection results when bacteria which normally inhabit the digestive system act on these particles producing substances which are irritating to the lining of the sacs and the colon.

A cyclic effect may occur since irritation from the inflamed sacs can cause the intestinal musculature to contract in such a way as to interfere with the normal passage of material through the colon. This can result in constipation, further pressure on the muscle wall, and production of additional diverticula. The process may remain localized and may subside spontaneously within a few days. In serious cases, the involved diverticula may be pierced, allowing the infection to spread throughout the abdominal cavity, or even to the muscular walls of the abdominal cavity, to the urinary bladder, or to an artery or vein in the wall of the colon resulting in rectal bleeding.

Recent research indicates, however, that it may actually be the process of muscle thickening (combined with the increased intestinal pressure) which is responsible not only for the appearance of diverticula but also for some of the symptoms which used to be attributed to inflammation. According to this explanation, the symptoms of diverticulitis as well as the muscle thickening precede rather than follow the occurrence of actual inflammation.

Emotional factors may precipitate muscular contractions, as reported in a study of both clinical and laboratory observation of patients with sigmoid contractions. Occurrence of these contractions were found to coincide with periods of stress, emotional upset and tension.

WHAT TO LOOK FOR

Acute diverticulitis usually produces pain in the lower left side, but the pain can also occur on the right side, and is therefore often confused with the onset of appendicitis. Nausea, vomiting, abdominal distention and alternating diarrhea and constipation are frequently reported. In acute and occasionally in chronic cases, tenderness and resistance to compression occur over the affected bowel, often accompanied by abdominal spasm. Although bleeding is a dangerous potential complication, diverticulitis is rarely a cause of chronic, daily loss of fresh blood.

HOW IS IT TREATED?

In cases of diverticulosis with no accompanying symptoms, no medical treatment is indicated except a supervised diet. Patients with an irritated colon are usually advised to keep stools soft, but not liquid, by using non-irritating laxatives given orally at bedtime. Stronger laxatives and enemas cause an increased pressure in the colon which can be harmful and should not be used.

Treatment of diverticulitis includes bed rest and use of antibiotics. Occasionally antispasmodic drugs (anticholinergics) may be used, but urinary retention is a dangerous potential side effect, particularly in elderly males. Analgesics may be used for discomfort. In the uncomplicated case, clear fluids alone are permitted, but in those with vomiting or intestinal distention or both, fluids are given intravenously and nothing is given by mouth.

Surgery is the accepted method of treatment of diverticulitis with complications.

WHAT ABOUT DIET?

Many doctors believe control of both diverticulosis and diverticulitis is best accomplished through a proper diet. Some feel, however, that diet makes little difference, and at best its effectiveness varies with each individual case. The diet most often prescribed is high in bulk-producing foods to facilitate the easy opening of bowels and to prevent strong intestinal wall contractions.

A therapeutic diet includes plenty of fluids, cooked fruits and cooked leafy fibrous vegetables, coarse bread and cereals, all of which give bulk to the bowel content and stimulate the intestinal muscles, which in turn aids the movement and tone of the intestinal wall fibers.

Water consumed in large quantities helps to prevent feces from becoming hard and small and tends to prevent constipation. Food containing small seeds (figs, raisins, strawberries and tomatoes) should be avoided, as well as food containing hard particles such as

cracked wheat. Gas-producing foods, such as beans, cabbage, cauliflower and Brussels sprouts, as well as carbonated drinks, soda water, and Vichy water should not be taken.

A LOOK TO THE FUTURE

Disorders of the gastrointestinal system, which include diverticulosis, peptic ulcer and ulcerative colitis, are among the most common serious illnesses in this country. Aided by support from the National Institute of Arthritis and Metabolic Diseases, a component of the National Institutes of Health of the Department of Health, Education, and Welfare, the momentum of gastroenterological research has been increased.

In addition to this Institute's support of research, new laboratory and clinical technics being constantly developed may bring about a more complete understanding of diverticulosis and diverticulitis. In the meantime, however, medical treatment continues to focus on combating the underlying muscle abnormality which has been found to be a cause of diverticulosis and its symptoms.

Dr. STEINFELD. In fiscal year 1968, the expenditures by the NIAMD alone on digestive disease research and training amounted to a level of \$13.3 million. In fiscal year 1970, the level was \$12.4 million, a reflection of the overall budgetary limitations throughout the Federal Government.

A special indepth study in 1965 established the total expenditures of the NIH related to nutrition research at a level of \$23.8 million. A similar expenditure was made for nutrition research in fiscal year 1968, in addition to an expenditure of approximately \$1.3 million for nutrition research training. The estimated expenditure level for nutrition for year 1970 is approximately \$23 million, which does not reflect diminished concern with nutrition but rather current Federal fiscal constraints. Despite these constraints, such levels of support are evidence that research and training in the fields of digestive diseases and nutrition are being given a high priority by the NIH.

Beyond these research activities related to nutrition and nutritional disorders, HEW also conducts a program of technical consultation and assistance to States and local communities. Responsibility for this activity has recently been transferred to the newly renamed Center for Disease Control—formerly the Communicable Disease Center—in Atlanta. This transfer was made in recognition of the change in major function of the nutrition program from data collection to technical assistance. The Center for Disease Control has had many years of successful experience in working with States and local areas. It also has laboratory and epidemiological expertise and resources which should help to delimit health problems related to nutrition and to relate nutrition to other aspects of health.

The Department is opposed to the further proliferation of categorical grant programs such as the proposed categorical program of formula grants for community programs to control digestive diseases and nutritional disorders. States are now eligible to include digestive and nutritional disorders within their State comprehensive health services plan under the partnership for health program, where funds are presently allotted to the States by formula to assist in the provision of adequate public health services. Project grants for this purpose are also available under section 314(e) of the Public Health Service Act. In addition, we have high hopes for the enhanced effectiveness of the nutrition program under the aegis of the Center for Disease Control, and look forward to its continued efforts to encourage the development of community programs of digestive diseases and nutrition control.

Certain information activities are proposed in S. 3063 which are already in existence. Realizing the importance of a rapid and effective exchange of information on research, prevention, diagnosis, and treatment of digestive diseases, the NIAMD publishes on a regular basis a highly regarded monthly "current-awareness" publication, Gastroenterology Abstracts and Citations. We submit for the record the most recent issue. This publication contains abstracts of, and bibliographic references to the most recent scientific publications in the field of digestive diseases extracted from the current scientific literature throughout the world regardless of the original language or country of publication, and makes it available as promptly as possible to its

readership. The issues of Gastroenterology Abstracts and Citations, which contain about 1,000 individual references each month, are sent free of charge to over 5,000 physicians and investigators in the field of digestive diseases. This specialized information service is aimed at making available to research worker and practitioner alike the latest findings in the field, important for research, diagnosis, treatment, and prevention of diseases of the gastrointestinal tract; this information activity is the only one of its kind in the world and has consistently received high praise from the community of physicians and scientists using it.

(The information referred to may be found on p. 133.)

Dr. STEINFELD. In addition, NIAMD disseminates widely an annual summary of the latest advances of grant-supported research in digestive diseases as well as specialized lay information material in this area.

The NIAMD and the National Institute of Child Health and Human Development contracted with Vanderbilt University for the preparation of a Guide to Nutrition Terminology—a thesaurus of nutrition terms—the first indispensable step toward establishment of an orderly and useful current-awareness publication effort in the field of nutrition; this useful aid to nutrition research will be published in the next few weeks. Here again the assistance and advise of experts from the United States and abroad have been obtained to make this future information activity as successful as the ongoing one for digestive diseases.

Realizing the importance of good nutrition for the American people, the NIAMD is distributing annually many thousands of its very popular booklet Facts About Nutrition which provides clearly presented nutrition guidelines for everyday situations as well as for special conditions such as pregnancy and lactation, infancy, old age, and obesity.

Mr. Chairman, your committee is as well aware as we are of the constant pressure for the establishment of new national institutes at the National Institutes of Health, with each group identified with a particular disease or group of diseases preferring to have a distinct national institute in Bethesda devoted exclusively to its field of interest. Unquestionably, the establishment of a separate institute for digestive diseases and nutrition science would be satisfying and encouraging to those concerned with these fields. It is easy to foresee, however, that following the successful passage of legislation to establish a National Institute of Digestive Diseases and Nutrition, there will be proposed similar bills, each devoted to other organs of the body or to other specific diseases. In fact, several such bills have been introduced within the last 2 years.

This is neither a desirable nor an effective way to conduct and support research into the health problems of the Nation. Indeed, the proliferation of new institutes for each of many program areas desiring such status could have a devastatingly harmful effect on medical research in the United States. Clearly, this process is inefficient, further fragmenting the resources of the National Institutes of Health in a time of fiscal and personnel constraints throughout the Federal Government.

Under the present organization of the National Institutes of Health, research and training in a related group of diseases, for example, cancer or heart disease, are the responsibility of one Institute. So, too, the National Institute of Arthritis and Metabolic Diseases presently interrelates a reasonably natural grouping of the major chronic and debilitating diseases affecting a major segment of the population. This arrangement at the NIH permits flexibility to allocate funds within an Institute appropriation to capitalize most effectively on emerging and unexpected research opportunities.

Further fragmentation into smaller, more highly specialized national institutes will result in greater administrative overhead for dealing with each disease or organ system, but will not necessarily stimulate better or more productive research devoted to the particular field. Actually, a considerable financial expenditure would result from the unnecessary and costly duplication of existing administrative structures and facilities. We estimate the additional administrative cost associated with the establishment of this new institute to be over \$1 million. Equally important would be the need to duplicate experienced scientific and science-management staff, the supply of which is extremely limited.

We doubt seriously whether the establishment of a new and distinct National Institute of Digestive Diseases and Nutrition would enhance the current effectiveness of the attack now being carried out on the problems of digestive diseases and nutrition. This current, coordinated attack allows utilization of a broad base of skilled manpower and technical resources of the NIAMD—and in the case of nutrition, from other National Institutes as well—which could not be assembled under a single new Institute without seriously weakening existing organizations. Furthermore, these efforts are being conducted within the framework of well established and organized management and operational systems which would have to be developed and perfected *de novo* if a new National Institute of Digestive Diseases and Nutrition were to be established.

Mr. Chairman, we are neither disinterested in, nor unsympathetic to the major problems posed by digestive diseases and nutrition, nor to the case which is made for establishing a National Institute for them. Digestive diseases, as you have indicated, are among the most important health problems: 13 million Americans suffer from digestive diseases, including, e.g., peptic ulcer, colitis, hepatitis, and cirrhosis of the liver, and an estimated \$8 billion per year is lost to the nation's economy as a result of these conditions.

Nevertheless, we believe that it is essential that we find some other satisfactory means of giving recognition to these and other important disease problems, other than the creation of new institutes at the National Institute of Health. Elevation of organizational status is not a solution; no mere change in organizational form will cause a research area to flourish. Such a change does not provide an assured solution where the main problems are trained manpower and good research ideas. The broader nature of the problems in digestive diseases is illustrated by the fact that presently available research training opportunities go unfilled. Substantive scientific and technical problems in the diseases and conditions themselves represent addi-

tional impediments to more rapid progress. Undoubtedly, current Federal fiscal constraints pose additional impediments. None of these impediments is eliminated by creation of a new institute.

Two recent actions provide some indication of our concern for these important fields. On September 1, Dr. Nathan Smith, professor of pediatrics at the University of Washington School of Medicine will assume full-time duty as special assistant to the Assistant Secretary for Health and Scientific Affairs for Nutrition programs. Dr. Smith will be an important addition to the health staff of HEW, and he will provide a needed focus for analysis and evaluation of nutrition programs and proposals.

In addition, an associate director for digestive diseases and nutrition will be designated in the National Institute of Arthritis and Metabolic Diseases to facilitate increased attention to research and training in this field at NIH.

If I might depart from my prepared statement for a moment, Senator Yarborough and Senator Dominick, we are aware of the problems of not highlighting some of the most important diseases, and not having a coordinated program and focus in the Federal Government. We have, in the last year, been trying several different mechanisms for providing this focus short of establishing new institutes with the attendant administrative and financial charges.

The proposed associate director for digestive diseases and nutrition, who will provide a focal point for these important areas within NIAMD, will review the status of the field and make recommendations for additional activities, where they seem appropriate.

Our goal is to try new administrative procedures and to report back to the Congress where these new techniques are successful and can be successful substitutes for what we feel to be unnecessary bureaucratic duplication.

In conclusion, let me reiterate that the Department is in complete sympathy with the basic objectives of this proposed legislation—to promote research and training and community service in the fields of digestive diseases and nutrition. We feel, however, that adequate authority and an effective mechanism for their achievement are already available and functioning. In these times of fiscal constraints, we recommend against the added burden of establishing a new National Institute for Digestive Diseases and Nutrition at the National Institutes of Health. We, therefore, recommend against enactment of S. 3063.

Thank you. Dr. Sherman and Dr. Whedon and I will be pleased to attempt to answer any questions.

The CHAIRMAN. Dr. Steinfeld, on pages 4 and 5 of your statement, you say that in fiscal year 1968 expenditures on digestive diseases research and training amounted to \$13.3 million and in fiscal 1970 the level was \$12.4 million. That is a vast decline not merely in round dollars of about $\frac{1}{13}$, some 7 percent, but also due to the inflation; what would you estimate that reduction to be—20 percent?

Dr. STEINFELD. I do not know what percent inflation would account for, but there is no question that the Federal Government's distribution of funds, not only for research and training has been changed in the last few years as we have moved through Medicare and Medicaid into the payment for health services. I believe that medical

schools and certain people conducting research are now subsidizing certain of their activities utilizing health service funds, rather than research funds as has been the traditional technique in the past.

The CHAIRMAN. In other words, since Medicare and Medicaid, in the area of training of medical personnel and paramedical personnel, the Federal Government's contribution has declined in total purchasing power. Is that what you are saying?

Dr. STEINFELD. I was at the University of Southern California in hematology and oncology, and as the research funds for these fields declined, we found funds from other sources to train people in hematology and oncology. What I am saying is that I think the faculties of medical schools are quite right to do this to make use of funds which are available. However, this is not the ideal way.

I agree with you but I think the figures per se may not accurately reflect what is going on in the country.

The CHAIRMAN. Do you mean the figure is inaccurate?

Dr. STEINFELD. These figures are accurate as they are.

The CHAIRMAN. Do you mean they are getting more out of \$12.4 million in 1970 than \$13.3 million in 1968?

Dr. STEINFELD. They may be utilizing other funds to carry out the same activities. We do not have a good system for determining the exact level of training.

The CHAIRMAN. I have sent out an appeal to the medical schools of the country to admit 10 percent more students or, if they can't admit 10 percent more, to ask them what additional percentage they could admit. I thought they might come back and say 2, 2½ or 5; but thus far there is not a single school that said they would admit one more medical student. Each of these medical schools exist principally on Federal funds.

In the State of the distinguished senator who is sitting here with me, Senator Dominick, the percentage of physicians relative to people is 22 percent higher than the national average. They are in much better circumstances than my State, but even then there are some counties in Colorado without a doctor, as is also true in my State.

I will yield to the distinguished Senator from Colorado.

Senator DOMINICK. That is because of our clean Rocky Mountain air and spring water which makes the best beer.

The CHAIRMAN. That is not what they have told me.

Dr. STEINFELD. I agree with you that we have a shortage, and I think we need more than a 10-percent increase in medical students. I think we need considerably larger increases in students and at the same time we need to improve our systems for the delivery of health care.

The other thing we must do is that we cannot keep on doing business the same old way. We have to figure out new ways to support medical education whether it be having two classes per year, to have classes year-round, or to alter the traditional technique requiring a lot of duplicative laboratory courses in the first 2 years. We have a problem and we have to take a look at the total picture. If we continue to support the schools in the same old way, it is going to be extremely expensive and an extremely long time before we can solve our physician shortage. We agree something has to be done. We have to look at the total picture and attempt to make changes taking advan-

tage of the good parts of our system, but making the appropriate changes to overcome the doctor shortage.

The CHAIRMAN. You can't make the appropriate changes by emasculating the medical education at this time, can you? I don't believe the way to improve the system is to destroy it first.

Dr. STEINFELD. We don't want to do that at all, but we have to look at these funds. I think there are real opportunities here for significantly increasing the output of physicians.

The CHAIRMAN. After a subcommittee of this committee made on-the-spot investigations at veterans' hospitals, I went to the veteran's hospital south of Dallas to talk with the director there. I found they were doing their best under an exceptionally able director to see that the level of service did not decline. He said it didn't but as it was inevitable to me it did decline because the average cost of all medical services and supplies have gone up in 1 year at a rate of inflation far beyond the average in the country.

In 1965, you had a total expenditure at NIH related to nutrition research at a level of \$23.8 million, and that went down by 1970. If you think of all of the inflation that took place between 1965 and 1970, plus the increase in population in the country growing all the time plus a decrease in funds, to me, that is a pulling out, that is a negation, that is absolute negation.

I think that one big trouble we have in this country is with the Bureau of the Budget. Last year, for the first time, I became chairman of the subcommittee that deals with the Bureau of the Budget and found out that it had 42 examiners assigned to the Defense Department to look at its budget of \$75 billion a year. The other 136 were cutting away the budget of the Departments of HEW, Interior, Agriculture, Commerce, Transportation and other important domestic programs.

Dr. STEINFELD. Could I make a comment about an earlier point, Senator Yarborough, which relates to how one identifies particular disease entities through research. When I was in the Cancer Institute from 1952 to 1958, I was measuring protein turnover in cancer patients. I was at the National Cancer Institute at Bethesda. At the National Heart Institute, Dr. Bartter had a patient who had unexplained edema, unexplained swelling all over her body. To make a long story short, we found after some extensive studies she was losing protein into her gastro-intestinal tract, something never known to have occurred before. We developed the technique for measuring protein loss into the bowel and identified several new syndromes. This was an investigation between the Cancer Institute and the Heart Institute and the implications were of interest to gastroenterologists around the world. They have had international meetings on the subject.

So, it is very difficult in any given budget in medical research to identify what is going on in a particular area. I am not saying that the other way is the right way. But I am saying that if people are doing research and are communicating with each other, we may find answers regarding cirrhosis or other problems carried out by individuals who do not have the title of gastroenterologist. The numbers by themselves are extremely important, but they do not tell the whole story. When we worked on this novel gastrointestinal condition, we

never got any funds through Dr. Whedon's predecessors. We carried out all of our work within our own cancer institute budget. He just said we had cooperation, which I agree we did.

The CHAIRMAN. You mentioned your work in the Cancer Institute at NIH. Does the NIH Cancer Institute Research Division have data on the types of cancer? I assume you do.

In dealing with cancer in males, what percentage of the cancer in male citizens of America is cancer of the digestive tract?

Dr. STEINFELD. A very large percentage. If you take males and females together, cancer of the digestive tract becomes the leading category. If you separate it, I would say bronchocarcinoma or lung cancer may be greater.

The CHAIRMAN. If you add male and females together, cancer of the digestive tract is the prime type of cancer?

Dr. STEINFELD. Yes, sir.

The CHAIRMAN. What would you say that was?

Dr. STEINFELD. About a third of all of the cancer deaths, because many persons have skin cancers.

The CHAIRMAN. We have just phoned to the National Institutes of Health since the start of this hearing asking about the number of deaths. The latest figure they gave us is 330,000; so a third of those, 100,000, would be, the G.I. tract. With cancer now having reached epidemic proportions, don't you feel this research into digestive diseases is very material in leading into the great studies as we try to conquer cancer by 1976?

Dr. STEINFELD. I think it is extremely important. There are interesting leads. Stomach cancer is high in Eastern Europe and Japan. It is declining in this country without any apparent reason for it, while colon cancer and rectal cancer is increasing rapidly.

The CHAIRMAN. Is cancer of the colon increasing rapidly?

Dr. STEINFELD. Yes, sir. I don't know if it is increasing as rapidly as lung cancer, but we need leads for the etiology.

The CHAIRMAN. Are you doing any specific research on what food additives are doing to people in this regard?

Dr. STEINFELD. The possibility of a relation between food additives and cancer is a problem that is studied inadequately, I would say.

The CHAIRMAN. I did not mean additives alone. Is any research being done on the possible effect of hormones, the shots they give baby chicks or calves to make them grow faster, to make chicken broilers grow faster or calves to grow faster? Is any research being done on that in relation to cancer in the human beings?

Dr. STEINFELD. Some of the hormones that have been used have been relatively recent. The increase in gastrointestinal cancer and colon cancer has probably antedated the use of some of these. We don't have good leads on colon or rectal cancer in terms of etiology. There is all kinds of speculation regarding things that may be related to stomach cancer. For instance, in Iceland they eat a lot of smoked salmon or smoked mutton. The smoking process does produce a carcinogen, benzo(a)pyrene and this is ingested in relatively large amounts in population groups in Iceland, and they have a very high rate of stomach cancer.

Similarly, in Japan, they eat a lot of smoked products. In addition, people in Eastern Europe and other areas may be exposed to rice and other grains contaminated by growth of the mold *aspergillus flavus*

which produces aflatoxin which is one of the most potent chemical carcinogens known to man. This may be related to stomach cancer, but we can't relate it to lower bowel cancer in this country because we have greater control over contaminated grains. It is unlikely that our population is exposed to such things.

Such work as is required in the sorting out process can be done just as effectively in the Cancer Institute as could be done in another Institute.

The CHAIRMAN. I am not attempting to pass any professional judgment on that because you are the expert in that field.

Now, how much money is being devoted specifically to digestive diseases at the NIH this year?

Dr. STEINFELD. We can provide for the record a summary over the years.

The CHAIRMAN. Do you have it roughly for this year in round numbers?

Dr. WHEDON. About \$18,890,000 is being devoted to gastroenterology and digestive diseases by all the Institutes at NIH. Of this, the National Institute of Arthritis and Metabolic Diseases, the focal Institute for this field, expended \$12.4 million in fiscal year 1970. The balance of the total expenditure for gastroenterology and digestive diseases represents specific studies in or supported by other Institutes which are within their specific fields of responsibility, such as cancer, or fetal development. For instance, the National Cancer Institute devoted \$1,253,000 for studies ranging from the cytology and pathology of intestinal carcinoma to surgical and new drug treatment of gastrointestinal cancer. Because of the specific nature of these studies, this aggregate sum of \$6,490,000 would, in any event, remain an integral part of the budgets of these Institutes.

The CHAIRMAN. Do you think that is enough to deal with the problem, with the present seriousness in America, 300 million man-days lost in labor and industry in a year?

Dr. STEINFELD. Senator Yarborough, we have reviewed the budget and established a reasonable level for this research within the overall ceilings available to the Department. Those are the funds which are being spent on nutrition and digestive diseases, which result from a determination made not only by the Department, but by its advisers in collaboration with the councils and the study sections. I think the important point for us today is that we are appointing two new people, one in our immediate office, Dr. Egeberg's office and mine, who will review the nutrition programs and attempt to determine what is being done, what needs to be done, what the opportunities are, and a new associate director, in Dr. Whedon's Institute, for Digestive Diseases and Nutrition who will do the same thing—call meetings, review the status of the field, meet with the council and act as spokesman for digestive diseases and hopefully lay out a long-range program that we can submit to the Congress for future action.

The CHAIRMAN. The figures on illness, the number of man-days lost brings a new dimension to another problem.

You take all of the strikes, lockouts, wildcat strikes, the number of man-days lost is only one-tenth of the days lost from workmen being killed or injured on the job.

This brings up another dimension. How much is lost from temporary illness?

I have a question of Dr. Whedon and Dr. Steinfeld.

Is research into arthritis being dropped at the National Institute of Arthritis and Metabolic Diseases? Has it been pulled down? Has research into the cause of arthritis lessened?

Dr. WHEDON. No changes have been made at the present time in our apportionment of funds for research grants and training grants among our various areas of responsibility. We are, in these times of constraint, however, concerned about the proper proportion among our various fields. This came up particularly in discussion at the June council meeting of our advisory council, and we expect to spend a considerable amount of time at our November meeting in discussion of this particular matter.

I think it is a difficult thing to consider moving funds from one area to another at a time when most of the areas, most of the proponents in other areas would feel that they, too, are in a critical shortage with respect to the support for their area.

The CHAIRMAN. I have been told you abandoned research into certain causes of certain types of arthritis, specifically rheumatoid arthritis. What was being done 10 years ago in research into the cause of rheumatoid arthritis and what is being done now, or 5 years ago if you don't have the figures for 10 years ago.

Dr. WHEDON. I have the figures here, Mr. Chairman, and there has been a gradual increase in the support of arthritis research.

The CHAIRMAN. What about rheumatoid arthritis? That is the most painful of all, is it not?

Dr. WHEDON. It is the most serious and most crippling type, and our major efforts in research really are on that type of arthritis.

The CHAIRMAN. I have been told by people in the arthritis field in private practice, medical field, the NIH has practically pulled in its horns and quit research.

Dr. WHEDON. I would be glad if they would write me.

The CHAIRMAN. I think they have some knowledge of what goes on out there.

Dr. WHEDON. Senator, my information is correct, and we would be delighted to correct the record.

The CHAIRMAN. I would like to know what the facts are.

Dr. WHEDON. Specifically, in 1960, we were spending \$6,700,000 in arthritis and rheumatic diseases. We have moved up in 1968, for example, to \$11,100,000. It has nearly doubled in the 8 years from 1960 to 1968.

The CHAIRMAN. What about 1970?

Dr. WHEDON. In 1970 the figure for arthritis is \$10,965,000. It is just about the same level as it was in 1968.

The CHAIRMAN. Well, just about. When you have \$200,000 less, plus the galloping rate of inflation in medicine. If you scale that down to a 10 percent decline, you would have some deans of medical schools arguing with you that it is more than 10 percent loss. I have talked to a number of them. What about rheumatic arthritis?

Dr. WHEDON. The figures that I gave you include our effort in rheumatoid arthritis.

The CHAIRMAN. In rheumatoid arthritis, what has been the change in the last 5 years up to now? I have been told by doctors who practice in that field there has been a great decline in effort in the last 5 years and the NIH has practically given up.

Dr. WHEDON. Senator Yarborough, this is completely mystifying to me, how this sort of information could get abroad.

The CHAIRMAN. This is not among laymen but medical men.

Dr. WHEDON. The facts are, Senator, rheumatoid arthritis is the most crippling and affects more people in a very serious and debilitating way than any other type of arthritis. We have put our major efforts on that disorder and the examination of our research grants support and our intramural research operation in Bethesda in the clinical center will show the emphasis we have put on that. We are particularly excited about the prospects of making a real change in our knowledge of the cause of rheumatoid arthritis. The impact of an altered immunologic reaction on the part of the body has given us some very definite clues. There may be a small virus, or a small bacteria-like organism, which causes the initial insult to the body, which sets in motion a stream of changes in the body's reaction to disease which ultimately winds up in the crippling form of arthritis. We are absolutely concerned and are devoting a great deal of effort in that direction.

The CHAIRMAN. I am very relieved to hear this, because it is contrary to what I had been told in medical circles, also outside of NIH. How many people suffer from arthritis?

Dr. WHEDON. Estimated, about 16 million.

The CHAIRMAN. I don't mean people who have just arthritic pains and who get over those pains, but those who suffer so that it is an impediment to their work.

Dr. WHEDON. The number of individuals who have arthritis of such severity that their work is impaired, I would estimate, is in the range of 5 to 6 million.

The CHAIRMAN. I don't mean they are totally disabled, but impaired.

Dr. WHEDON. The number of 16 million is given for those who have arthritis of serious enough degree to have to go to a doctor.

The CHAIRMAN. I think that is a viable figure because people don't go to a doctor with every little thing.

Dr. WHEDON. Those with just aches and pains would make the figure much larger. We have 1965 figures from the last national health survey which set the number of arthritics completely disabled at 680,000, those unable to work or keep house at 2,076,000, and those partially disabled at 3,481,000.

Dr. STEINFELD. I think you hit on an important subject because rheumatoid arthritis is also being studied in the National Institute of Allergy and Infectious Diseases in regard to viruses, in the Cancer Institute for the cancer chemotherapy response, and you have a whole series of crossovers and interrelationships throughout NIH. So, I think you have hit on a particularly apt illustration of what is needed to carry on a really adequate program. The field may have veered in the last 5 years into more immunology and infectious etiology from the way we have looked at in the past.

Senator DOMINICK. I appreciate your coming here, Dr. Steinfeld. I have enjoyed listening to the questioning and to you as you read your statement.

In your prepared statement, you say, and I quote: "Adequate legislative authority exists under the Public Health Service Act for all of the functions envisaged for the proposed Institute."

I wonder if you would supply for the record the legislative authority which you feel does give you that power.

Dr. STEINFELD. We would be pleased to do so.

(The information subsequently supplied follows:)

AUTHORITY FOR PROPOSED INSTITUTE NOW EXISTS UNDER THE PUBLIC
HEALTH SERVICE ACT

(1) Authority to promote research into the problems of diagnosis, prevention, and treatment of digestive diseases and nutritional disorders:

Section 301, PHS Act—"The Surgeon General shall conduct in the Service, and encourage, cooperate with, and render assistance to other appropriate public authorities, scientific institutions, and scientists in the conduct of, and promote the coordination of, research, investigations, experiments, demonstrations, and studies relating to the causes, diagnosis, treatment, control, and prevention of physical and mental diseases and impairments of man. . . ."

In carrying out this mandate, the Surgeon General is authorized to:

Collect and make available information concerning such research and other activities. Sec. 301(a).

Make available research facilities of the Service to appropriate public authorities and scientists engaged in special study. Sec. 301(b).

Make grants-in-aid to universities, hospitals, laboratories, and other public or private institutions and to individuals for research. Sec. 301(d).

Secure the assistance and advice of experts, scholars, and consultants. Sec. 301(e).

Enter into contracts for research. Sec. 301(h).

Adopt such additional means as he deems necessary or appropriate to carry out the purposes of the section. Sec. 301(i).

In addition, he is authorized to establish or abolish institutes, or expand the functions of any institute to include functions with respect to any disease. Sec. 431(b).

As indicated in the testimony, the National Institute of Arthritis and Metabolic Diseases (NIAMD) is the Institute at the NIH charged with responsibility for diseases of the digestive tract and related organs. This Institute is also charged with responsibility for most nutrition and nutrition-related program activities.

(2) Authority to provide for specialized training in the diverse, relevant scientific disciplines related to these conditions:

In carrying out the mandate of Section 301, the Surgeon General is authorized to:

Establish and maintain research fellowships in the Service. Sec. 301(c).

Make grants-in-aid to universities, hospitals, laboratories, and other public or private institutions, and to individuals for research training projects, and for general support of research training programs. Sec. 301(d).

Again, with respect to activities related to nutrition and digestive diseases, these functions are carried out primarily by the NIAMD.

(3) Authority to assure appropriate community service and demonstration programs:

In addition carrying out those activities authorized by Sec. 301, the Surgeon General is authorized to make "grants to any public or nonprofit private agency, institution, or organization to cover part of the cost of (1) providing services (including related training) to meet health needs of limited geographic scope or of specialized regional or national significance, or (2) developing and supporting for an initial period new programs of health services (including related training)." Sec. 314(e).

Senator DOMINICK. Could you tell me how many health institutes we now have in operation?

Dr. STEINFELD. We have 10.

Senator DOMINICK. Could you outline what they are?

Dr. STEINFELD. There is the National Cancer Institute; the National Heart and Lung Institute, the National Institute of Allergy and Infectious Diseases; the National Institute of Arthritis and Metabolic Diseases; the National Institute of Environmental Health Sciences; the National Eye Institute; the National Institute of Neurological

Diseases and Stroke; the National Institute of Child Health and Human Development; the National Institute of General Medical Sciences, and the National Institute of Dental Research.

Senator DOMINICK. It is my understanding from your testimony and also from the preview of Dr. Hightower's testimony that there is a feeling that gastroenterological and nutrition research overlaps with cancer research; is that correct?

Dr. STEINFELD. Certainly cancer is a major problem in the gastrointestinal tract, yes.

Senator DOMINICK. Cancer also involves the heart and the lungs, does it not?

Dr. STEINFELD. Research can be done in that Institute, the Cancer Institute or Heart and Lung Institute, that relates to the gastrointestinal tract; there would be a relationship formed there.

Senator DOMINICK. Dental problems can also cause internal problems, can they not?

Dr. STEINFELD. Indeed they can.

Senator DOMINICK. And vice versa, bad food can bring on dental problems.

Dr. STEINFELD. Inappropriate food, yes, sir.

Senator DOMINICK. You now have particular research into arthritis and metabolic diseases. There is a relationship between arthritis and gastroenterology, is there not?

Dr. STEINFELD. It comes more under the rubric of metabolic disease, but patients with arthritis have seen mandibular joint involvement and they have tremendous problems as do those with gout having GI problems as well as in terms of the food they can eat.

Senator DOMINICK. Is it not true also that some of the problems related to arthritis may be caused by the type of diet that a person is on?

Dr. STEINFELD. This is certainly proposed and is thought to be the case for those with uric acid problems.

Senator DOMINICK. The point I am making is that the field we are dealing with here is interrelated with the work of the institutes that we now have going. My question is, What would we gain by establishing a separate institute here in terms of additional research?

Dr. STEINFELD. We think we would have a net loss due to the administrative costs of setting it up, the personnel who would be removed from doing other activities, the dollars currently going for research and for training. We, therefore, agree that we can do the job within the present framework. I think the challenge to us, Senator Dominick, is to find a mechanism for getting the research done and the training done within our existing bureaucracy, so that our funds are spent appropriately on research and training and not on magnifying the number of Federal executives; so, we agree completely.

Senator DOMINICK. Dr. Steinfeld, you and the chairman carried on a very interesting dialogue concerning present research on certain diseases. What has happened to the average life span of Americans in the last 50 years?

Dr. STEINFELD. It has increased remarkably from probably 54 or so years to 67 to 74 years depending upon whether one is a male or female.

Senator DOMINICK. How much of that increase has occurred, if you know, in the last 20 years? Can you explain or extrapolate that?

Dr. STEINFELD. We can provide it for the record, but I think the major increase in lifespan has been due to the control of contagious and infectious diseases through prevention. I think the point you are leading to, and Senator Yarborough mentioned earlier, regarding digestive diseases, work accidents, and so on, is that we have forgotten prevention in our haste to take care of disease as it has occurred. Our possibilities for the future, I think, lie in the knowledge of preventable disease and injury. If we can prevent these, it is far less costly and better for the patient.

Senator DOMINICK. When we talk about the patients afflicted with cancer and the number of deaths occurring from that, do we have a breakdown on age categories?

Dr. STEINFELD. Yes; we do, and we can provide that for the record. (The information subsequently supplied follows:)

Estimated Number¹ of new cancer cases in the United States, 1970

Age:		
0-9	-----	4,803
10-19	-----	5,178
20-29	-----	16,644
30-39	-----	28,240
40-49	-----	67,061
50-59	-----	117,724
60-69	-----	156,551
70-79	-----	154,268
80+	-----	76,300
Totals deaths	-----	626,769

¹ Estimated by applying Connecticut incidence rates to estimated U.S. population for 1970-71, series C.

Source: Population Estimates and Projections, U.S. Department of Commerce, Bureau of the Census, series P-25, No. 448, August 6, 1970. Christine, B. W., Suvillivan, P. D., Connelly, R. R.: Cancer in Connecticut, 1966. Connecticut Health Bulletin 84: 5, May 1970.

Number of cancer deaths in the United States, 1967

Age:		
0-9	-----	2,979
10-19	-----	2,551
20-29	-----	2,866
30-39	-----	7,303
40-49	-----	25,653
50-59	-----	57,371
60-69	-----	83,630
70-79	-----	84,917
80+	-----	43,673
Total deaths	-----	310,943

Source: Vital Statistics of the United States, 1967. U.S. Department of Health, Education, and Welfare, Public Health Service.

Senator DOMINICK. It occurs to me all too often, and I indulge in this and I won't say the chairman does, but I certainly do—I think we sometimes lose sight of the fact that everybody is going to die sooner or later, whether it is of a heart problem or cancer or arteriosclerosis, or whatever it may be. I think the interesting figure would be whether or not there has been an increase in the age level of the cancer patients. In other words, do they get cancer more often in the older years now? Do we know how many of the patients we are

talking about get cancer as a terminal disease, toward the end of their life, as opposed to their productive working days?

Dr. STEINFELD. Cancer occurs in youngsters, of course, for example, the acute lymphomas. There is no doubt that since we have controlled infectious diseases, people are then dying of degenerative diseases—heart disease, cancer, and some of the others.

Senator DOMINICK. Is it not also true that part of the statistical increase in the specific diseases that have been mentioned—and I will use cancer as an example—are in part attributable to better diagnosis so that we know what the disease is?

Dr. STEINFELD. I think, indeed, that is the case. In years gone by, when a person died of a pulmonary affliction, it may have been called tuberculosis and, indeed, it may have been called something else entirely, and the same would hold for many digestive diseases where autopsies had not been performed.

Senator DOMINICK. In your prepared statement, I was extremely interested where you say that elevation of the organizational status is not a panacea. No mere change in organizational form will cause a research area to flourish. Such a change does not provide an assured solution where the main problems are trained manpower and good research ideas.

How much of your present effort is going into the manpower and research ideas insofar as the proposed institute on digestive diseases?

Dr. STEINFELD. We can supply for the record a review of the funds being spent for digestive diseases and nutrition. We can also supply for the record our best estimates of the administrative costs of setting up a new institute and the number of personnel involved.

(The information subsequently supplied follows:)

FUNDS FOR DIGESTIVE DISEASES AND NUTRITION

At the present time the NIH is devoting a total of \$18,890,000 to digestive diseases and gastroenterology. Of this, the National Institute of Arthritis and Metabolic Diseases (the focal Institute for this field) is expending \$12.4 million. At the same time, the NIH is devoting an overall total of \$23,149,000 for research and training in the field of nutrition. The following table details the cost of a minimum overhead structure for the proposed National Institute of Digestive Diseases and Nutrition:

MINIMUM OVERHEAD STRUCTURE—PROPOSED DIGESTIVE DISEASES AND NUTRITION INSTITUTE

	Present NIAMD		Digestive diseases and nutrition in NIAMD		Digestive diseases and nutrition institute minimum requirement		Additional positions and administrative costs necessitated by creation of a new institute	
	Positions	Amount	Positions	Amount	Positions	Amount	Positions	Amount
Office of the director (program direction).....	21	\$330,000	1	\$15,700	20	\$314,000	19	\$298,300
Office, Program Planning and Evaluation.....	4	65,000	0		4	65,000	4	65,000
Office, Research Information..	8	120,000	1	15,000	5	75,000	4	60,000
Office, Associate Director for Extramural Programs.....	60	2,150,000	11	393,800	22	787,600	11	393,800
Office, Associate Director for Coll. R. & D.....	20	290,000	1	14,500	5	72,500	4	58,000
Office, Associate Director for Intramural Research.....	3	80,000	1	27,000	3	81,000	2	54,000
Total.....	116	3,035,000	15	466,000	59	1,395,100	44	939,100
Intramural research.....			41	1,670,000	50	2,027,000	9	360,000
Total.....							53	1,289,100

¹ Includes planning funds for all activities, including consultants, symposia, and conferences.

It is important to note that the minimal overhead cost as described in the table amounts to about \$1.4 million and is devoted to administrative expense and program direction only. It must also be understood, if one wants to be realistic, that any new Institute will have an intramural research component estimated, minimally, on the table at \$2,027,000. The additional positions and administrative costs which would be necessitated by creation of a new Institute will amount to \$1,289,100 and 53 positions above and beyond the current cost of engaging in the digestive disease and nutrition effort within the present administrative framework (where a judicious sharing of administrative and overhead costs with other disease fields within the National Institute of Arthritis and Metabolic Diseases permits a minimal outlay for such expenditures which do not contribute directly to research and training efforts).

Senator DOMINICK. Somewhere in your statement you said you thought the additional administrative expenses would be in the neighborhood of \$1 million.

Dr. STEINFELD. Yes; the table will show the total additional cost as approximately \$1.3 million.

Senator DOMINICK. That, presumably, unless we got additional funding, which seems to be hard to get for anything these days, would come out of the existing budget that you would start with; is that correct?

Dr. STEINFELD. Unfortunately, yes; and this is why we feel we need new mechanisms to accomplish the highlighting of an area, the seeking out of new research leads, the intensifying of the recruiting and training for a particular area. We hope, by these new mechanisms that I mentioned earlier when I elaborated on the prepared remarks, that these will provide the techniques for so doing.

Senator DOMINICK. In that same paragraph, you state that the main problems of trained manpower and good research ideas are involved, and then you go on to say in the next sentence, "The broader nature of the problems in digestive diseases is illustrated by the fact that presently available research training opportunities go unfilled." Is this because of a lack of interest, or because of a lack of manpower, or because of some other unexplainable situation?

Dr. STEINFELD. I cannot explain specifically why more young physicians have not gone into gastroenterology. We have 126 funded trainee positions for postdoctoral trainees available through NIAMD support of which only 102 are filled. Why they are not filled is probably a combination of the interests of the young doctors, of the enthusiasm of the persons in the training programs; in modern medicine, the glamorous areas shift from year to year or every few years. I cannot explain why this is so, but unfortunately, it is so.

Senator DOMINICK. Somewhere during your statement, or in your colloquy with Senator Yarborough, you referred to the fact that treatment of cirrhosis of the liver is part of a training effort that you are engaging in presently under one of the existing institutes. It is my thought, and this shows probably why I am a layman and not a doctor, cirrhosis of the liver is caused largely by excessive use of alcohol. Am I wrong?

Dr. STEINFELD. The people who have cirrhosis of the liver use alcohol excessively and usually have an inadequate diet as well, and there may be other dietary factors involved, too. There are areas in the world where individuals may develop cirrhosis because of parasitic infection or because of tremendous ingestion of iron where they have hemosiderosis leading to cirrhosis, so there are multiple causes.

In this country, we find the major origins are from alcohol and insufficient diet.

Senator DOMINICK. So, the recent bill we have reported out in drug abuse and alcohol should be of assistance in this area?

Dr. STEINFELD. You are correct; that is another relationship that should be supported in this broad area.

Senator DOMINICK. It is my understanding at least that Dr. Egeberg on a previous occasion has expressed his support for the establishment of a separate institute. Is that accurate, and would you comment on it?

Dr. STEINFELD. I discussed this with Dr. Egeberg as recently as last Friday afternoon, and it is his feeling, as it is mine, the best thing to do is not to proliferate institutes but to highlight these research and training areas through other mechanisms, through the appointment of a special associate director in NIAMD who would have cognizance of this area, and the appointment of an individual in our own office who would look at nutritional problems. I think we would like to coordinate and facilitate research and highlight it and related training programs by means other than this very expensive proliferation of institutes. We are in agreement on the approach which has been described this morning.

The CHAIRMAN. Dr. Egeberg is in agreement with you on this?

Dr. STEINFELD. Yes, sir, we had a long discussion Friday afternoon and Friday evening on this.

The CHAIRMAN. I have not talked to Dr. Egeberg about this, and one reason I was pushing this so far in the closing days was that I had been told by people of very high stature in the medical world that Dr. Egeberg supported it. I felt that this late in the game the only opportunity we had to pass the bill through both Houses was to have his support. I was not going to ask the question on hearsay here, but since Senator Dominick brought it up, I make that comment.

Dr. STEINFELD. Dr. Egeberg and I both feel, as I am sure you do, that gastrointestinal diseases are extremely important, and we must have a way of highlighting them. The two new things we are doing are designed to do that—we are not saying we have done everything—but we are appointing a new associate director for NIAMD and a special assistant for nutrition in our own office. These are the mechanism we hope will accomplish the same purposes which you want to accomplish without all of the additional bureaucracy and expense required for a new institute.

The CHAIRMAN. Thank you. I have no further questions, Dr. Steinfeld. Thank you very much for your contribution here. We have ranged far afield this morning.

I have one more question concerning age and cancer. Is it true that cancer is the number one killer of children between 1 and 14 years of age?

Dr. STEINFELD. Yes, I believe I mentioned earlier acute leukemias and some other rapidly growing tumors are the number one killers.

I would like to say, in addition, that the cancer chemotherapy programs involve the use of drugs that are most useful in these rapidly growing, rapidly dividing tumors. A number of what we hope are cures have occurred in children with Wilms's tumor, with myocarcinoma, acute leukemia, and some of the others, even when the child

appears to have no evidence of the tumor. So, it is a number one problem; and we do have extremely good leads in the therapy. Prevention is another problem and the viral oncology program is addressing that.

The CHAIRMAN. Again, thank you very much, gentlemen.

Our next witness is Dr. John S. Fordtran, Professor of Internal Medicine, University of Texas, Southwestern Medical School, Dallas, Tex. You may proceed in your own way, Dr. Fordtran.

STATEMENT OF DR. JOHN S. FORDTRAN, PROFESSOR OF INTERNAL MEDICINE, UNIVERSITY OF TEXAS, SOUTHWESTERN MEDICAL SCHOOL, DALLAS, TEX.

Dr. FORDTRAN. Mr. Chairman, I previously wrote an article in opposition to this separate institution for digestive diseases and nutrition which I supplied for the record. I do not plan to outline that today exactly, but I would like to give a summary statement.

The CHAIRMAN. Your statement will be printed in the record, Doctor. Due to the length of time we questioned Dr. Steinfield, we have impinged on the time of the rest of you, so if you can digest your statement, it would be helpful.

(Dr. Fordtran's article follows:)

ON THE ESTABLISHMENT OF A NATIONAL INSTITUTE OF DIGESTIVE DISEASES AND NUTRITION

We are pleased to present, on the following pages, two points of view regarding the very important question of the establishment of a separate institute in the National Institutes of Health. The outcome of this vital issue will concern us all in the years to come.

MARVIN H. SLEISENGER, M.D.
 Editor

The Case Against a Separate Institute

On November 4, 1969, a letter was sent to members of the American Gastroenterological Association stating that "after the introduction of the 'AGA White Paper' in 1967, your organization decided that it was in the best interest of the public if gastroenterology had, together with nutrition, a separate institute in the National Institutes of Health." The letter further stated that Congressman Staggers and Senator Yarborough have introduced in the House of Representatives and in the Senate a bill to establish such an institute. The letter listed the following reasons why such a bill should be supported.

1. A need for research in digestive diseases and nutrition.
2. High level of bed occupancy in civilian, veteran, and military hospitals by digestive disease patients.
3. High work absence rates due to digestive disease and their importance to labor, industry, and public.
4. Other reasons in the White Paper or in Senator Yarborough's introduction to the bill.

This letter to AGA members was pre-

Received January 21, 1970.

Address requests for reprints to: Dr. John S. Fordtran, Department of Internal Medicine, Southwestern Medical School, 5323 Harry Hines Boulevard, Dallas, Texas 75235.

pared by the Congressional Liaison Committee of the AGA and signed by Hugh R. Butt, Chairman.

In the bill before Congress, reasons for supporting a separate National Institute of Digestive Diseases and Nutrition (NIDDDN) were presented. The following is a summary of these reasons.

1. Frequency of digestive diseases; for instance, one-third of all cancer deaths are due to cancer of the digestive tract, and cirrhosis of the liver ranks as the fourth most common cause of death in adults at the present time.
2. Digestive diseases are the leading cause of industrial absenteeism among male employees.
3. The economic loss in this country due to peptic ulcer alone is \$1 billion per year.
4. Of all nonobstetrical surgery, 23% is performed for digestive diseases.
5. Education and training of doctors to cope with digestive diseases has lagged seriously. National Institutes of Health (NIH) figures show that 141 trainees in digestive diseases have been helped in their training, compared with 1146 in cardiovascular diseases. The average medical school has only three teachers in digestive diseases, as compared with four in hematology and six in cardiovascular diseases.
6. Digestive diseases receive less than 5% of the extramural research support funds of the NIH.
7. Fewer than 1500 physicians in the country treat digestive diseases as such (presumably fewer than 1500 specialize in digestive diseases).

In spite of the preceding argument, we are opposed to removing digestive diseases from the auspices of the National Institute of Arthritic and Metabolic Dis-

eases (NIAMD) and establishing a separate institute. Our reasons are 3-fold. First, we think that the statistics and data presented in the White Paper and in the Congressional bills are irrelevant to the question of how the NIH should support research and training in gastroenterology. Second, there is no evidence that financial support by NIH under current arrangements is rate-limiting to the training of additional academic gastroenterologists. Third, and by far the most important, we feel that the public, the NIH, and gastroenterology would be harmed by the establishment of a separate NIDDK.

Our conclusions are based on the following considerations.

I. The data in the White Paper and in the Congressional bills are irrelevant.

A. Of course digestive diseases are important, but even if every figure in the Congressional bills is correct, this has no bearing on whether or not we should have a separate institute or be part of the NIAMD. In our opinion there is only one possible reason to support a digestive diseases institute and that would be if the NIAMD has discriminated against gastroenterology in favor of other specialties which it supports. There is absolutely no evidence that this is the case. (The NIAMD even helped to collect the data published in the AGA White Paper.) *All of the problems raised by the White Paper and in the Congressional bills can be handled by devoting our energy to getting more support for the NIAMD.*

B. Some of the figures cited in the Congressional bills may be misleading.

1. Studies on cancer of the digestive tract and hepatitis, infantile diarrhea, cholera, etc., receive support from the National Cancer Institute and the National Institute of Allergy and Infectious Diseases. Are

these and other such examples included in the small amounts alleged to be spent for digestive diseases?

2. Many surgeons in medical schools specialize in treatment of digestive diseases. General surgery is, to a large extent, surgery of the digestive system and thoracic surgeons specialize in diseases of the esophagus. Are these included when ratios of heart, blood and gastrointestinal specialists are computed? If gastroenterology is to receive credit for all digestive diseases (\$1 billion per year for duodenal ulcer, gallbladder problems, etc.), then we have to count all doctors who take care of these problems.
3. The contention that only 141 trainees in digestive diseases are helped in their training by NIH compared with 1146 in cardiovascular disease also may be misleading. These figures apparently are taken from an article by Clifton entitled "Manpower in Gastroenterology" (*Gastroenterology* 53: 353, 1967), although the numbers are not exactly the same (Clifton's article gives 141 trainees in gastroenterology compared with 1446 in cardiology). Clifton qualifies the data as follows: "The data for support of cardiology by the National Heart Institute are not comparable to those for gastroenterology and hematology, which are funded by the National Institute of Arthritis and Metabolic Diseases. The National Heart Institute supports many training programs whose activities are not limited to cardiology but encompass a variety of related

- disciplines." Furthermore, the figure for digestive diseases may be an underestimate, since it does not apparently include surgical trainees, who are usually supported through the National Institute of General Medical Sciences. In another place in his article (p. 356 and figure 7), Clifton states that departments of medicine have approximately 60% as many research trainees in gastroenterology as in cardiology (source of support not specified).
- C. Although it is impossible to predict from where breakthroughs in digestive diseases will come, some of our major problems such as hepatitis (a viral disease), alcoholic cirrhosis (a sociological disease), and cancer are not likely to be solved by individuals trained in digestive diseases, but rather by research specialists in other disciplines. It is misleading to suggest that any amount of money allocated to an NIDDM would hasten a solution to these important diseases. For such an institute even to attempt to support basic research in virology, cancer, and sociological diseases would create a tremendously wasteful overlap at the NIH.
- D. Clifton's article does show that there are twice as many cardiologists as gastroenterologists in the medicine department of the average medical school. However, no evidence has been presented that this is not fully justified, especially since many digestive diseases are treated by surgeons, whereas a relatively small percentage of cardiology problems are handled by surgeons. Furthermore, the amount of teaching and research required on a certain disease is not necessarily related to its over-all frequency in the general population.
- II. There is no evidence that the training of academic gastroenterologists is rate limited by lack of financial support. We base this opinion on the following statistics, which we obtained by writing to the NIH. First, as of July 1, 1969, there were 43 active training programs in gastroenterology (not including surgical trainees), with 126 authorized and available positions. However, only 101 of these positions were actually filled. This means that approximately 20% of available traineeships in gastroenterology are not being used. Second, during the past 2 years only five new applications for training grants in gastroenterology have been reviewed by the NIH and all five were disapproved. It is emphasized that these were outright disapprovals, not approvals which could not be supported for lack of funds. The Training Grant Committee is well staffed with gastroenterologists and it must be concluded that no new training grant applications judged to be of high quality have been reviewed by the NIH during the past 2 years (three new applications have recently been received but not reviewed as of December 24, 1969). How can these figures be reconciled with the idea that present NIH support in gastroenterology is grossly inadequate? It should be pointed out that, even if financial support does become rate-limiting, this in itself would not constitute a reason to separate ourselves from the NIAMD and set up a digestive disease institute.
- These figures might be used to argue that, since 20% of our available fellowships are unfilled, something is wrong with our ability to appeal to prospective candidates. However, even if this is true, we do not believe that this in any way justifies the establishment of a separate digestive diseases institute. Good men are attracted into gastroenterology mainly through contact with gastroenterologists. We do

this best by working hard at our research, teaching well, and by being good clinicians. The relative popularity of gastroenterology and cardiology in the minds of the general public, medical students, interns, etc., should have nothing whatsoever to do with decisions regarding a separate institute.

III. It would be detrimental to the public, to the NIH, and to the subspecialty of gastroenterology to establish a separate National Institute of Digestive Diseases and Nutrition.

A. The cost of establishing and maintaining a separate institute would be enormous. (The net additional administrative cost of a separate eye institute was estimated to be \$800,000 per year (Hearing before the Subcommittee on Public Health and Welfare of the Committee on Interstate and Foreign Commerce, House of Representatives, 90th Congress, first session on H.R. 128431)). Higher overhead resulting from a separate institute has two deleterious effects. First, the public must pay more money for each trainee and each research project. Second, a separate institute would tend to take money away from rather than create more money for active disease-oriented research and training, since administrative costs must be paid before any research or training is carried out.

Supporters of a separate institute will argue that in time we can get enough money through a separate institute to cover our administrative costs and still have more left over for research and training than we do at the present time. It is by no means certain that this assumption is correct, but, even if it is, the over-all effect of a separate institute still would be bad because it would establish a precedent that would lead to a proliferation of new in-

stitutes (it will have been proved that the way to get ahead is by a separate institute). Many subspecialties other than gastroenterology also want their own institutes and ultimately the NIAMD might be replaced by 11 separate subspecialty institutes, each with a large administrative overhead. It is very important that the interests of special groups not be allowed to harm or reduce the effectiveness of the NIH.

B. Grants can be more fairly and objectively awarded by the NIAMD than by a separate institute. Unfortunately, unless all money allocated to any granting agency is spent, its support in future years is jeopardized. In the NIAMD broad options are available and, while priorities for certain diseases can be recognized, in general the best research projects are supported regardless of subspecialty. If the NIAMD is subdivided, each subspecialty institute will be under pressure to spend all of its allocated money, even though it may mean the support of some poor research and poor or mediocre trainees. This might result in the support of a poor research project in one disease while a good project in another disease could not be funded. For this reason, we believe that the competition we now have with nephrologists, immunologists, rheumatologists, etc., within the NIAMD is healthy. Although it might be argued that this is healthy over-all but not for gastroenterology in particular, it should be recalled that knowledge gained in seemingly unrelated fields may benefit gastroenterology (note the Australia antigen story).

C. A separate digestive disease institute would tend to isolate gastroenterology from the rest of the academic community. The inti-

mate contact we now have with nephrologists, rheumatologists, geneticists, and immunologists is highly stimulating to academic gastroenterology and should not be broken. We should maintain and strengthen these ties and not isolate ourselves. *Clinical subdivisions are not necessarily the best way to subdivide the National Institutes of Health.* A multidisciplinary approach is needed to find a cure for most digestive diseases.

- D. A separate digestive disease institute might be a relatively weak and low priority institute and, if so, it would diminish rather than enhance the image of gastroenterology. It will not be easy to staff this institute with excellent people and competition for funds at the Congressional level, for beds and laboratories in the clinical center, for administration space, etc., will be stiff. Our present supporters in the NIAMD will become our opposition. The care and feeding of a separate institute might turn out to be a burden rather than the pride and joy of academic gastroenterologists.

Even if a digestive disease institute turned out to be strong, however, it should be re-emphasized that its ultimate effect might still be bad since its own success would foster a proliferation of other subspecialty institutes, with higher and higher administrative costs for the NIH, and ultimately

a cutback in funds for actual research and training in all areas of medicine. Furthermore, if an NIDDK is successful, there is no assurance that other groups presently considered within the family of digestive diseases might not decide they need their own separate institutes. If everyone gets an institute, no one will be better off and the NIH will be ruined.

We agree that additional support for medical research is needed, but we think that a broad view of the problem must be taken and that the welfare of the NIH, medicine in general, and the public must be carefully considered. Why not work for more support for and through the NIAMD, maintain the close ties we now have with specialists in nephrology, metabolic diseases, genetics, and immunology, and use for research and training that money which would otherwise be wasted in the support of a new administrative hierarchy? If any real reasons for a separate institute exist, they should be clearly stated and the advantages of a separate institute be contrasted with the disadvantages of breaking away from the NIAMD. We don't believe that there are any valid arguments for a separate institute and for the reasons outlined above we feel that a separate institute would be harmful to the public, to the NIH, and to gastroenterology.

JOHN S. FORDTRAN, M.D.

JOHN M. DIETSCHY, M.D.

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Dr. FORDTRAN. My reason for opposing the separate institute are three:

First, I do not think that such an institute would hasten the conquest of digestive diseases;

Second, I think it would divert money away from research and training;

Third, I believe it would reduce the effectiveness of the National Institutes of Health.

Now, concerning the first point, that the new institute would not hasten the conquest of digestive diseases, I believe this to be true, because I think digestive diseases are already well supported by the National Institutes of Health. My opinion that the present NIH support for digestive disease research is good is obviously in direct conflict with the proponents of this legislation whose statistics suggest digestive diseases are poorly and inadequately supported by the NIH under the present arrangements, but I think their statistics are misleading. They say, for instance, that inadequate money is now allocated by the NIH for training of academic specialists in digestive diseases, but they fail to mention NIH offers 126 training positions in digestive diseases each year and that 20 percent remain unfilled. Actually, the NIH is giving us more support for training specialists in academic digestive disease that we can use.

Proponents of a separate institute say that medical schools have a deficiency of digestive disease specialists compared to cardiologists and hematologists. But they don't count the many surgeons in medical schools who treat digestive diseases, including ulcer, cancer, and gallstones.

In addition, many specialists in internal medicine, radiology, and pathology have special competence, training and interest in digestive diseases, even though they do not limit their practice to the field of gastroenterology or call themselves gastroenterologists. As a matter of fact, one might argue that we in medicine are already too specialized, and that our greatest need is for physicians interested in and able to treat the whole patient, rather than for an increased number of super-specialists.

Proponents of a new institute note the high incidence of digestive cancer, but they fail to mention the Cancer Institute, which is actively engaged in cancer research and treatment (including cancer of the digestive system). Regardless of whether or not a new institute is formed, digestive disease cancer research will continue to be sponsored by the Cancer Institute.

In fact, none of the statistics offered by proponents of a new institute justifies the conclusion that digestive diseases are inadequately supported by the NIH under the present arrangement. In my opinion, our specialty is well supported by the NIH, and I do not think the establishment of a separate institute will hasten the solution of any of our digestive diseases.

My second reason for opposing a separate institute is that its establishment would divert money away from research and training. The net additional cost of establishing and maintaining a separate institute would be over \$1 million just for the administrative costs of the new institute alone. Thus, a separate institute would take money away from rather than create new money for research and training since

administrative costs must be paid before any research or training is carried out. One million dollars a year would support about 20 research grants in digestive diseases. Why waste this money by creating additional and unnecessary administrative positions?

My third reason for opposing the new institute is it would reduce the efficiency of the NIH. In my opinion, if digestive diseases and nutrition get a new institute, there would be a proliferation of new institutes at the NIH.

The National Institute of Arthritis and Metabolic Diseases currently supports 11 clinical subdivisions of medicine. In the clamor for more recognition, many of these will feel the need to seek their own institutes if digestive diseases get their institute. If they are successful, the effectiveness of NIH will be greatly reduced by duplication of effort and unnecessary and enormous administrative costs.

Under the present arrangement, with digestive diseases supported by the NIAMD, great strides are being made. Forty-three active training programs in digestive diseases are supported by the NIH. In my opinion, no good research ideas have not been funded, at least until the recent cutback in funds; and during the recent recession those engaged in digestive disease research have been treated fairly.

In addition to support of research and training in the Nation's medical schools and hospitals, excellent research in the digestive diseases has emanated from the intramural program of the NIH—cystic fibrosis, disorders of protein-losing enteropathy, and hepatitis are examples.

Furthermore, the NIH has directly sponsored epidemiologic research in digestive diseases in the field—such as the Pima Indian gallbladder study in Arizona, and its cholera research program.

In summary, I want to say that we in digestive diseases have excellent support from the NIH under the present arrangement. I do not think a reorganization of the NIH, as proposed by this legislation, will be helpful in any way. It will be costly, it will divert money away from research, and it will reduce the effectiveness of the NIH. In my opinion, it will not hurry the conquest of our diseases.

The CHAIRMAN. Thank you, Doctor. I realize that your statement is a condensation of this and you have been studying this.

What was the Pima Indian gallbladder research?

Dr. FORDTRAN. This work is going on near Phoenix to discover the cause for the extremely high incidence of gallstones in American Indian populations. By the age of 70, 80 percent of all American Indians have gallstones, and research is going on to try to find the cause for this. Recently, strong evidence, based on the study of Indians, has shown that the cause of gallstones is an abnormal secretion of liver bile.

The CHAIRMAN. Do you mean all tribes?

Dr. FORDTRAN. As far as I know, all tribes of American Indians, including Navajos, Hopi, Zuni, et cetera.

The CHAIRMAN. You mentioned all those in the desert area. What about the woodland area?

Dr. FORDTRAN. I am not absolutely certain but I think they all have a very high incidence of gallstones.

The CHAIRMAN. Do you think it is due to a change in diet?

Dr. FORDTRAN. No, sir; I don't believe that it is that. That is what was believed for a long time, but not currently.

The CHAIRMAN. You say in your editorial that the number of Americans sick and disabled with digestive diseases is irrelevant to the manner in which the NIH supports training and research in the bill. Isn't it important to think about the whole? Isn't everything about this health relevant when you are dealing with something that disables so many millions of Americans; with something that, if you just look at it from the cold, hard, materialistic standpoint, causes a loss of 300 million man-days work a year? Wouldn't that be very relevant?

Dr. FORDTRAN. No, sir; I don't believe that it is that. That is what we have good research done and to have good research carried out and to have it economically done, and the National Institutes of Health, I think, ought to work out their administrative problems the most efficient way they can so they can use as much money as they have available for actual research and not waste it in unnecessary administrative costs.

I agree digestive diseases are tremendously important. I spend every day working on them. The thing I want to see is the support for all diseases given out in the most efficient way. I don't think that the numbers have anything to do with how the NIH ought to organize itself. The common cold and the flu, as you mentioned, are extremely important, but we don't have a national institute specifically for those problems.

The CHAIRMAN. Isn't the important thing that sick Americans get the best possible informed help?

Dr. FORDTRAN. Absolutely.

The CHAIRMAN. A section of this bill enables the proposed institute to establish and maintain organized community programs of digestive diseases and nutrition control, and many feel these new concepts are vitally important to the health of our citizens. How could such programs be instituted under the current national institutes as now organized?

Dr. FORDTRAN. I think the way it could be handled would be this: Simply write up an application and submit to the National Institutes of Health; they will direct it to the place where people are concerned administratively with that type of application you are making. I don't know of anything that has been suggested specifically by the proponents of this legislation that can't be handled by the National Institutes of Health as it is now constituted.

The CHAIRMAN. Of course, with the present budget restrictions, not much can be done; less can be done than they have done in the past. My primary question is to get this back on a realistic footing.

Dr. FORDTRAN. And keep administrative costs as low as possible so we have all of the money available for actual research and training that we can have.

The CHAIRMAN. Of course, that is important in any operation.

Dr. FORDTRAN. An overhead of \$1 million is quite a bit when you consider that would pay for 50 research grants a year.

The CHAIRMAN. Who is going to make the research grants without the machinery? How would they be applied?

Dr. FORDTRAN. I believe we have the machinery.

The CHAIRMAN. The problem is not met by just saying we won't do this because the overhead would be too much. We have inefficiency

in many branches of government, but you can't abolish government because some branch is inefficient. The problem is to step up the efficiency of that branch.

Dr. FORDTRAN. I agree with that.

The CHAIRMAN. Your overall problem—government, industry, education, everything—the problem is built-in inefficiency because vast operations and a lot of people.

To me, the fact that you have some overhead does not mean that you kill the plan, kill the building, kill the research. You just fight for efficiency.

Senator DOMINICK.

Senator DOMINICK. I don't think I have any questions. It seems to me Dr. Fordtran has made a very forthright presentation of his position, and it seems to fit pretty well what Dr. Steinfeld said.

I have no further question or comments.

The CHAIRMAN. Our next witness is Dr. Nicholas C. Hightower, vice president, American Gastroenterological Association. Scott and White Memorial Hospital, Temple, Tex.

Dr. Hightower, we welcome you to the committee and we appreciate your patience in taking the witness stand after the hearings were supposed to have been over.

I note that there are attachments to your prepared statement. Those documents will be incorporated by reference.

You may proceed, Dr. Hightower.

**STATEMENT OF N. C. HIGHTOWER, M.D., PH. D., PRESIDENT-ELECT,
THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION**

Dr. HIGHTOWER. Mr. Chairman and members of the subcommittee, I appear before you today to speak on behalf of establishing a National Institute of Digestive Diseases and Nutrition within the National Institutes of Health. Legislation to create a National Institute of Digestive Diseases and Nutrition has been introduced by the chairman of this committee. My name is Nicholas Carr Hightower, Jr., and I am a doctor of medicine and a doctor of philosophy in physiology having obtained by degrees from the Medical Branch, University of Texas, Galveston, Tex., and the University of Minnesota, Minneapolis. I am the director of the Division of Research and Education of the Scott and White Memorial Hospital Foundation in Temple, Tex. My professional specialty is gastrointestinal physiology in which I have been engaged for over 20 years. My research activities during these years have been almost exclusively concerned with problems of digestive diseases and nutrition.

I am here today representing the American Gastroenterological Association of which I am currently president elect. The American Gastroenterological Association is the oldest professional specialty organization in the world, having been founded in 1897. It currently has a membership of approximately 1,000.

Mr. Chairman, I propose to limit my remarks to problems of digestive diseases and specifically to the role that a National Institute of Digestive Diseases and Nutrition could play in resolving some of the important problems that are facing this Nation today. Others here today will speak to the importance of such an institute to resolving nutritional problems.

DEFINITION OF DIGESTIVE DISEASES

Digestive diseases are disorders of the stomach, intestines, biliary passages, liver and pancreas. The causes of a few digestive disease are known and include cancer, alcoholism, genetic defects and reactions to life stress. However, we do not know the etiology or cause of most of the major digestive diseases. In less time than is required for me to read my prepared statement today, seven Americans will have died 137 Americans will have gone to the hospital and 23.6 million dollars in economic loss will have occurred; all as a result of digestive diseases.

DIGESTIVE DISEASES AS A NATIONAL PROBLEM

A few years ago the officers of the American Gastroenterological Association became concerned by the lack of public recognition of the impact of digestive diseases on the Nation's health. In February of 1967, the association sponsored jointly with the National Institute of Arthritis and Metabolic Diseases and the Digestive Disease Foundation, a conference on digestive diseases as a national problem. This meeting was held at Bethesda, Md. There, for the first time, representatives of industry, government, health agencies, the Armed Forces and scientific and educational organizations met to bring together, from many sources, accurate facts on digestive diseases. Many data were supplied by the National Center for Health Statistics. As a result of this meeting, the American Gastroenterological Association in 1967 published a monograph entitled, "Digestive Disease—An Unrecognized National Problem * * * a Report in the Public Interest." This document is attached to my prepared statement as appendix I.

Mr. Chairman, I would now like to provide the committee some data which vividly reveals the national problem that this Nation faces as far as digestive diseases are concerned.

The magnitude of the problem of digestive diseases is great for they account for one out of every six illnesses in the United States. In addition—

1. Digestive disease chronically affects 12,800,000 Americans;
2. Digestive disease hospitalizes 5,100,000 Americans each year—more than any other category of disease;
3. Digestive disease accounts for 17 percent of all hospital admissions each year;
4. Digestive disease in the acute form, as infectious diarrhea, is the most common sickness in our army in Vietnam.

The disability caused by digestive diseases is staggering for it ranks second among all disease categories as to cause of disability due to illness.

1. Digestive disease is responsible for 300 million man-days away from work each year.
2. Digestive disease prevents 190,000 Americans from working each day.
3. Digestive disease is the leading cause of disability due to illness among male employees of major industries accounting for one-fifth of such illnesses.
4. Digestive disease is one of the leading causes of noneffectiveness in the U.S. Armed Forces.

The mortality from digestive disease is also great for it causes more deaths from cancer than any other category of disease.

1. Digestive disease is a primary cause of 163,000 deaths each year in the United States, a contributing cause of 89,000 more.

2. Digestive disease is responsible for 31.4 percent of all cancer deaths.

3. Digestive disease kills four times as many people as do automobile accidents each year.

The cost of digestive disease to the United States is tremendous and currently represents 1 percent of the gross national product each year—or currently approximately \$8 billion.

1. Digestive disease ranks third among all disease categories as a cause of economic loss.

2. Digestive disease costs a single large corporation \$12,222,222 each year in disability benefits.

3. Digestive disease is responsible for the loss of \$1 billion each year due to peptic ulcers alone.

4. Digestive disease's greatest impact is on middle-aged men and women, breadwinners, taxpayers, the heads of families.

The CHAIRMAN. I don't want to belabor this point. You say less than one-fourth of 1 percent of the 300,000 physicians in the United States are certified specialists in digestive diseases. How many are specialized in cancer?

Dr. HIGHTOWER. There is no recognized specialty in cancer, Senator Yarborough.

The CHAIRMAN. How many in heart disease?

Dr. HIGHTOWER. I don't have the exact figure, but I would suspect it is three or four times the number in digestive diseases.

The CHAIRMAN. How many of these physicians are certified specialists in different diseases, if you add up all of the specialists? Some are specialists of the eye, and throat and chest. If you add up all of the specialists, how many would there be?

Dr. HIGHTOWER. Probably 15 to 20 percent of the total physician population, because the growth in certification has grown rapidly in the past ten years.

The CHAIRMAN. You now even have a specialist in family practice?

Dr. HIGHTOWER. That is the most recent one.

The CHAIRMAN. I agree with you that it is amazing to have so few, because some new diseases have been recognized; but people have recognized diseases of the stomach for a long time.

Dr. HIGHTOWER. A measure of our national effort.

The question was asked, 'How great is this Nation's manpower to deal with the problems of digestive diseases?' The following facts were uncovered:

1. Less than one-quarter of 1 percent of the 300,000 physicians in the United States are certified specialists in digestive diseases.

2. Medical schools have, on the average, less than three full-time teachers of digestive disease compared to six cardiologists. Some medical schools have none.

3. No national programs, governmental or private, encourage young physicians to specialize in digestive disease.

4. One digestive disease research trainee is supported by the National Institutes of Health for every eight trainees in heart disease.

Mr. Chairman, now let us look at the national and other efforts that have been brought to bear on the problems of digestive diseases. The effort in terms of dollars expended has, indeed, been inadequate.

1. Federal support for digestive disease has been less than \$30 million annually compared with \$111 million for cardiovascular diseases.

2. Digestive disease is responsible for 16 percent of illnesses in the United States but has received only 5 percent of National Institutes of Health research support.

3. The National Institutes of Health intramural programs supports only one full-time physician scientist in digestive disease as compared to 95 assigned to the Heart Institute.

4. There is no large public philanthropic foundation which has digestive disease as a major interest.

5. There is little support from industry for digestive disease. The pharmaceutical industry is concerned primarily with applied drug research. Industry, suffering great absenteeism, provides none. Disability insurance companies provide none.

Mr. Chairman, the above data are only a brief summary but they indicate the magnitude of the problem of digestive diseases and clearly show the inadequacies of both manpower and dollars expended. The facts that I have just presented were summarized by the Digestive Disease Foundation in a brochure which is attached to this prepared statement, as appendix II.

THE COMMUNIST APPROACH

It is interesting, Mr. Chairman, that in some of the communist countries, the national problem of digestive diseases and nutrition have been recognized and great efforts are being exerted to cope with them. I had a recent opportunity, as a visiting scientist, to personally inspect the major institutions in Czechoslovakia and the Soviet Union that are concerned with digestive disease and nutritional problems. In Prague, Czechoslovakia, there are a group of institutes somewhat similar to our National Institutes of Health. The Institute of Digestive Diseases and Nutrition was the largest, one of the best equipped and there was no shortage of professional and technical staff. In the Soviet Union, the new Institute of Gastroenterology in Moscow which was opened less than 2 years ago is probably the finest institute in that country.

I was impressed by the fact that the Soviet Union had established special polyclinics and spas to deal exclusively with digestive diseases and nutritional problems. In these clinics and spas, patients are instructed in dietetics and preventive measures. Although it was obvious that the technology and facilities available and the methods of therapy used are far inferior to those available in the United States, one could not fail to recognize that these two countries were exerting a major national effort with the capabilities available to deal with the problems of digestive diseases and nutrition.

The CHAIRMAN. I was in Tashkent last fall. At the University of Tashkent they had 15,000 students and 7,500 of them in the medical school. Their ratio of doctors, of course, per 100,000 population is about double ours now. They have not finished educating enough doctors. When they finish in another 5 years they will have at least twice as many doctors for 10,000 population as we have.

Senator DOMINICK. Maybe that is because under communism they have more sick people.

The CHAIRMAN. It could be. We don't have data on that. We have studies here and we received their publications. They are pretty hardy people, though.

Dr. HIGHTOWER. I would now like to address myself to the role that a National Institute of Digestive Diseases and Nutrition could play in overcoming the great losses in lives, health, and dollars this Nation suffers due to digestive diseases.

A separate Categorical Institute within the framework of the National Institutes of Health would provide a physical symbol that the Congress and citizens of this country could identify with. It would stand as a monument to the fact that our Government had identified a national problem and would symbolize to the citizens that something was being done to resolve the problem. It would extend the legal and philosophical reasons that initiated the National Institutes of Health being created.

I cannot state it better than Dr. Robert Marston when he recently appeared before the Subcommittee of the Committee on Appropriations, House of Representatives, 91st Congress, 1st Session, Subcommittee on Department of Labor and Health, Education and Welfare and Related Agencies when he said :

Effective action against disease requires, first of all, a knowledge of what is wrong and availability of some means of doing something about it. In general, the better our understanding of the cause and usual course of disease, the more likely it becomes that we will be able to develop some means of coping with it, that, in essence, is the purpose of biomedical research: the constant expansion of knowledge and its translation into applicable preventive or therapeutic methods.

The record of several of the institutes makes clear that these broad purposes are accomplishable. I believe that the same would be true for a National Institute of Digestive Diseases and Nutrition.

In a recent editorial, published in *Gastroenterology* (vol. 58, No. 6, June 1970, p. 898 (app. III)), Dr. Thomas P. Almy of Dartmouth Medical School clearly points out the potential accomplishments we might expect from such an institute.

1. The council in each of our national institutes has the authority and responsibility to investigate broadly the means by which needed health manpower can be developed. A categorical institute can and does directly influence the supply of trained manpower in its field and in a number of ways which go far beyond the familiar graduate research training grant. It can develop categorical undergraduate teaching grants for medical schools under which the quality of teaching can be raised to a level comparable with that in other fields.

If deemed sufficiently important by the Council, the shortage of properly trained clinical specialists could also be directly attacked as it has been in the National Institute of Mental Health to supply this Nation with needed psychiatrists. In this country today, there are less than 2,000 doctors who indicate a special interest in, or have had special training in, the field of digestive diseases. In the field of gastrointestinal physiology, which I represent, there are probably less than 50 of us in this country. Many of our medical schools have no one on their faculty who has had training in gastrointestinal physiology.

2. In cooperation with voluntary and professional health agencies as well as professional organizations, a categorical institute could initiate cooperative controlled clinical trials of therapy for various digestive diseases. It could initiate nutritional surveys. It could contract to develop new technological advances, which are badly needed in the field of digestive diseases, as the National Heart Institute did in the development of an artificial heart. A categorical institute could establish special study groups to stimulate new work or coordinate existing effects in, for example, chemotherapy, vaccines, blood fractions, epidemiology, methods of providing medical care and many other areas where we need new information.

3. A categorical institute would develop our future scientists, teachers, and clinicians.

4. There is another important role that a separate national institute would play in serving the public interest. It could provide professional educational and public information. The full range of communications media could be used in collaboration with voluntary health agencies to upgrade standards of care, to disseminate new information about diagnosis and treatment of diseases, to fight quackery, and to promote sound health practices among the laity. In turn, this heightening of public interest in a field would be reflected in science education in the schools and could thus influence the career choices of future physicians and scientists.

ARGUMENTS AGAINST A SEPARATE INSTITUTE

Mr. Chairman, I am aware that arguments have been offered against the establishment of a separate categorical Institute for Digestive Diseases and Nutrition. (Fordtran, John S. and Dietschy, John M.: *A Case Against a Separate Institute*, *Gastroenterology* 58:898, 1970) (app. IV). I agree with Dr. Almy that the arguments against the creation of a separate institute are based upon a narrow concept of the functions of the National Institutes of Health. It has been stated that the administrative costs of a separate institute might be as high as \$800,000 a year and would drain away dollars that are now being used for research in digestive diseases. Even if the administrative costs were to be as high as \$800,000 per year, it would still be but one ten-thousandth of the economic loss caused by digestive diseases.

It has been stated that a separate institute would tend to isolate gastroenterologists and nutritionists from the rest of the academic community. It has also been argued that a multidisciplinary approach is needed to find a cure for most digestive diseases and that this would not exist in a separate institute. This has certainly not been the case in previous institutes established. In fact, interdisciplinary programs have been strengthened, particularly in the Cancer Institute and the Heart Institute. It is unlikely that the creation of a separate institute will bring about major breakthroughs in medical science and suddenly provide cures for some of our major digestive diseases. I need not remind the members of this committee that even though the National Cancer Institute has been in existence for almost three decades, we still do not have a cure for cancer today.

ADDITIONAL NEEDS

As I see it, the creation of a National Institute of Digestive Diseases and Nutrition would represent only one segment or area of strength that must be brought to bear on the problem under consideration. There is an urgent and great need for a national voluntary organization devoted to the support of research, education, and public information in digestive diseases. A National Foundation of Nutrition has been active for a number of years. This country needs a National Digestive Disease Foundation and one has recently been activated under the leadership of Dr. James L. A. Roth of Philadelphia. A distinguished group of physicians and laymen have been appointed to a medical advisory board. An executive secretary has been employed and offices have been appropriately established in the Beaumont Building in Bethesda, Md.

This national voluntary health agency will seek support from the private sector, industry, labor, and from others to achieve its objectives which are:

1. To increase public support for research, education, and awareness of the resources available for prevention and cure of digestive diseases.

2. To promote professional education, establish standards, and improve facilities for care.

3. To support research and research training in the area of digestive diseases.

The organizational pattern of the National Digestive Diseases Foundation will be somewhat similar to the American Heart Association. It is planned that there will be regional units as well as State chapters.

PROFESSIONAL SUPPORT

Another important factor that will lend strength to our efforts is the recent establishment of a Federation of Professional Societies interested in Digestive Diseases and Nutrition. The American Gastroenterological Association has joined with the American College of Gastroenterology, the American Association for the Study of Liver Disease and the American Association of Gastrointestinal Surgeons, the Gastroenterology Group, and the American Society for Gastrointestinal Endoscopy to form a federation. As other professional groups join the federation, there would then be within one organization, practically all of the professional people in this country who have an interest in digestive diseases and nutrition.

Attached to this statement as appendix V are approximately 100 letters in support of S. 3063; included are letters from some of the most distinguished physicians and scientists in this country. Also included is the support of the section of gastroenterology of the American Medical Association and a supporting petition signed by over 50 physicians in California.

SUMMARY

In summary, Mr. Chairman and members of the subcommittee, the American Gastroenterological Association strongly supports the legislation that would create a National Institute of Digestive Diseases and Nutrition. Digestive diseases and nutritional disorders are a

national unrecognized problem. Too little is being done in terms of training manpower, funding research, delivering medical care, and developing preventive programs. The American Gastroenterological Association is of the opinion that a separate categorical institute, devoted exclusively to this national problem, would save many lives, prevent disability, drastically reduce the staggering economic loss and eliminate misery and suffering of millions of our citizens and their families.

I thank you for your interest and for the privilege of testifying here today.

The CHAIRMAN. Thank you, Dr. Hightower, for your very thorough documentation of your position on this and the statement of support from the American Gastroenterological Association.

I have studied this appendix III that you offered, the case for a separate institute by Dr. Almy, Dartmouth Medical School at Hanover, N.H. Since I note that in Dr. Fordtran's statement from the Journal that these are two conflicting position, I am going to direct that this statement by Dr. Almy be printed in full in the record since it is kind of a debate between Dr. Almy and Dr. Fordtran. They were printed in the Journal of Gastroenterology. Looking at the length of it, it is not as precise as Dr. Fordtran's, but I think it would be well to have those two conflicting opinions printed in the record at the appropriate places.

(The information referred to follows:)

[From *Gastroenterology*, June 1970, vol. 58, No. 6]

THE CASE FOR A SEPARATE INSTITUTE

(By Thomas P. Almy, M.D.)

Since 1965, the Governing Board of the American Gastroenterological Association has acted on the premise that it has an obligation to provide leadership in the nation's efforts toward the control of digestive diseases (DD). The first need was to assemble facts on the importance of DD as a public health problem and this task led to a working conference at Bethesda in February 1967 and to the publication later in that year of a White Paper entitled "Digestive Disease: an Unrecognized National Problem" (*Gastroenterology* 53:821-833, 1967), followed by other related papers, in this Journal. This information now forms the basis for a proposal that a National Institute of Digestive Diseases and Nutrition (NIDDN) be established within the National Institutes of Health (NIH). This recommendation was presented for open discussion by the membership of AGA through publication in the *AGA News* in September 1968 and reported upon at the annual business meetings in 1968 and 1969. As no previous objections, and many expressions of concurrence, were heard, the Governing Board and its National Liaison Committee have moved ahead in the belief that their actions are heavily endorsed by the membership.

In spite of this, the question raised and opinions expressed by Drs. Fordtran and Dietsch indicate the need for further clarification of the motives for the NIDDN proposal. I write as a former member of the Governing Board and as a party to most of the earlier development of our program of national liaison. My feeling that I can reply responsibly to the objections now raised is heightened by the fact that most of these points had been considered carefully in the early deliberations of the National Liaison Committee.

First of all, the facts in the White Paper were developed with the kind cooperation of people in the National Center for Health Statistics and at all levels of the NIH, as well as expert statisticians in industry and in voluntary health agencies. At the time we had no preconceived notion of our needs and initially the sole purpose of collecting the data was to measure the impact of DD on the nation's health. A number of the high level administrators at NIH admitted that they were as surprised as we were at the magnitude of the problem revealed by the data thus assembled and agreed that some corrective action was indicated.

Specifically, support for gastrointestinal programs from all of the institutes at NIH, whether primarily or peripherally identifiable with DD, was included in the totals. This is made clear on page 827 of the White Paper cited above. Support for programs in general surgery was not considered categorical support for DD, any more than support for programs in general medicine (if there were any) would be considered support for programs in heart disease. I acknowledge the limitations of the data obtained, but they were the best available. The very incompleteness of present sources of information on the prevalence of digestive disease and on manpower resources is a measure of the need for better focusing of attention on DD as a public health problem—much better data are available for those categories of disease for which specific governmental and voluntary agencies exist.

The present proposal for a separate institute was not intended to denigrate the contribution made by the National Institute of Arthritis and Metabolic Diseases, whence has come our most substantial support for research and training, nor to suggest that DD has been treated unfairly vis-à-vis the 10 other fields that institute must serve. We have been blessed with the most effective system of peer review yet devised and no special consideration within that system is now asked for research workers in DD. The creation of a NIDDN would not alter the desirability of evaluation of individual research projects by experts in relevant aspects of biochemistry, fine structure, immunology, or whatever other basic discipline is involved. Where clinical studies are proposed, hopefully the research plan would be evaluated by gastroenterologists rather than by orthopedists or nephrologists, even as at present. As the study sections of NIH are organized under the Division of Research Grants and are administratively distinct from the categorical institutes, and as the advisory council of each institute includes both professional and lay members, the present objectivity in the review of research grants would not be threatened by the new institute.

It is equally clear that the case for a separate institute cannot be based upon expectation of one or more major breakthroughs in basic research which would be unavailable under the present system. In over 30 years the National Cancer Institute has not yet brought for us a cure for cancer and a NIDDN should not be expected to cure alcoholic cirrhosis or peptic ulcer. However, to wait for general virologists to resolve the problem of hepatitis and for sociologists to abolish alcoholism, while the attack on heart disease is led by cardiologists, does not seem rational to me.

An institute is more than a conduit for extramural research funds and the price of its administration buys more than the processing of grant applications. The example set by several other institutes, each responsible for one or two categories of disease, has made clear how many fruitful and effective means can be utilized to exert leadership in health progress in their fields. We feel that progress in DD will be retarded if we continue without similar assistance.

In each institute, the Council has authority and responsibility to investigate broadly the means by which needed health manpower can be developed and new programs of research can be encouraged; it can, thus, by itself or in collaboration with voluntary health agencies, sponsor nutritional surveys and cooperative clinical trials or contract for the development of new technological advances such as the artificial heart. It can set up special study groups to stimulate new work or coordinate existing efforts in, for example, chemotherapy, vaccines, blood fractions, epidemiology, and many other areas. This is too much to expect for DD when it is represented, at the level of the Advisory Council, by one physician-scientist and one layman.

A categorical institute can and does directly influence the supply of trained manpower in its field and in a number of ways which go far beyond the familiar graduate research training grant. It can develop categorical undergraduate teaching grants to medical schools, under which the quality of teaching can be raised to a level comparable with that in other fields, particularly in relevant aspects of the basic sciences. By this means the extraordinary national shortage of full time gastrointestinal physiologists could be progressively overcome and as one secondary result the unfilled traineeships in NIH-supported gastrointestinal research training programs would almost certainly become a thing of the past. If deemed sufficiently important by the Council, the shortage of properly trained clinical specialists could also be directly attacked, as it has been in the National Institute of Mental Health, by direct grants in support of clinical training and the gap between basic knowledge and its more uniform application could be closed or narrowed in DD as it has been in other fields. It is a tribute to the scholarly excel-

lence of many academic gastroenterologists that they have begun to compete effectively with exponents of other branches of medicine for the interest of bright young medical students and graduate fellows. This personal leadership will continue to be an essential factor in manpower recruitment, but it need not and should not be required to operate alone.

Another critically important contribution of the institutes to manpower recruitment in their fields has been a by-product of their intramural research programs. A large proportion of today's leaders of academic medicine have realized a significant phase of their career development while working as research assistants at NIH. The extremely small size of the intramural gastrointestinal research program at NIH has sharply limited this kind of input into the nation's manpower resources for DD. It would be unreasonable to expect more for DD, when it is formally represented at NIH by just one small laboratory!

As to the direct operation of intramural research, it is difficult to avoid the conclusion that DD has been unreasonably restricted. If our data are even an approximate indication of its importance as a health problem and if a good many gastrointestinal research workers do meet NIH criteria of scientific merit for approval of their extramural research grants, why cannot NIH justify employing more investigators of DD on its campus?

Other means of serving the public interest which are available to a categorical institute have to do with professional education and public information. The full range of communications media are used often in collaboration with national voluntary health agencies, to upgrade standards of care, to disseminate new information about diagnosis and treatment of diseases, to fight quackery, and to promote sound health practices among the laity. In turn, this heightening of public interest in a field is reflected in science education in the schools and can thus influence the career choices of future physicians and scientists.

It is these advantages, above and beyond the present equitable treatment in the dispensation of extramural research funds, which we seek from NIH. Even if the administrative cost of setting these processes in motion were to run as high as \$800,000 per year (an arbitrary and poorly documented figure), it would still be but 1/10,000 of the economic loss it is designed to mitigate and should not be beyond reasonable consideration. The cost of operating the programs referred to above is calculable from the experience of existing institutes, the establishment of which was opposed on the same grounds as those presently used to argue against a NIDDN. By what criterion of logic can the present number of institutes be regarded as ideal? In the current climate of fiscal stringency, many will say these things could never be done for DD, and yet sooner or later it will again be realized that it is less expensive for the nation to fight chronic disease than to give in to it.

In my view, the arguments against the creation of a National Institute of Digestive Diseases and Nutrition are based upon a narrow concept of the functions of the National Institutes of Health, which ignores their legal and philosophical reason for being. In testimony before the Subcommittee of the Committee on appropriations, House of Representatives, 91st Congress, First Session, Subcommittee on Departments of Labor and Health, Education and Welfare and Related Agencies, Dr. Robert Marston recently declared: "Effective action against disease requires, first of all, a knowledge of what is wrong and availability of some means of doing something about it. In general, the better our understanding of the cause and usual course of the disease, the more likely it becomes that we will be able to develop some means of coping with it. That, in essence, is the purpose of biomedical research: the constant expansion of knowledge and its translation into applicable preventive or therapeutic methods." The record of several of the institutes makes clear that these broad purposes are accomplished by many measures besides extramural grants. We believe that we have clear evidence that these other measures are not being adequately employed in the attack upon DD.

We are presumptuous. I am sure, in standing outside the federal establishment and discussing by what administrative arrangements these aims for the control of DD can best be served. Perhaps there are ways other than the establishment of a new institute, but maintaining the status quo is not one of them. At this juncture, and viewing the record of leadership and influence of NIH in public health during the last 20 years, we are obliged to conclude that the establishment of a categorical institute is the most effective way it could help secure for our field stronger leadership in research, an increase in trained manpower, better measures of health protection, and fuller public understanding and support.

Dr. HIGHTOWER. I would like to comment on a statement by Dr. Steinfeld. He seemed somewhat vague when you were questioning him with regard to the support for digestive diseases. I think there are many of us in this room who are recipients of research grants from NIH, specifically the National Institute of Arthritis and Metabolic Diseases. They have supported me for over 15 years in my research activity. But last year with a new grant I was asked to reduce the budget 20 percent. This is 20 percent of inflated dollars that were awarded.

I am also informed that only about one-third of research grants, good research grants are approved. We are unable to fund the others.

The CHAIRMAN. Do you mean that two-thirds are not funded at all?

Dr. HIGHTOWER. That is correct. I think this is very material. NIH funded only one-third of the research grants that were found to be beneficial grants, good grants, that had been approved.

The CHAIRMAN. And even those have been reduced in amount; have they not?

Dr. HIGHTOWER. Yes, sir.

The CHAIRMAN. According to that, the research would have been reduced by more than two-thirds. I think this is very valuable information and if you have specific tables, they would be valuable.

Dr. HIGHTOWER. I do not have specific tables.

The CHAIRMAN. Thank you very much for your contribution here representing the American Gastroenterological Association.

Senator DOMINICK. I will not take long, but I do have some things I think may be pointed out.

I understood you to say that less than a half of one percent of the 300,000 physicians are certified specialists in digestive diseases. Is it not true, however, that there are certified specialists in diseases which also involve digestive diseases, such as any of the ones you have been talking about—cirrhosis of the liver, the liver problems or surgeons who are operating on chest and stomach, and things of this kind. Are you including those in the one-half of 1 percent?

Dr. HIGHTOWER. No, sir; I was specifically referring to the number of certified physicians who are certified by the American Board of Medicine in gastroenterology. It is between 700 and 800 physicians of the 300,000 in this country.

Senator DOMINICK. The point I am making, however, is that there are a number of other specialties in which people are certified which deal with the same problems.

Dr. HIGHTOWER. Yes, sir; a certified surgeon by the American Board of Surgery would be qualified to treat peptic ulcer surgically, not medically.

We made a survey of the entire United States and we can only identify less than 2,000 physicians in this country who indicated even an interest in digestive diseases. This included all physicians.

Senator DOMINICK. Being a chronic user of Gelusel myself and having talked to you about this before, I know that all internists treat patients for ulcers, one of the so-called digestive diseases, whether they are certified specialists or not—

Dr. HIGHTOWER. That is right, specialists in internal medicine. Fortunately, we have them because they are taking care of the great bulk

of digestive diseases problems because we don't have enough gastroenterologists.

Senator DOMINICK, I know you are interested in increasing the life span of man. I could detect this from some of your questions to Dr. Steinfeld. I would like to point out, however, that simply adding years to life, although important, we must consider the important aspect of adding life to years. I think this is one of the things that we must conquer in digestive diseases, because of their chronicity and the fact that millions of people suffer from them.

Senator DOMINICK. I have no objection to that at all. What we are really talking about is whether the Institute would be helpful to do this. You think it is and some others do not. Your example of the Soviet Union, with their new institute, of course, it has only been going for less than 2 years, but then you go on and say the technology and facilities available and the methods and therapy are far inferior to those available in the United States even though they have an institute.

Dr. HIGHTOWER. Yes, sir; that is correct.

Senator DOMINICK. Dr. Marston, whom you quote on page 7, is that the Dr. Marston who is head of NIH?

Dr. HIGHTOWER. Yes, sir.

Senator DOMINICK. He opposed the new Institute, did he not?

Dr. HIGHTOWER. Yes, sir. We met with Dr. Marston, Dr. Sherman who is here, Dr. Whedon who is here, last year. Before we decided that we should push for a separate Institute, I discussed this many times with Dr. Whedon, and Dr. Sherman and I have been personal friends for almost 20 years and Dr. Whedon for 10 years.

I think, Senator, the problem Dr. Marston has, he does not want the same amount of money from Congress put into 11 pots instead of 10. He told us privately that he would not oppose it if we could get it funded. We intend to work just as hard to get it funded as we have been working to get it established.

Senator DOMINICK. Thank you, Dr. Hightower. That is all I have.

The CHAIRMAN. I have a question here.

The American male lives an average shorter life than the male citizen of some 18 other countries. Is that correct? I am comparing that to the Western industrialized nations. A male child at birth in America has a shorter life expectancy than a male child in some other Western nation. Is that roughly correct?

Dr. WHEDON. I believe that is correct.

The CHAIRMAN. Isn't it true that 15 years ago we rated much higher than that? There were not 18 nations ahead of us, but while the life expectancy has increased in the United States, it has increased even more rapidly in the modern nations of Western Europe than it has in the United States. In world health statistics, when it comes to longevity, and we have slipped in the last 15 years, have we not?

Dr. WHEDON. I believe that is so.

The CHAIRMAN. We have slipped in our national ratings among the nations of the earth in the last 15 years when it comes to the longevity of the American male. Is that true of females also? We rate about 14th among the nations of the world for females with some 14 other nations that have a female child at birth who will have a

longer life expectancy than in the United States. Is that correct relative to the 13th or 14th or 15th place?

Dr. WHEDON. I think so. Knowing the hardiness of the American female, I doubt she has slipped very much in relation to the females of other nations.

The CHAIRMAN. I think you will note my question dealt mainly with the American males.

I think this is extremely important. In your opinion, would the administrative cost of the proposed institute reduce research and training in digestive diseases, nutrition and training?

Dr. HIGHTOWER. I really don't think this is a pertinent argument. As you have stated it so eloquently previously, we would have to bear some overhead, but if we are not willing to bear any overhead, we are not going to have a program.

The CHAIRMAN. You are not trying to set this up—

Dr. HIGHTOWER. I do accept the fact that there is overhead. We would save more tax dollars if we could concentrate our efforts in one area instead of having them fragmented and duplicating of overhead services in so many institutes and bureaus and divisions. I just can't conceive in an organizational structure that would not be more effective and more efficient if it were under one central control.

The CHAIRMAN. While this hearing has been going on, I have just telephoned the Bureau of Labor Statistics to see how many man-days were lost due to strikes a year, how many man-days were lost due to industrial injuries. We have the latest data for 1969. There were 42,869 man-days lost due to strikes. In 1968, there were 245 million man-days lost due to industrial injuries. So, the number of man-days lost is minuscule contrasted with that due to injuries; but those due to industrial injuries is one-third less than the 300 million lost due to digestive tract disabilities or diseases.

Do you feel the current level of training for digestive disease and nutrition is adequate or inadequate?

Dr. HIGHTOWER. Senator, I would have to disagree strongly with Dr. Fordtran when he said they were adequate. I think the magnitude of the problem, if you look at that and look at what we are expending in dollars to resolve the problem, they are not about to become where one equates one with the other. The fact that we have proved research grants that cannot be funded indicates that there is inadequate support. There are good research projects being proposed that cannot be funded. One of the reasons is that the Administration at the Arthritis and Metabolic Institute is so fair; they have 11 categories of specialties that they must fund, and they have certainly been fair with digestive diseases and nutrition. We have not been discriminated against. The problem is, the funds this Institute gets must be divided among some 10 other disciplines and, frankly, there is not enough to support digestive diseases and nutritional problems as they should be if you are looking at it in terms of the magnitude of the problem.

The CHAIRMAN. Thank you very much for this very important contribution to this hearing, Dr. Hightower.

The next witness is Dr. Hans Popper, professor of medicine, Mt. Sinai Medical School, New York City, N.Y.

STATEMENT OF HANS POPPER, M.D., PH. D., PROFESSOR OF PATHOLOGY, MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK, N.Y.

Dr. POPPER. My name is Hans Popper, M.D., of the University of Vienna and Ph. D. of the University of Illinois, with honorary doctor's degrees of the Universities of Leuven, Vienna and Bologna. I am dean of academic affairs and given foundation professor and chairman of the department of pathology of the Mount Sinai School of Medicine in New York.

I am a fellow of the American Academy of Arts and Sciences. I am past president of the American Association for the Study of Liver Diseases and of the International Association for the Study of the Liver, at present I am vice President of the Digestive Disease Foundation. I am basically a pathologist with primary interest in liver diseases.

While my testimony is intended to support the creation of a National Institute of Digestive Diseases and Nutrition, I will restrict my remarks to one group of diseases, the diseases of the liver, as an example of a digestive and nutritional disease with an established social impact on the population of this country. I wish first to present some major aspects of this impact. Cirrhosis of the liver has been stated to be the fourth or fifth cause of death in patients over 40 years of age. Moreover, the death rate from cirrhosis has risen in the last decade more than that from other diseases, most of which have declined during this period (exhibit 1). The increase of alcoholic cirrhosis has been particularly great in the black population, especially in black women, in whom the disease occurs earlier and is more severe.

Alcoholic liver injury is the most important cause of cirrhosis in this country. The total cost to society of cirrhosis in alcoholics has been estimated to exceed \$2 billion a year in this country. While the social and behavioral aspects of alcoholism are of major interest to governmental and other agencies concerned with the problem of alcoholism, the consequences in the liver resulting from this alcoholism have received far less attention. Nevertheless, death from cirrhosis is a far more frequent consequence of alcoholism than is death from accidents or mental disorders (exhibit 2).

This does not take into consideration the long-term social cost of protracted disability and hospitalization. Evidence has been obtained that alcoholic hepatitis and cirrhosis are curable diseases if intake of alcohol is discontinued. A significant number of patients with alcoholic liver disease from all strata of our society is first seen by physicians without the patients having preceding significant personal problems requiring psychiatric attention or contact with the police. Alcoholism and alcoholic liver injury are diseases of an affluent society; however involving more so the lower economic strata. These diseases are particularly prevalent in the poor, in whom the consequences in the liver are aggravated by nutritional deficiencies and other sanitary hazards like infections.

The second cause of cirrhosis, the incidence of which is not established yet, is viral hepatitis. The virus has not been identified, al-

though the recent discovery of a blood factor, the hepatitis-associated or Australia antigen, in some patients with acute liver disease is a promising lead for at least some forms of this disease. The epidemiology of this disorder is actively being studied in this and in other countries. Nevertheless, the size of the problem is today not known. This is significant because viral hepatitis causes cirrhosis and acute fatal hepatic failure, both of which might be preventable by the development of a vaccine. Viral hepatitis is increasing in frequency because of its common occurrence in drug addicts in all strata of society. This problem has reached almost epidemic size in the disadvantaged.

Liver disease, moreover, has become a sometimes dangerous and even fatal side effect of the administration of potent and useful drugs and is a limiting factor in the use of many medications.

I also want to point briefly to another disease of the biliary system, namely, gallstone disease. It affects about 15 million Americans, occurs in 15 percent of all persons age 55 to 69, and produces medical care expenses in excess of \$500 million annually.

Despite this social importance of liver disease, patient care facilities and manpower trained and interested in prevention and management of these diseases are limited in the United States. By contrast, interest in liver disease is greater in the Latin countries, with their well-known preoccupation with the "sick liver." The result in the United States is limited facilities for hospitalization, particularly for the patient with alcoholic cirrhosis and for the disadvantaged group. It is the impression of all of us interested in liver disease that mortality from acute hepatic failure could be reduced.

This means that this disorder, which may be caused by hepatitis or an adverse drug reaction, is transient and potentially reversible. Complete cure may depend on the knowledge and interest of the attending physician. In the case of cirrhosis, restoration of a socially and emotionally satisfactory life is also possible. The lack of medical manpower is in part explained by the fact that many, even distinguished, institutions have no, or few, experts in liver disease, and that the teaching of liver disease including alcoholic liver injury in the curriculum varies in the medical schools throughout the country.

The various National Institutes of Health, especially the Institute for Arthritis and Metabolic Diseases, have provided large amounts of money for research in the liver, and we want to express our deep gratitude at this point for this excellent support. However, the bulk of this money has been devoted to normal and abnormal biology of the liver, an excellent model in which to study many biological processes. Relatively little money, however, has been awarded for research in liver disease, particularly its management, and this support is fragmented by being spread throughout several institutes.

The National Institute for Arthritis and Metabolic Diseases is concerned with metabolic aspects. The study of infectious hepatitis is supported by the National Institute for Infectious Diseases and Allergy and by the Research and Development Command of the U.S. Army. The study of alcoholic liver disease is mostly supported by the National Institute of Mental Health. The toxicologic aspects are

covered by the National Institute for General Medical Sciences and the Environmental Health Service. Support also comes from the National Cancer Institute, the National Institute of Child Health and Human Development, and the National Heart Institute.

Extramural support by, and intramural research in, the proposed National Institute for Digestive Diseases and Nutrition may go a long way to consolidate these efforts and may direct them toward better delivery of health care for patients with liver disease. Such an institute, which exerts leadership in a field by initiation and organization of coordinated research in basic science, in clinical science and in improved health care, and also in demonstration of methods of management which this bill provides, will lend prestige to the field.

Students, young physicians and paramedical personnel may be attracted to digestive disease, an area now less popular than fields given prominence by the existence of a recognized national effort. Since public information and education are key devices in prevention of these diseases, a governmental effort will be of great significance.

Categorical institutes are considered by greater experts than myself as useful devices to combat disease, educate physicians and the lay public, and deliver health care. Therefore, an Institute for Digestive Diseases and Nutrition is considered an important tool by my colleagues and myself. Specifically, all members of the board of directors of the Digestive Disease Foundation endorsed this proposal yesterday.

Moreover, the Steering Committee of the American Association for the Study of Liver Disease formally supports this proposal and this committee is already on record on the social impact in liver disease in an article published in the *New England Journal of Medicine*, an article which Senator Javits previously read into the Congressional Record (exhibit 3).

Thank you for permitting me to make this statement.

The CHAIRMAN. Thank you, Dr. Popper.

Dr. Popper, is hepatitis more related to digestive diseases than to other categories?

Dr. POPPER. Hepatitis is considered a disease of the liver and therefore a digestive disease.

The CHAIRMAN. In one reference on page 3, you mention "hepatitis-associated or Australia antigen, in some patients with acute liver disease is a promising lead for at least some forms of this disease." What is the origin of the "Australia"? Is that where it was discovered?

Dr. POPPER. The antigen was first found in the serum of an Australian aborigine, incidentally, and from this incidental discovery, the name Australia arises. It was discovered in this country by Dr. Blumberg working in Philadelphia.

The CHAIRMAN. Thank you very much for your contribution here. I might have had some questions but time will not allow them. Thank you.

Our next witness is Dr. Carroll M. Leevy, professor of medicine, New Jersey College of Medicine and Dentistry, Newark, N.J.

Dr. Leevy, you may proceed in your own way.

STATEMENT OF CARROLL M. LEEVY, M.D., PROFESSOR OF MEDICINE, COLLEGE OF MEDICINE, SETON HALL UNIVERSITY, JERSEY CITY, N.J.

Dr. LEEVY. Mr. Chairman and members of the subcommittee, my name is Carroll M. Leevy, M.D., of the University of Michigan Medical School. I am professor of medicine and director of the Division of Hepatic Metabolism and Nutrition of the New Jersey College of Medicine and Dentistry in Newark. I am certified by the American Board of International Medicine, and Clinic Nutrition.

I am president of the International Association for the Study of the Liver, a past president of the American Association for Study of Liver Disease, a member of the American Society of Clinical Nutrition, the American Institute of Nutrition and a member of the editorial board of the American Journal of Clinical Nutrition. I am engaged in teaching, research and patient care in the field of liver disease, and clinical nutrition. At the present time nine young physicians are being trained in my unit as hepatologists and nutritionists.

I wish to testify in support of bill S. 3063 to establish an Institute of Digestive Diseases and Nutrition. Much knowledge has been acquired, but more information is urgently needed so that we can detect digestive and liver disease with greater facility in its early phase and prevent crippling end stage illness. Digestive and liver disease constitute the single most frequent cause of hospitalization in the United States. The lack of manpower to care for these patients is stressed in a recent article by Dr. Malcolm Tyor of Duke University (exhibit 1) which is attached to my statement.

This is illustrated by the attached map (exhibit 2) which shows four States in the Union have no physicians trained or expressing a special interest in digestive diseases and eight additional States have only one or two. It is therefore essential that we focus attention and effort on control of digestive diseases equal to that currently given to heart disease, cancer, and mental disease. If this is done, we can interrupt the alarming increase in morbidity and mortality from digestive and liver disease.

This thesis is supported by studies of both ghetto and affluent populations where there has been a two to threefold increase in incidents of liver disease largely due to escalation of causative factors without concomitant increase in trained personnel or facilities for proper diagnosis and treatment. An Institute of Digestive Diseases and Nutrition as described in the proposed bill is needed to train more specialists in digestive and liver disease and to elucidate better methods to prevent and treat this group of diseases.

Development of a cohesive, broad, nationally supported research and educational program on various aspects of intestinal, pancreatic and liver disease would permit us to significantly reduce the morbidity and mortality and associated economic loss from these disorders in our country. Particularly attractive is the provision in the bill to foster demonstrations, to update information by practicing physicians on the cause, prevention and methods of diagnosis and treatment of

digestive diseases and malnutrition while relaying to practitioners information on the application of new research findings.

The recent public acknowledgement of the high incidence of under-nutrition in many sections of our country has led to now Federal emphasis and support for nutrition which is much appreciated. This was reviewed in the September 1969 issue of *Today's Health*, an AMA publication for the laity (exhibit 3). It was pointed out that 35 to 55 percent of a representative segment of Americans studied in nutritional surveys suffered from one or more nutrient deficiencies. Our own studies in New Jersey indicate that over 80 percent of randomly selected hospitalized, indigent patients have clinical or laboratory evidence of vitamin deficiency.

The current programs administered by the Institute of Child Health and Human Development, the National Heart Institute, the Institute for Mental Health and other Federal agencies have made significant impact on further understanding the causes and methods needed to control both under and overnutrition. Clinical nutritionists usually focus attention primarily on nutritional aspects of surgery, obstetrics, medicine, pediatrics, and various subspecialties such as heart, kidney, or liver disease. This is appropriate since it is necessary to develop ways and means to improve nutrition in the newborn, the growing child, the expectant mother, the aged and the sick and injured. Thus, all patients with liver disease require additional nutrients to repair cellular damage.

The discovery of the importance of folic acid for liver repair represents a major breakthrough. We need additional practical advances of this nature. This requires increased support for basic and clinical research, more trained professional and paramedical personnel, and expansion of facilities to solve the problems related to food availability and composition, as well as nutrient intake, absorption, and utilization in health and disease. It is necessary to coordinate research, education, and health care activities in nutrition which presently exists in various agencies without curtailing any interest or need. This should occur through the establishment of an Institute of Digestive Diseases and Nutrition which would simultaneously insure continuity of purpose and objective.

Much progress has been made in improving health of the average American because of the various programs of the National Institutes of Health. Priorities emphasized in the past were most appropriate. The rapid, recent increase in environment imposed medical illness makes it now necessary to reorient priorities, to permit solution of the increased problems of digestive disease and malnutrition. A formally organized institute especially devoted to research, education and improvement in health care as described in bill S. 3063 is essential for this purpose. A national program of this nature will begin to fulfill our long sought objective of providing adequate health care for all Americans regardless of their area of residence.

Thank you for the opportunity to make this statement.

The CHAIRMAN. We will place in the record at this point the exhibits which are attached to your statement.

(The exhibits referred to follow :)

EXHIBIT 1

The Gastroenterologist 'Gap'

MALCOLM P. TYOR *Duke University*

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The Gastroenterologist 'Gap'

MALCOLM P. TYOR *Duke University*

Since digestive disorders produce more hospitalizations than any other disease category, a great deal of gastroenterology is being practiced – but not by gastroenterologists. The result is that patients do not benefit adequately from new knowledge gained in recent years. A plea is made for more physicians to take the opportunity today's gastroenterology provides for blending scientific research with scientific practice.

Lest there be a shortage of gaps, I wish to nominate and puzzle over yet another one: the gastroenterologist gap. Certainly the gap exists; the need for more gastroenterologists is suggested by all we know or suspect about the incidence of gastroenterologic disorders. The National Center for Health Statistics reports that digestive diseases affect 12,800,000 Americans and are *the* major source of hospital admissions, requiring more than any other disease category. They appear to comprise the only group of diseases that is rising in morbidity and mortality. In a study of some 500,000 patients referred annually for diagnosis and treatment to a group of major medical centers, digestive diseases accounted for 16%, the largest single group of patients. The number of patients hospitalized for digestive diseases in such centers is 1.5 to 3 times that for cardiovascular disease and 4 times that for blood disorders.

Nevertheless, two to three times more medical students elect cardiac or hematologic specialties than gastroenterology, in a rather bewildering inverse ratio to the need and in spite of the fact that jobs are begging and a trained gastroenterologist can practically take his pick of appointments even before his fellowship ends.

Admittedly, gastroenterology, being short on glamor, has had a bad press. A disordered digestion tugs the public heartstrings neither in the poignancy of its manifestations nor in the pathos of the population group mainly affected. Imagine the dilemma of an artist asked to illustrate a poster making a sentimental appeal for funds for gastroenterologic research! The growl of a stomach can scarcely compete for TV prime time with the thump of a heart, even though, significantly, it does far better in commercials. Digestive disorders are generally considered more uncomfortable and unattractive than life-threatening, and the paraphernalia of gastroenterologic diagnosis and treatment offends the usual oral and anal cultural biases of polite society. Medical men, although they should know

better, are not entirely swayed by such considerations, especially in their earlier and more romantic years.

But if there is no tug at the heartstrings, the nation's purse strings are mightily yanked. The loss of workdays and dollars reflected by the morbidity data given above is incalculably vast. Digestive diseases incapacitate more fighting men in our armed forces than any other cause. Taking just the incidence of gallstones, some 10% to 12% of the Medicare population is involved. About \$300 million is spent each year for cholecystectomies alone.

With this kind of patient load, a great deal of gastroenterology is of course practiced, but not by gastroenterologists. And that is the nub of the problem. The larger proportion of patients with digestive disorders are being "dealt out" of the most effective and up-to-date methods of diagnosis and treatment because of the shortage of professionals trained in such methods. The gap between the level of "gastroenterology" practiced by the general practitioner and internist and that practiced by a trained gastroenterologist is wide and is getting wider. New procedures, requiring expertise and special equipment, have entered the field. Old procedures have been completely reevaluated and altered or abandoned. As a result, the modern practice of gastroenterology under optimal conditions is a great deal more objective and scientific than most medical students (whose exposure to gastroenterology is ordinarily shallow) would suspect, or than most physicians currently practice.

I want to highlight this changing scene in gastroenterology for a number of good reasons. It is interesting. It mirrors a promise and a crisis in medicine generally. But the most candid reason is that the field is in sore need of recruits.

The most critical changes occurred in the last 10 to 15 years. They were brought about because a new breed of physician-scientist entered the field, simultaneously with the greater availability of research funds, and infused the fresh blood of other disciplines into the clinical theater. These were research physicians with special talent and training in basic science, in morphology, physiology, bio-

Dr. Tyor is professor of medicine and chief of the division of gastroenterology, Duke University Medical Center.

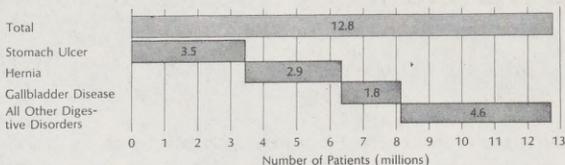
chemistry. In applying the methods of their special training to the field of gastroenterology, they sought more verifiable and objective data concerning digestive disorders. We at last had an era of professionalism in clinical research, which had formerly been conducted mainly by clinicians untrained and untried in the laboratory.

It is characteristic of the new professionals that they did not permit either their research or their findings to stagnate in the laboratory. From the beginning their work had a strong clinical orientation and tie. Those patients, therefore, fortunate enough to have access to these centers of research received a level of care considerably above that available to those with less geographic advantage. Unfortunately, this latter situation still largely prevails; the methods and skills pioneered by these investigators have not been broadly disseminated into gastroenterologic practice but remain available mainly to patients within the orbit of the research centers. The chief reason for this lies in the continuing shortage of trained manpower.

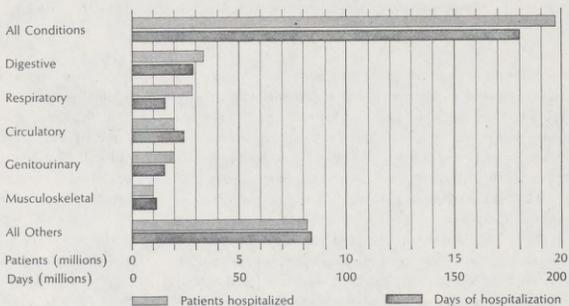
Consider the impact of morphology on the field. In the past, morphologic techniques were for the most part relegated to the anatomy laboratory or the pathology laboratory, concerned mainly with posthumous considerations and tissue, and not at all related to the clinical situation. While the precise morphologic techniques of mounting and analyzing tissue specimens furnished much knowledge concerning the structure of health and the demolition of disease, the diagnostic application was regrettably *ex post facto*. If one could only conduct the same kind of microscopic examination and analysis on the digestive tissues of living patients, how much could be learned about GI tract disease!

The means of acquiring such tissue from living patients was made possible by the development of the small bowel biopsy tube, in England by Margot Shiner and in this country by Cyrus Rubin (*HOSPITAL PRACTICE*, December 1968). A tiny, guillotine-type knife device at the end of a flexible tube, activated either by air or a trip wire, can either be swallowed or inserted caudally (depending on whether the diagnostician is interested in stomach, small intestine, or colon),

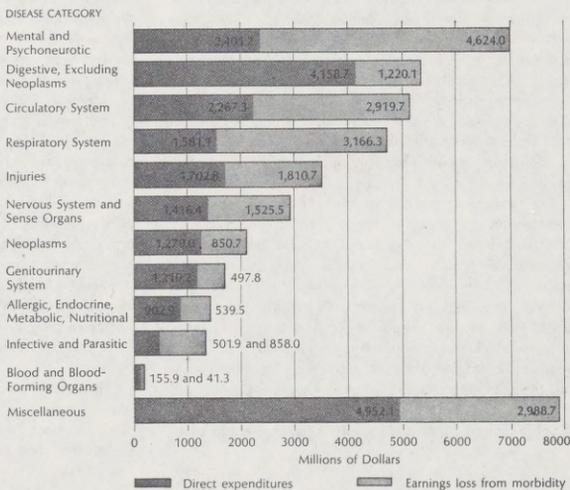
Prevalence, Hospitalization, and Costs of Digestive and Other Diseases



Graphs are based on data presented at national conference on digestive diseases held in 1967 at Bethesda. Prevalence figure broken down above is for 1963 through 1965.



In number of both patients and days, digestive diseases outranked any other single category of conditions as the primary cause of hospitalization in the U.S. during 1964.



When economic costs of illness are defined in terms of direct expenditures plus earnings lost by not working, digestive diseases ranked second in 1963 only to mental illness.

Tests Which Should Be Used More Widely in
Diagnosis of Gastroenterological Disease

TEST	INDICATION*
<i>Gastric cytology</i>	Pernicious anemia; gastric ulcer; suspected gastric cancer
<i>Gastric mucosal biopsy</i>	Pernicious anemia; suspected gastritis
<i>Fiber-gastroscopy with photography</i>	Gastric ulcer; suspected gastritis; hemorrhage
<i>Fiber-esophagoscopy</i>	Suspected portal hypertension; hemorrhage; suspected esophagitis with or without hiatal hernia (by x-ray)
<i>Fluorescein tube</i>	Hemorrhage
<i>Percutaneous liver biopsy</i>	Differential diagnosis of jaundice, e.g., viral hepatitis, drug hepatitis, extrahepatic obstruction; suspected infiltrative disease, e.g., cancer, granuloma; identification of stage of disease, e.g., alcoholic liver disease, chronic active hepatitis (subacute necrosis); portal hypertension
<i>Splenic-portography and pulp pressure</i>	Suspected portal hypertension
<i>Arteriography</i>	Hemorrhage; suspected portal hypertension; suspected pancreatic cancer; suspected pancreatic islet cell adenoma
<i>Secretin with and without cytology</i>	Suspected pancreatitis; suspected pancreatic cancer; cystic fibrosis
<i>Fat balance</i>	Suspected malabsorption of any origin, e.g., chronic pancreatic disease, small-intestine disease, subtotal gastrectomy
<i>Small bowel biopsy</i>	Suspected malabsorption
<i>Schilling</i>	Suspected malabsorption, e.g., ileal disorders, "blind-loop" syndrome; pernicious anemia
<i>Rectal biopsy</i>	Diarrhea, e.g., ulcerative colitis, granulomatous colitis, amebic colitis; suspected amyloidosis; melanosis coli; suspected Hirschsprung's disease
<i>Stool collection (24 hr) for weight and electrolytes</i>	Subacute or chronic diarrhea
<i>Presence of phenolphthalein and its conjugates in urine</i>	Subacute or chronic diarrhea (suspected laxative abuse)
<i>Microscopic examination of freshly collected feces</i>	Differentiation of purulent diarrhea, e.g., shigellosis, salmonellosis, ulcerative colitis; amebiasis from non-purulent diarrhea, e.g., viral, "irritable bowel," laxative abuse

* not meant to be all inclusive

thus obtaining for analysis a small piece of the lumen, from 2 to 10 mg wet weight. The procedure is painless and tolerable with only minor discomfort when performed by skilled hands. The tissue sample is fixed, sectioned, and examined under gross dissecting microscopy and light and electron microscopy. With good morphologic training and a keen eye for structure, the well-trained gastroenterologist has been able to differentiate among a number of digestive disorders, establish the method as the definitive objective diagnostic procedure for these diseases, and evaluate the course of therapy.

Nor is the procedure applicable only in arcane diseases. The number of disorders that may be diagnosed or for which useful information may be obtained by mucosal biopsy of these tissues adds up to 5 to 10 a week in almost any physician's practice, provided he recognize that the problem is there.

The availability of this procedure to patients depends on the availability of one vital factor that happens to be in short supply: skilled personnel. There is no aspect of the technique that cannot be taught, but it does require someone willing to learn and to take the time. While per rectal biopsies are obtained with no more difficulty than taking a temperature, small bowel biopsies are something else. Peroral biopsies require some skill and experience in getting patients to swallow the device and in maneuvering it through the stomach and the pyloric sphincter. Fluoroscopic observation with image intensification equipment providing minimal radiation is essential not only to facilitate guidance of the tube but also to ensure that the sample will be taken from the precise site.

Getting the sample is but the first part of the story. The biopsy material must be properly and promptly set, stained, and serially sectioned. Technique is all-important here; if the sample is not properly oriented and if the cuts are not true and sharp, the needed information will either be lacking or distorted. Lastly, the slides must be interpreted by someone with enough experience to provide a comparative frame of reference.

There simply are no commercial or hospital laboratories set up to perform such procedures. Even if there were,

it is doubtful that the gastroenterologist could depend on them for consistency. So important is the consistency and precision of each phase—site of sample, preparation, interpretation—that it is essential that the entire procedure be performed either by the gastroenterologist (who would be the only one interested in developing the facility and the skills) or by gastroenterologic trainees under his close direction.

None of this implies that there is anything insurmountably difficult about any phase of the procedure. In the main, simple but precise operations are involved and most of them, except for interpretation, might possibly be accomplished by technicians. The essential ingredients are the gastroenterologic-morphologic training, orientation, and interest that tie all phases together.

Similar considerations accompany the question of liver biopsy, an older surgical procedure but one still used more sparingly than it should be. The liver tissue is obtained percutaneously at the bedside in just a bit over five minutes, and it can be done by a wide variety of medical personnel. The bottleneck, however, is in the special methods of preparation and staining and chiefly in the ability to interpret the results. There are few morphologist-gastroenterologists capable of satisfactorily analyzing these liver specimens, a shortage that assumes critical dimensions outside the teaching medical centers. And yet I suggest there is little question that any other liver test or diagnostic study of hepatic function even approaches the diagnostic potential of liver biopsy.

The biochemical approach is much the same story with a different cast of characters. At the crudest level, there simply is no substitute in the practice of gastroenterology for such a simple measurement as the chemical analysis of feces for fat, yet the difficulty of getting this done properly causes serious delay and even error in diagnosing a wide variety of malabsorptive disorders. The difficulty is related not to any rare skills or difficult procedures but rather to the distaste of the average, unmotivated, laboratory technician and of not a few physicians to handle fecal matter, especially in the large quantities required for this type of determination. There is a tendency

to rely too heavily on the many simple screening tests that are available but that miss from 20% to 50% of steatorrheic patients. Thus, those patients have been lucky indeed who have had access to a no-nonsense gastroenterologist with no hesitation about collecting stools and seeing to their proper preparation for analysis.

It is left to the gastroenterologist to initiate and become competent in this as well as other biochemical assays simply because nobody else is interested or appreciates their importance. The well-trained gastroenterologist, when running a test for xylose absorption, will measure specifically for pentose when presented with a diabetic patient with suspected sprue. In most instances, to make sure it is done correctly, he may have to do it himself. Rarely, he may need a test such as that for blood ammonia, but when he does need it he had better be able to do it himself, for it is generally not available in most commercial and hospital laboratories. Another procedure that, although rarely needed, must

nonetheless be available is the biochemical assay of intestinal mucosa biopsies for specific enzymes, lactase, and other disaccharidases. Such enzymatic deficiencies can be diagnosed in no other way. Indeed, such tests arose only because there were gastroenterologists bringing a morphologic and biochemical method to the field, and they or others trained by them will be the only ones ready and able to do this test.

Some tests, like that of biopsy materials for enzymes, are obviously so specialized that it may not be essential for every gastroenterologist to develop facilities for them. However, it is important for patients with enzymatic defects to have access to a physician who will recognize the possibility of such a defect and send the patient (or, better, a part of the patient) to the right source for assay. This physician is most likely to be a gastroenterologist who can obtain the biopsy himself.

A great deal of movement has also occurred in the radiologic wing of the gastroenterologic diagnostic arsenal.

Here, however, the contributions were not so much those of gastroenterologists with a special background, as in the morphologic and biochemical advances, but rather those of radiologists with a special gastroenterologic interest. The result has been further clarifications of oral cholecystography and the interpretation of barium studies. Also extremely helpful in the diagnosis of a number of occult gastrointestinal disorders has been the application of angiographic techniques. Radioisotopic scanning techniques have aided the diagnosis of liver ailments. But again, the availability of many of these procedures is contingent on the patient's good or bad geographic fortune with regard to the proximity of radiologists having these special interests and of gastroenterologists who call upon them. A greater

Departments of Medicine in U.S. Medical Schools (1966)

SPECIALTY	TOTAL FULL-TIME STAFF	MEAN	RANGE
Gastroenterology	192	2.9	0-12
Cardiology	395	6.0	1-20
Hematology	242	3.6	1-10

number of gastroenterologists, aware of these techniques, creating a demand for and developing an interdisciplinary interest in them, would help.

The new science at work in gastroenterology has shown up some errors. For example, thorough physiologic reevaluation of the long-standing procedure dubbed gastric analysis has shown it to be consistently overused, mismanaged, and misinterpreted. Not only was the demonstration of the presence or absence of free acid without significance for many of the cases under investigation, but in most cases the samples of gastric juice were taken randomly without reference to the all-important question of site and then titrated with an indicator, Topfer's reagent, which has no physiologic meaning. We have learned that the tube must be positioned correctly under fluoroscopic image intensification, that the aspirated material should then be evaluated with a pH

meter, and that the determinations are valueless in most instances unless compared with a sufficiently long baseline of similar tests before and after the administration of a secretagogue. Further, we know that the test is truly indicative only for a few disorders; it chiefly documents the presence of pernicious anemia with histamine-fast achlorhydria, differentiates between gastric ulcer and gastric cancer, distinguishes the patient with Zollinger-Ellison syndrome, and determines residual ability to secrete acid in patients who have had surgery of the stomach or vagotomy.

It is possible that among internists there exists a fairly high level of knowledge about new gastroenterologic methods, although it would be a mistake to take such information for granted. It is possible that many internists may even have been associated with one or another of these morphologic or biochemical tests during their residencies. For the general practitioner, however, it is still unfortunately possible to go through medical school and the obligatory internship without any exposure at all to these procedures. In my own medical school education our only experience with passing a tube into the stomach was such as to permanently bias most graduates against the procedure and indeed against gastroenterology itself; we experimented on one another and ourselves under the inexperienced direction of a nongastroenterologist who had himself last done the procedure in medical school.

The educational obligation, I feel, lies with gastroenterologists rather than with the institutions of medical school and hospital. It is up to us in gastroenterology to inform the physician population about what is available, to recruit more gastroenterologists, and to correct some of the omissions in medical education.

But the educational obligation of the gastroenterologist is most urgent on himself and his specialty. Radiologic, morphologic, and biochemical interpretation must be based on the patient as a whole and the only person who can put all the pieces together is the knowledgeable gastroenterologist. This requires continual discourse and mutual enrichment with the radiologist, the pathologist, and the bio-

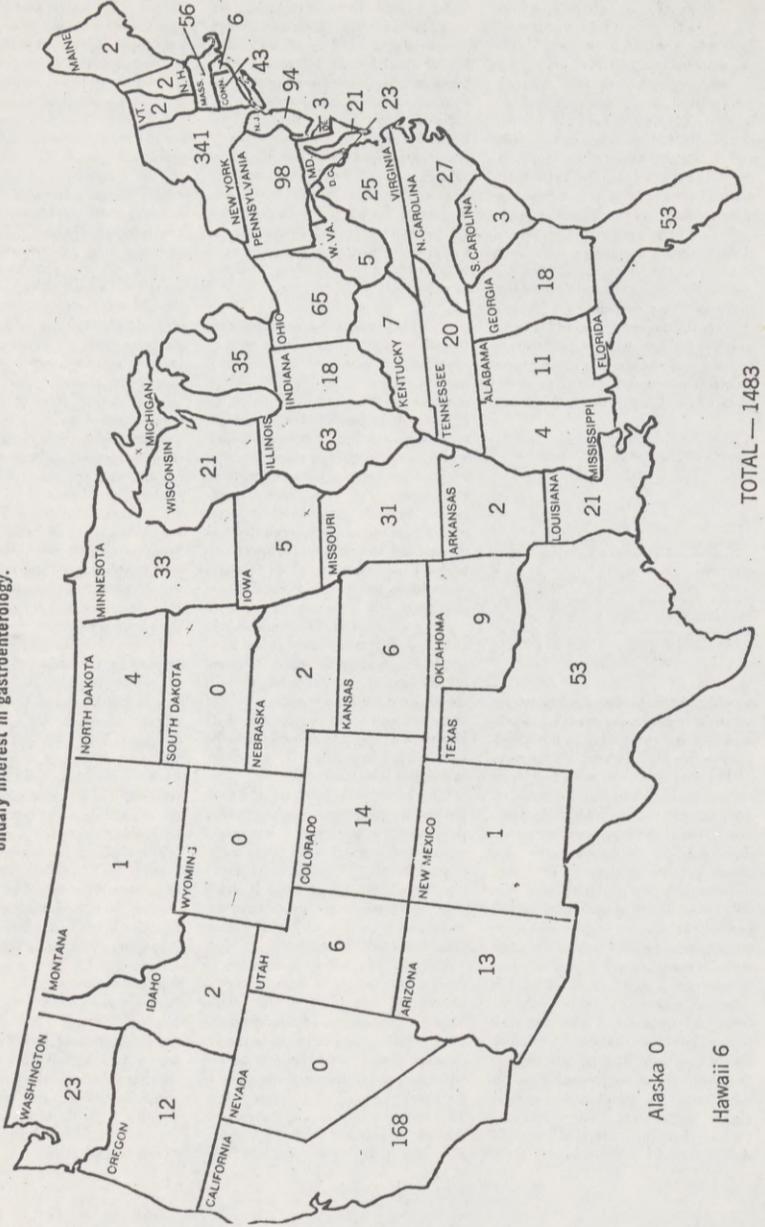
chemist — not only to understand the contributions these other disciplines have made to his field but also to seed and fertilize new developments.

Gastroenterologic education is extremely important at yet another level — that of paramedical personnel. So far it has been necessary for the gastroenterologist to be his own mechanic, technician, and lab worker, mostly because the skills have been considered too specialized to entrust to generalized technicians. But there is no reason why gastroenterologic technicians and physician assistants cannot be developed. Most importantly, there is a large manpower pool available. With training and continuing guidance, such personnel can take and prepare biopsies and perform many diagnostic laboratory determinations. With such help, freed of the time-consuming aspects of these tests, the gastroenterologist could multiply his patient load, spending more time analyzing and comparing the results his technicians put before him. Not only would this help the manpower gap but by spreading available skills over a broader area, it might induce more gastroenterologists to make greater use of these procedures, which they previously resisted because they took time from patients.

If the gastroenterologist gap was created by the influx of a new breed of researcher, the possibility exists that it can be closed by a new breed of practitioner. Today's physician understands better than his predecessors that it is no longer necessary to fall back so much on the unknown. His training has included greater emphasis on hard data and quantification. If he has been through a good medical school and an up-to-date house officership and training program, the chances are good that at one time or another he has been identified with a laboratory and is comfortable with the language, goals, and ways of research. Unquestionably he has also been influenced by the fact that the old gap between researcher and practitioner has been closing; it is no longer a wry truth that the research physician never sees a patient and does not practice medicine. Indeed, the field of gastroenterology offers some unique opportunities for blending scientific research with scientific practice. And that is an invitation. □

EXHIBIT 2

Figure 1
Distribution by states of physicians indicating a primary or secondary interest in gastroenterology.



[From Today's Health, September 1969]

[EXHIBIT 3]

FINALLY, FACTS ON MALNUTRITION IN THE UNITED STATES

TO FIND OUT IF THERE IS WIDESPREAD HUNGER IN THE LAND, HEW INITIATED A SURVEY. THE SURVEY DIRECTOR ANALYZES FINDINGS IN THIS EXCLUSIVE INTERVIEW—FIRST IN A "TODAY'S HEALTH" SERIES ON MALNUTRITION IN THE UNITED STATES

(By F. Glen Loyd)

Hunger and malnutrition, we are told with mounting stridency, are as American as apple pie and ice cream. Are they?

The Citizens' Board of Inquiry Into Hunger and Malnutrition—a private group—started dishing out the bad news April 22, 1968, in its report "Hunger U.S.A." It was estimated in the report that 10 million Americans are underfed or malnourished.

One month later, a CBS television documentary, "Hunger in America," backed the Board's report, and in the words of one publication, "brought the many faces of starvation into homes all over the nation."

Although the accuracy of both reports was (and still is) sharply challenged by several government agencies, the Senate chartered the Select Committee on Nutrition and Human Needs. Last March, chairman George McGovern led committee members to southern Florida to tour villages of migrant farm workers. "We have seen diet and living conditions that one might expect to find in Asia, not in America," said Senator McGovern afterwards. "Most cattle and hogs in America are better fed . . ."

There was little doubt now that the problem existed, but were 10 million Americans actually underfed or malnourished? There are no hard facts to determine this, Harvard's Frederick Stare—an M.D. and a top nutrition authority—testified before the House Committee on Education and Labor. "'Hunger U.S.A.' is . . . an attention-attracting document which I assume it was intended to be. It is, however, based largely on testimony and opinion and not on facts as to the extent and severity of malnutrition . . ."

The report's principal contribution, said Doctor Stare is "emphasis on the absence of knowledge on . . . malnutrition and hunger in this country."

The first comprehensive survey to assess the nutritional status of the U.S. population was initiated in June of 1968 by the Department of Health, Education, and Welfare (HEW). Organizers and directors of the National Nutrition Survey are Arnold E. Schaefer, Ph.D., chief of the HEW Nutrition Program and his deputy, Ogden C. Johnson, Ph.D. With field work completed in many of the 10 states in the study—Texas, Louisiana, Kentucky, Washington, Michigan, New York, West Virginia, California, South Carolina, and Massachusetts—Doctor Schaefer analyzes findings to date in the following interview with TODAY'S HEALTH.

Doctor Schaefer, how much malnutrition have you found in the states you have studied so far?

We've found more malnutrition than I ever expected to see in a society described as the best fed in the world. If our findings are repeated in subsequent studies—as we expect they will—then there are very many people in the United States who are seriously malnourished.

Before going any further, I should qualify this answer. Keep in mind that we are now studying a random sample from those areas where some 75 to 80 percent of the families are either in poverty or are awfully close to it. Over 55 percent of our sample families have an income of less than \$3000 a year. Family income ranges from \$185 a year to \$43,000—some people in our sample are not poor but live in poor areas. If our sampling structure is right, our study will be representative of a quarter of the U.S. population.

- Fifteen percent of all children studied showed evidence of growth retardation. Children between one and three years were considerably below the average height of U.S. children the same age. Some children were retarded by two years at age six. Average growth retardation was nine months. These children run a risk of never catching up in physical development. And they may not develop mentally to their maximum capacity.

- One of the biggest shockers of our findings is that 35 to 55 percent of the total number of people studied suffered from one or more nutrient deficiencies.

- One-third of the children studied had anemia (shortage of red blood cells and hemoglobin) to a degree that a pediatrician would prescribe therapy right away. Two out of five were severely anemic. About 13 percent of the entire population studied—children and adults—had anemia.

- One-third of all children studied suffered from apparent vitamin A deficiency as measured by tissue concentrations of the vitamin. Ninety-two percent of children in the preschool Head Start program at one school were found to have greater vitamin A deficiencies than found in children blind because of the deficiency.

- Four percent of the children up to six years of age showed evidence of vitamin D deficiency—rickets. Some of the symptoms are bowed legs, enlarged joints, and beading of the ribs—you can just feel knots on the ribs.

- Four to five percent of the subjects exhibited potbelly, symptomatic of protein and calorie malnutrition.

- Five percent of all people examined had an enlarged thyroid gland (goiter). Goiter is usually due to low iodine intake. The problem was thought to be eradicated 35 years ago. But consumption of iodized salt in America is going down.

Have you found any hungry or starving people yet?

Quantity of food in most of these families is all right—it's the quality.

I've seen mass starvation from famine in foreign countries. We haven't found this type of starvation. But we found seven children who were suffering from severe calorie and protein starvation. These children weren't fed enough. One child—18 months old—weighed only 11 pounds. Most babies weigh this much when they're three months old, not 18 months. In each of the seven cases, the mother didn't realize the child was ill fed and would look for some other reason to explain his condition. In one case, the parents didn't know that the child was really suffering. The baby didn't cry. He was just lackadaisical. Perhaps he was a little sickly, the parents thought, but he would grow out of it. They didn't realize they had to feed him properly. We didn't expect to find such conditions in the United States.

Are 10 million Americans malnourished?

If our figures hold, they will suggest that there may be 10 million such Americans in the lower quarter of the population. The other three-quarters of our population might be suffering from various degrees of malnutrition—especially anemia. I would say that the figure of 10 million is conservative.

Why has malnutrition—as widespread as it apparently is—escaped notice until now?

Malnutrition is obscured here. The general health of malnourished people in the United States is better than that of people in the hunger areas abroad. Our poor don't live in the filth found in foreign lands. They aren't exposed to such hostile, disease-ridden environments which help to bring out severe signs of malnutrition. We have no doubt that if the sufferers of malnutrition in this country were transplanted to a backward nation, they would promptly explode with a galaxy of physical signs of partial or near starvation.

How can there be malnutrition in this land of plenty?

Quite naturally, as these unexpected findings began to appear, we asked ourselves about their cause. Although we are far from arriving at any conclusions, we cannot resist the temptation to speculate on the probable reasons for such widespread malnutrition in a land of agricultural surpluses.

First and foremost, of course, is the fact that these people are poor. The poor man has very little money to spend for food and he, therefore, must spend more wisely than the rich man. The rich man can make nutritional mistakes in the supermarkets that would be disastrous for the poor man.

Second, a corollary to the first, from our interviews we suspect the poorer people don't know what foods to buy.

Third, we have been struck quite forcibly by the suspicion that in America our food fortification programs are not what they should be. Most of these programs are voluntary. Anyone can sell bread that is not enriched. Anyone can sell milk that contains little or no vitamin D and from which the vitamin A has been removed along with the cream. And anyone can sell salt that is not iodized. Most people don't know the difference. To them milk is milk; bread is bread; salt is salt.

We cannot begin public health nutrition programs as we did in 1930, when nearly all milk contained vitamin D, and then forget these programs and the

needs they met. Rickets was virtually eradicated at no cost to the consumer, but it is certain to return if the sale of nonvitamin D milk continues to increase as it is doing in the District of Columbia. It would be a good idea if physicians and dietitians would look into the sale of nonfortified milk into their communities.

Ironically, in one instance we have been sending to undernourished people overseas a product superior to that given to the poor in our own country. Our group—which has considerable experience with international programs—was struck by the fact that the nonfat dry milk distributed in the United States under the food commodity distribution program for poor children was not fortified with vitamins A and D. In 1965, our office was instrumental in persuading the responsible authorities to fortify the milk being sent overseas. However, it was not until a few months ago that the same widely used product was given our own people in a fortified form!

Another area in which food fortification seems to have slipped is in the use of iodized salt. Iodine fortification of salt is on the decline and, largely because of this, we are facing the return of the day when goiter might be endemic in America. This is especially surprising since the United States was one of the first nations to launch an aggressive program to have all salt iodized (voluntarily). In the 1920's, it was found that this was a cheap, effective, and harmless way to prevent goiter and cretinism—a physical and mental stunting caused by severe thyroid deficiency. We should not fortify foods in one generation and not do so in the next.

Are the federal and state programs to feed the needy working out?

There has been a failure in America to reach poverty groups. I have yet to see a program effectively addressed to this segment of the population. I think we just need to be frank enough to admit that they haven't been successful or we wouldn't be finding these problems.

How many people on welfare get enough money to eat properly?

The families we have studied are not getting sufficient funds through welfare or any other means to enable them to purchase the least-cost diet that would be nutritionally adequate.

Are school lunch programs in the United States adequate?

From what we've seen, the lunch itself is nutritionally adequate. But many children are sent to school without breakfast—the lunch doesn't furnish them with enough nutrients for 24 hours. In poor areas it would be highly desirable for the schools to provide breakfast, too.

How are the middle- and upper-income groups faring nutritionally?

If there is a defect in our study, it is that the results are not representative of everybody in a given state. But the statistics are an accurate reflection of the nutritional status of people in the state's low-income areas. We haven't had the money—or perhaps even the expert manpower—to tackle the middle-income areas and places where the rich live. We strongly suspect they, too, would furnish us some surprises, but a study of the well-to-do will have to wait until we have had a good look at the nutritional status of the group that is most likely to be in trouble.

Why this seemingly sudden concern for the nation's nutrition?

During the past five years, interest in the whole subject of nutrition has steadily increased. This has set off what could almost be called a chain reaction. It has accelerated the search for knowledge about nutrition. The more we have learned about the medical effects of nutrition, the more aware we have become of its social implications. Considering the awakening social consciousness in America that has taken place at the same time, it's not surprising that the people we elect to govern us should begin asking if we Americans are well fed.

We know that pellagra can cause maniacal behavior, that the sight of a child crying from hunger can drive a father to desperate behavior, and that less well-defined troubles with food must cause much unexplained abnormality of behavior. Thus this interest in nutrition has also been spurred by the terrible outbursts of violence and destructiveness in our cities.

What action—if any—do you think the National Nutrition Survey will spur?

The National Nutrition Survey is of national importance because the final results should give us a reliable picture of the nutritional health status of the people living in the lower-income areas of America. The study will certainly have an impact on medical care throughout the country. Possibly, interpretation of these results will help the food industry produce foods that are even more nutritious. And, no doubt, what we learn will provide a basis for revision of our nutrition education classes and government food distribution programs.

The CHAIRMAN. Thank you very much.

I am intrigued by the headline of the article which is attached hereto as one of your exhibits. The Senate of the United States initiated this survey as done by this Labor and Public Welfare Committee that meets in this room. The most active Senators on it were Senator Robert Kennedy of New York, Senator Joe Clark of Pennsylvania, although others rotated from time to time on the hearings; I took part in some of the hearings; and Senator Murphy. This committee was widely attacked in the American press in editorial after editorial that there was no hunger in America and that this committee was a bunch of headline hunters.

Within 1 year's time, the case was proven so strongly that many of those newspapers that said a year earlier that there is no widespread malnutrition in the United States recanted on that and wrote editorials saying there is hunger in America that must be ended.

Now, with this national recognition of the problem, you would think there would be a great and growing interest to solve it, but once we got the national recognition that was there, the combat forces have sort of swept the problem under the rug.

Dr. LEEVY. This was a major breakthrough to start the studies in this country, to point it up, and the people who really profited have been those who have been malnourished. We have to seek out more and do more for them.

The CHAIRMAN. That is right.

This Committee of Labor and Public Welfare brought a consciousness of this problem to the American people. I am hopeful that that consciousness will not die until we have solved that problem.

Thank you very much for your statement.

I will leave the record open for 2 more days for additional statements.

NEW ORLEANS, LA., August 2, 1970.

HON. RALPH YARBOROUGH,
Senate Office Building,
Washington, D.C.

Please file this wire in committee record in support of bill S. 3063.

DR. GEORGE WELCH.

NEW ORLEANS, LA., August 2, 1970.

HON. RALPH YARBOROUGH,
Senate Office Building,
Washington, D.C.

Please file this wire in committee record in support of bill S. 3063.

DR. DONOVAN C. BROWNE.

NEW ORLEANS, LA., August 2, 1970.

HON. RALPH YARBOROUGH,
Senate Office Building,
Washington, D.C.

Please file this wire in committee record in support of bill S. 3063.

DR. GORDON MCHARDY.

NEW ORLEANS, LA., August 2, 1970.

HON. RALPH YARBOROUGH,
Senate Office Building,
Washington, D.C.

Please file this wire in committee record in support of bill S. 3063.

DR. LOUIS BALART.

GASTROENTEROLOGY

ABSTRACTS

AND

CITATIONS

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE

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PREFACE

GASTROENTEROLOGY ABSTRACTS and CITATIONS is a publication of the National Institute of Arthritis and Metabolic Diseases. This specialized information medium has been initiated to fill an existing great need in the field of gastroenterology and to assist the Institute in meeting its obligations to foster and support laboratory and clinical research into the nature, causes, and therapy of diseases of the gastrointestinal tract. Publication of GASTROENTEROLOGY ABSTRACTS and CITATIONS makes available citations of all current papers relevant to this field from medical journals published throughout the world. Approximately one-third of the citations dealing with the major aspects of gastroenterology have accompanying abstracts.

The issuing of GASTROENTEROLOGY ABSTRACTS and CITATIONS under the auspices of the National Institute of Arthritis and Metabolic Diseases will provide a much needed current awareness tool to scientists and will facilitate greater integration of research and clinical efforts in this field. The number and great diversity of publications in the area of gastroenterology makes it imperative that an appropriate service be available to investigators and practitioners so that they may be apprised of progress with a minimum of delay. Our aim is to provide the readers with a readily systematized compilation of current published work. The publication will provide the greatest usefulness if these interested investigators will contribute their ideas and comments for consideration whenever possible.

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NOTE

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LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	It.	Italian
Ar.	Arabic	Jap.	Japanese
Bul.	Bulgarian	Kor.	Korean
Ch.	Chinese	Latv.	Latvian
Cz.	Czech	Lith.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
E.	English	Por.	Portuguese
Eston.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fl.	Flemish	Ser.	Serbo-Croatian
Fr.	French	Sl.	Slovak
Ger.	German	Sp.	Spanish
Gr.	Greek	Sw.	Swedish
Heb.	Hebrew	Th.	Thai
Hun.	Hungarian	Turk.	Turkish
Ic.	Icelandic	Uk.	Ukrainian
In.	Indonesian	Viet.	Vietnamese

ABBREVIATIONS USED IN ABSTRACTS

ACTH	adrenocorticotrophic hormone	mC, μ C	milli-, microcurie(s)
ADP	adenosine diphosphate	mg	milligram(s)
AMP	adenosine monophosphate	min	minute(s)
ATP	adenosine triphosphate	ml	milliliter(s)
BSP	sulfobromophthalein	mm	millimeter(s)
C	degrees centigrade	MTD	maximum tolerated dose
cm	centimeter(s)	ng	nanogram (10^{-9})
CNS	central nervous system	pg	picogram (10^{-12})
cpm	counts per minute	p.o.	orally
DNA	deoxyribonucleic acid	ppm	parts per million
e.g.	for example	r	Roentgen
g	gram(s)	RBC	red blood cells (erythrocytes), red blood count
μ g	microgram(s)	resp.	respectively
hr	hour(s)	Rev.	review (only in citations)
i.m.	intramuscular	RNA	ribonucleic acid
i.p.	intraperitoneal	s.c.	subcutaneous
IU	international unit(s)	sec	second(s)
i.v.	intravenous	SGOT	serum glutamic-oxalacetic transaminase
kg	kilogram(s)	SGPT	serum glutamic-pyruvic transaminase
LD ₅₀	median lethal dose(s)	U	unit(s)
LDH	lactic acid dehydrogenase	UV	ultraviolet
m	meter(s)	WBC	white blood cells (leukocytes), white blood count
M	molar	yr	year(s)
mEq	milliequivalent(s)		
mM	millimolar		
μ M	micromolar		

PRE-CLINICAL SCIENCES

MORPHOLOGY, CELLULAR STRUCTURE AND HISTOCHEMISTRY

- 3024 THE CELLULAR LOCALIZATION OF ENTEROKINASE. (E.) Nordstrom, C. (Chem. Ctr., U. Lund, Sweden) and A. Dahlqvist. *Biochem Biophys Acta* 198(3):621-622, 1970.

The localization of enterokinase activity (units/mg nitrogen) within the duodenal wall of the rat was qualitatively studied by a cryostat cutting technique which allows the isolation of different parts of the villi and crypts by horizontal sectioning of fresh frozen pieces of the intestinal wall. A unit of enterokinase was defined as the activity producing 1 unit of trypsin per min. The highest specific activities of enterokinase (0.017 units/mg nitrogen) occurred in the apical halves of the villi and the activity decreased steeply towards the crypts. Within crypts and the Brunner glands of the duodenum, there was negligible enterokinase activity. Apparently, enterokinase is a villous enzyme and its function (as for other villous enzymes) is confined to the epithelial cells.

- 3025 5-HYDROXYKYNURENINE DECARBOXYLASE IN RAT INTESTINE. (E.) Noguchi, T. (Wakayama Med. Coll., Japan), H. Kaseda, R. Kido and Y. Matsumura. *J Biochem* 67(1):113-121, 1970.

A homogenate of rat small intestine was found to catalyze the conversion of 5-hydroxykynurenine to 5-hydroxykynurenamine and 4,6-dihydroxyquinoline. The decarboxylase activity for 5-hydroxykynurenine was localized in the fraction (F-II) of small intestine precipitated by centrifugation at 700 to 5000 x g and the decarboxylase activities of liver, kidney and heart were mostly present in the mitochondrial fraction. The enzyme activity of F-II was highly specific for 5-hydroxykynurenine (neither kynurenine, 3-hydroxykynurenine, tryptophan or 5-hydroxytryptophan could replace 5-hydroxykynurenine) and could be determined without addition of monoamine oxidase to the incubation medium.

- 3026 APPENDIX AND γ M-ANTIBODY FORMATION: I. IMMUNE RESPONSE AND TOLERANCE TO BOVINE γ GLOBULIN IN IRRADIATED, APPENDIX-SHIELDED RABBITS. (E.) Hanaoka, M. (Yale U. Sch. Med., New Haven, Conn.), K. Nomoto and B. H. Waksman. *J Immunol* 104(3):616-625, 1970.

Immunologic effects of and tolerance to injecting a protein antigen, bovine γ globulin (ByG) were studied in irradiated (900 R), bone marrow and appendix-shielded male New Zealand albino rabbits. I.V. injection of 200 μ g. of alum-precipitated ByG into irradiated rabbits (shielded), gave rise to an early hemagglutinin response predominantly of the γ M immunoglobulin type; responses were delayed in onset and of short duration. This effect was exaggerated by direct injection of antigen into appendiceal artery or into appendix lumen. Injection by either route of antigen freed of aggregated material by centrifugation gave little immune response and appeared to inhibit γ M antibody formation on subsequent challenge with alum-precipitated antigen. Late formation of γ G antibody and development of memory (ability to give early γ G response after

secondary challenge) were not affected by irradiation of appendix, but were inhibited in animals whose bone marrow was not shielded during irradiation. Two antibodies, γ G and γ M, seemingly are produced by different populations of cells: γ M antibodies apparently are produced by cells in or derived from the appendix.

- 3027 INFLUENCE OF BILE ON THE CANINE GASTRIC-ANTRAL MUCOSA. (E.) Menguy, R. (Billings Hosp., Chicago, Ill.) and M. H. Max. *Amer J Surg* 119(2):177-182, 1970.

The influence of prolonged exposure (3 to 12 months) to bile (via biliary-antral anastomoses) on the morphology of the dog gastric-antral mucosa was studied by electron microscopy. After chronic exposure to the bile the antral mucosa was characterized by a marked increase in the number of mucosal folds and occasional polyp formation and there was no correlation between the duration of the biliary anastomoses and the severity of these changes, but there were no ulcerations, erosions, or mucosal hemorrhages. Microscopic changes included increases in mucosal, foveolar and glandular thickness (60, 77 and 38%, resp.), mitotic index (109%) and in the clear cells per crypt (122%), stratification of the epithelium lining the crypts, papillary infolding of the epithelium lining the foveolae, an increase in branching of the antral glands, follicular lymphoid hyperplasia with marked distortion of the glandular architecture, and heavy round cell infiltrate in the foveolar layer of the mucosa.

- 3028 ULTRASTRUCTURAL HEPATIC CHANGES FOLLOWING THE ADMINISTRATION OF BENZYLIDENEYOHIMBOL. (E.) De La Iglesia, F. A. (Warner-Lambert Res. Inst. Canada, Ontario), J. C. Sosa-Lucero and G. Lumb. *Toxic Appl Pharmacol* 16(1):239-255, 1970.

Morphological ultrastructural hepatic changes following administration of benzylideneyohimbol (potential non-steroid, anti-inflammatory) were studied in male, Wistar rats and purebred beagle dogs. Administration of benzylideneyohimbol (30 mg/kg of body weight daily for rats; 60 mg/kg in gelatin capsules, daily for dogs) together with nutritionally adequate diet, did not induce light microscopic or biochemical changes in liver of either animal group. After 4, 8, and 16 weeks of drug administration to rats, mitochondrial changes appeared at 4 weeks and were present at 8 and 16 weeks also. Bizarre-shaped organelles were found to be exclusively located in central areas of liver lobule. In dogs after 12 weeks of drug administration, hepatocytes also evidenced peculiar mitochondrial forms; the mitochondrial aberrations were located in peripheral zones of liver lobules. Other cytoplasmic changes, including smooth endoplasmic reticulum hypertrophy, were observed in both species. Morphological alterations found seemingly represent basic compensatory mechanisms aimed to support more fundamental cellular processes rather than the preservation of organelle architecture.

MORPHOLOGY, CELLULAR STRUCTURE AND HISTOCHEMISTRY

3029 A METHOD FOR QUANTITATION OF PROLIFERATIVE
INTESTINAL MUCOSAL CELLS ON A WEIGHT

BASIS: SOME VALUES FOR C57BL/6. (E.) Hagemann, R. F. (Allegheny Gen. Hosp., Pittsburgh, Penn.), C. P. Sigdestad and S. Leshner. *Cell Tiss Kinet* 3(1):21-26, 1970.

A method for determining the number of small intestinal mucosal crypts, S cells, and total proliferative cells on a weight basis in the mouse is presented. Following the injection of tritiated thymidine, the number of crypts was determined by dividing the disintegrations per min per mg of intestine by the disintegrations per min per crypt and the number of S cells per mg of intestine was determined by multiplying the number of crypts per mg by the number of labeled cells per crypt (which were determined autoradiographically). The number of proliferative cells per mg intestine was determined by dividing the number of S cells per mg by the fraction of proliferative cells in S cells (as obtained by cell cycle analysis). The mean values for the entire mouse intestine were: 1094 mg wet weight, 1.1×10^6 crypts, 1.0×10^8 S cells, and 1.8×10^8 proliferative cells.

3030 DISTRIBUTION AND PROPERTIES OF ALKALINE
PYROPHOSPHATASES OF RAT LIVER. (E.) Irie,

M. (Fac. Pharmaceut. Sci., Kyoto U., Japan), A. Yabuta, K. Kimura, Y. Shindo and K. Tomita. *J Biochem* 67(1):47-58, 1970.

The subcellular distribution of alkaline inorganic pyrophosphate phosphohydrolase and the presence of two electrophoretically different enzymes in mitochondria were studied in rat liver. Inorganic pyrophosphate phosphohydrolase activities found in purified nuclei and lysosomes were accounted for by contaminating mitochondria. All three enzymes were partially purified and exhibited an optimum activity at pH of 8 and an estimated molecular weight of 68,000. The enzymes were activated by Mg^{++} , were markedly inhibited by Zn^{++} , Mn^{++} , Hg^{++} , Cd^{++} , Ca^{++} and F^- , and were unstable to air oxidation and stabilized in the presence of cysteine. The three isoenzymes were different with regard to the effect of Mg^{++} substrate specificity and inactivation by urea. Excess Mg^{++} was inhibitory to all enzyme activity, and this inhibition was more pronounced with the cytosol enzyme. The cytosol enzyme was specific for pyrophosphate hydrolysis while mitochondrial enzymes also hydrolyzed nucleoside polyphosphates. The urea concentrations required for 50% inactivation were 1.2M for the cytosol enzyme and 2M for the mitochondrial enzymes.

3031 RENEWAL OF GOBLET AND PANETH CELLS IN THE
SMALL INTESTINE. (E.) Cairnie, A. B.

(Dept. Biol., Queen's U., Kingston, Ontario, Canada). *Cell Tiss Kinet* 3(1):35-45, 1970.

The mechanism of renewal of goblet cells and Paneth cells in the small intestine was studied by autoradiography in male and female rats injected with 3H -thymidine at various time intervals before sacrifice (one group of animals received a single i.p.

injection of labeled thymidine and the other received repeated injections before sacrifice). Both goblet and Paneth cells are non-proliferative cell populations which are renewed by differentiation from a precursor cell type. Goblet cells had a turnover time in the crypt of 40 hr and migrated to the villus in about the same time as taken by the columnar cells. The turnover rate of Paneth cells was slower than that of goblet cells. The precursor of the goblet cell seemingly is found among the columnar cells in the lower part of the crypt and the precursor of Paneth cells may be situated outside the mucosal epithelium.

3032 ENZYME HISTOCHEMISTRY AND HORMONES OF
THE DEVELOPING GASTROINTESTINAL TRACT OF
THE CHICK EMBRYO: III. ENTEROCHROMAFFIN CELLS --
THEIR POSSIBLE PRODUCTS, GLUCAGON, 5-HYDROXYTRYPT-
AMINE AND THE RELATION OF MONOAMINE OXIDASE. (E.)
Baxter-Grillo, D. L. (Dept. Anat., U. Ibadan,
Nigeria). *Histochemie* 21(2):129-135, 1970.

In Rhode Island Red chicken embryos, argentaffin granulations were present in the epithelial cells of the small intestine from the 6th day of incubation, and were numerous by the 19th day, when some were also present in the submucosa; in the stomach-complex they were present by the 8th day. Using fluorescent-labeled antilucagon sera, glucagon was found in the developing gastrointestinal tract on the 12th day. Monoamine oxidase activity was demonstrated histochemically from the 6th day in epithelial cells of the stomach-complex and intestine and assay of monoamine oxidase activity using C^{14} labeled 5-hydroxytryptamine showed fluctuating enzyme activity from the 10th day until hatching. A possible relation may exist between monoamine oxidase activity and serotonin-producing cells.

3033 ULTRASTRUCTURAL LOCALIZATION OF GASTRIC
PARIETAL CELL ANTIGEN WITH PEROXIDASE-
COUPLED ANTIBODY. (E.) Hoedemaeker, P. J. (Harvard
Med. Sch., Boston, Mass.) and S. Ito. *Lab Invest*
22(2):184-188, 1970.

An attempt was made to localize antigen in the human gastric parietal cell at an ultrastructural level. Anti-parietal cell antibodies from the sera of pernicious anemia patients were coupled to horseradish peroxidase and then were reacted with human gastric mucosa and with the parietal cells of rat, mouse, guinea pig and hog. Cryostat sections of fixed human gastric mucosa were incubated in a medium containing the peroxidase coupled antibodies, 3,3'-diaminobenzidine (DAB) tetrahydrochloride (75 mg/100 cc) and 0.001 per cent hydrogen peroxide. Peroxidase activity (demonstrating the sites of bound antibody) was located in or on the cell membrane forming the microvilli of the gastric parietal cell (other gastric epithelial cells did not show peroxidase activity). When the tissues were incubated in 3,3'-diaminobenzidine for more than 30 min, a dense reaction was observed in the mitochondria, due to endogenous cytochrome oxidase activity. A cross reaction with parietal cell microvilli of the rat,

mouse, guinea pig and hog was observed, but there was no cross-reaction with the epithelial cells of the frog stomach.

- 3034 ULTRASTRUCTURE OF PANCREATIC ACINAR AND ISLET PARENCHYMA IN RATS AT VARIOUS INTERVALS AFTER DUCT LIGATION. (E.) Boquist, L. (Inst. Path. II, U. Umea, Sweden) and C. Edstrom. *Virochows Arch Path Anat* 349(1):69-79, 1970.

The effect of pancreatic duct ligation on ultrastructural degenerative and regenerative changes in the exocrine and endocrine pancreas was studied (by light microscopy) in 14 female Sprague-Dawley rats, and these changes were compared with those evoked in the pancreatic parenchyma following administration of ethionine or excess methionine. The animals were about two months old and weighed 200 gm at the time of pancreatic duct ligation, and were sacrificed at the following time intervals after duct ligation: 1, 3, 5 days, 1, 2, 3, 4, 6 weeks, and 6 months. Duct ligation of the rat pancreas evoked degeneration and atrophy of the acinar cells, and the atrophied parenchyma was replaced by adipose and fibrous tissue (there was no regeneration of acinar cells). The islet β cells showed degranulation and a prominent endoplasmic reticulum and Golgi complex the first five days following ligation and there were degenerative changes and necrosis in some β cells, but the other islet parenchymal cells showed no obvious lesions. The ductules appeared to proliferate and showed mitosis and buds composed of agranular and granulated cells which appeared to develop into islets. The agranular cells were numerous in the ductules and islets particularly at 1, 2 and 3 weeks.

- 3035 EFFECT OF COLCHICINE ON INTESTINAL DISACCHARIDASES: CORRELATION WITH BIOCHEMICAL ASPECTS OF CELLULAR RENEWAL. (E.) Herbst, J. J. (Stanford U. Sch. Med., California), R. Hurwitz, P. Sunshine and N. Kretschmer. *J Clin Invest* 49(3):530-536, 1970.

Wistar rats were given colchicine (2.5mg/100ml of drinking water or 4-5 mg/kg/day) and the intestinal mucosa was examined biochemically for lactase, invertase, maltase, alkaline phosphatase, aspartate transcarbamylase, and dihydroorotase activities, and histologically to determine whether colchicine affects disaccharidase activities primarily through cellular renewal in the crypts or directly on the differentiated cells of the villus. Maltase, aspartate transcarbamylase and dihydroorotase activities were not affected by colchicine while lactase activity decreased by 80% (10.5 units to 2), invertase by 40% (59 units to 33), and alkaline phosphatase by 40% (270 units to 160) (these activities returned to normal within 48 hr after colchicine was removed from the drinking water). *In vitro*, colchicine up to 125 mg/100 ml did not affect invertase and maltase activities but at 5mg/100ml inhibited lactase activity. Histologically, colchicine-treated animals had increased crypt cells (from 36 to 48 cells/crypt), cellular migration along the villi, and increased uridine kinase activity, but no change in the length of

villi. Colchicine (in a small constant dose) directly affects the differentiating cells of the villus causing a decrease in some disaccharidase activity.

- 3036 A MICRO-TECHNIQUE FOR THE ASSAY OF INTESTINAL ALKALINE PHOSPHATASE: RESULTS IN NORMAL CHILDREN AND IN CHILDREN WITH CELIAC DISEASE. (E.) Hamilton, J. R. (Hosp. Sick Child., Toronto, Canada) and M. H. Kelly. *Clin Biochem* 3(1):33-43, 1970.

A simple quantitative micro method is described for the determination of alkaline phosphatase activity in whole homogenates of intestinal mucosal tissue employing the enzymatic hydrolysis of p-nitrophenyl phosphate. Optimal conditions for assay of human intestinal alkaline phosphatase at 30°C were found to be 0.75 mol 2-amino-2-methyl-1-propanol buffer, pH 10.0, 5 mmol/liter substrate, and 50 μ liter sample volume. Precision of the method was 18.0 \pm 0.9 U/ml on 10 within-day replicates of calf intestinal alkaline phosphatase, electrophoretically purified. Using duodenal biopsy tissue, alkaline phosphatase activity was decreased significantly in a group of 8 children with celiac disease when compared with a group of 10 normal children.

- 3037 IMMUNOFLOUORESCENT LOCALIZATION OF THE GASTRIN-SECRETING G CELLS IN THE PYLORIC ANTRUM OF THE PIG. (E.) Bussolati, G. (Inst. Path. Anat., U. Turin, Italy) and A. G. E. Pearse. *Histochemie* 21(1):1-4, 1970.

An indirect immunofluorescence technique, using anti-human gastrin serum, was applied to formalin-fixed, paraffin-embedded material from the antral tissues of porcine stomach. The results were photographed, and post-fixation in formalin was followed by the Grimelius silver technique. The argyrophil G cells were situated in the middle portion of the pyloric glands, showed a positive gastrin immunofluorescence, were oval or pyramidal in shape, and were easily distinguished from the yellow fluorescing enterochromaffin cells. Some weakly fluorescent cells failed to stain by the silver technique, indicating that this technique is less sensitive than immunofluorescence since it depends on the presence of granular storage product. The argyrophil G cells of the pyloric antrum were shown to be the gastrin-containing cells.

- 3038 ANOXIC AND SECRETORY VACUOLATION IN THE ACINAR CELLS OF THE PANCREAS. (E.) Tapp, R. L. (Physiol. Lab., Cambridge, England). *Quart J Exp Physiol* 55(1):1-15, 1970.

Vacuoles, 2-20 microns in diameter, develop in the acinar cells of the rat pancreas when small cubes (2mm³) of tissue are incubated for 1 hr at 20°C in oxygenated media such as Tyrode's solution or rat's serum. For vacuolation to occur the cells must be anoxic and have access to excess fluid containing Ca²⁺ and either Na⁺ or Li⁺. The vacuoles are bounded

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by a membrane and develop from or near the Golgi complex. Vacuolation is prevented if the medium is cooled to 0°C, if 270 m-osmoles of sucrose, glucose or glycerol is added to the medium, or if the essential cations are not available; it is not prevented by the addition of 270 m-osmoles of urea or propylene glycol, by the addition of poisons which block oxidative phosphorylation or glycolysis, or by substituting Li^+ for Na^+ . Vacuolation can be increased by allowing the tissue to stand at 20°C for 15 or 30 min before immersion in a suitable medium. Vacuolation apparently involves two distinct, passive movements of fluid; first, from the external medium into the cytoplasmic matrix, and then from the matrix into the vacuoles. The second movement appears to involve the enzymic breakdown of large, precursor molecules in some part of the Golgi complex.

3039 FRACTIONATION OF LIVER PLASMA MEMBRANES PREPARED BY ZONAL CENTRIFUGATION. (E.) Evans, W. H. (Natl. Inst. Med. Res., London, England). *Biochem J* 166(5):833-942, 1970.

Plasma membranes were isolated from crude nuclear sediments from mouse and rat liver by a rate-dependent centrifugation through a sucrose density gradient contained in the 'A' type zonal rotor. When the plasma-membrane fraction of sucrose density 1.17 g/cm³ was dispersed in a tight-fitting homogenizer, 2 subfractions of densities 1.12 and 1.18 were obtained by isopycnic centrifugation. The light subfraction contained 5'-nucleotidase, nucleoside diphosphatase, leucine naphthylamidase and Mg^{2+} -stimulated adenosine triphosphatase activities at higher specific activities than unfractionated membranes. The heavy subfraction was deficient in these enzymes but contained higher Na^+ -plus- K^+ -stimulated adenosine triphosphatase activity. The light subfraction contained twice as much phospholipid and cholesterol, and 3 times as much N-acetylneuraminic acid relative to unit protein weight as the heavy subfraction. Polyacrylamide-gel electrophoresis indicated differences in protein composition. Electron microscopy showed the light subfraction to be vesicular (vesicles probably derived from the microvillar surfaces of the bile canaliculi) while the heavy subfraction contained membrane strips with junctional complexes (probably derived from areas in contact with neighboring parenchyma cells) in addition to vesicles.

3040 DEVELOPMENT OF FECAL IMMUNOGLOBULINS AND COPROANTIBODIES IN INFANTS AFTER ARTIFICIAL ORAL COLONIZATION WITH *E. COLI* 083. (E.) Ladinova, R. (Inst. Care Mother Child, Prague, Czechoslovakia) and V. Wagner. *Experientia* 26(2): 188, 1970.

Coproantibody production was studied in 5 newborn infants following artificial colonization with *E. coli* type 983 (administered p.o. 5×10^8 organisms/ml, immediately after birth and then 3 times a week for 3 weeks). Blood and stool samples were taken every 2 weeks after colonization for a 25-week period, and antibodies were measured in stool filtrates

and in serum specimens using passive hemagglutination. The first immunoglobulins found in the stool samples were IgA and IgM (IgG was not demonstrated). Hemagglutinating antibody against *E. coli* 083 antigen was present in stool and serum in titers from 1:2 to 1:128 and a random infection with *Proteus* was followed by appearance of hemagglutinating antibody against the O antigen of the *E. coli* 083 in stool filtrates of 2 infants.

3041 RAPID LOSS OF CYTOCHROME P-450 AND HAEM CAUSED IN THE LIVER MICROSOMES BY THE PORPHYROGENIC AGENT 2-ALLYL-2-ISOPROPYLACETAMIDE. (E.) De Matteis, F. (Med. Res. Council, Carshalton, Surrey, England). *FEBS Letters* 6(4):343-345, 1970.

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- P:Secr:Stom (3146)
- P:Morph (3162) (3181) (3183) (3191) (3200) (3203) (3214) (3216) (3218) (3220) (3221) (3222)
- P:Secr:Int (3226)
- Diagproc (3280) (3311)
- Morph (3312)

- D:S.Intest (3416)
- D:S.Intest:Malabs (3437) (3440)
- D:L.Intest (3497) (3503)
- D:Pancreas (3522)
- D:Livbil (3549) (3557) (3565) (3566) (3576) (3577) (3579) (3580) (3581) (3588) (3590)
- D:Livbil:A.Nonv.Hep (3592) (3596) (3598) (3603) (3608) (3615) (3617) (3619) (3620) (3621) (3622) (3623)
- D:Livbil:A.V.Hep (3624) (3626) (3636)
- D:Livbil:C.Hep (3644)
- D:Livbil:Gal1b (3661) (3663) (3670) (3674) (3675) (3679) (3685)
- D:Gen (3707) (3736)
- D:Gen:Parasit (3784)

ABSORPTION-EXCRETION-TRANSPORT

3094 INTERRELATIONSHIPS OF CHLORIDE, BICARBONATE, SODIUM AND HYDROGEN TRANSPORT IN THE HUMAN ILEUM. (E.) Turnberg, L. A. (Manchester Roy, Infir., England), F. A. Bieberdorf, S. G. Morawski and J. S. Fordtran. *J Clin Invest* 49(3):557-567, 1970.

A triple-lumen constant perfusion system was used to study the aspects of ileal transport mechanisms in normal male and female volunteers, aged 21 to 35 yr. Chloride, bicarbonate and sodium ions exhibited net movements across ileal mucosa against electrochemical gradients and during perfusion with a balanced electrolyte solution simulating plasma, the ileum usually absorbed, but sometimes secreted fluid. When sodium movement was zero, there was a reciprocal net movement of chloride and bicarbonate, and increasing rates of sodium absorption were associated with decreasing bicarbonate secretion rates and decreasing bicarbonate absorption. Net chloride movement was sensitive to bicarbonate concentration in ileal fluid; chloride was absorbed from solutions containing 14 or 44 mEq/liter of bicarbonate, but was secreted when ileal fluid contained 87 mEq/liter of bicarbonate. Infusion of sulfate solutions (chloride-free) resulted in ileal absorption of sodium bicarbonate and acidification of ileal contents to pH values between 6.94 and 7.16, from normal values of 7.3 to 7.6. Neither infusion of plasma-like fluids nor replacement of chloride with sulfate in the perfusion

solution caused any significant change in potential difference (-9 mV) between skin and ileal lumen. Ileal electrolyte transport seemingly occurs by a simultaneous double exchange involving Cl/HCO₃ and Na/H and neither the anion nor the cation exchange apparently causes net ion movement.

3095 EFFECT OF AGE OF RAT ON DEVELOPMENT OF HEPATIC CARRIERS FOR BILIRUBIN: A POSSIBLE EXPLANATION FOR PHYSIOLOGIC JAUNDICE AND HYPERBILIRUBINEMIA IN THE NEWBORN. (E.) Grodsky, G. M. (U. California Med. Ctr., San Francisco), H. J. Kolb, R. E. Fanska and C. Nemecek. *Metab Clin Exp* 19(3):246-252, 1970.

A method for measuring the level of carrier proteins (which bind bilirubin and sulfobromophthalein (BSP)) in hepatic cytosol based on the competitive binding of either pigment between the carrier proteins and the highly cross-linked dextran particles in Sephadex G-10 was used to demonstrate the functional immaturity of the protein carrier system in the liver of fetal and newborn Wistar rats. Cytosol from liver, kidney, spleen and muscle of rats was collected two days pre-partum at regular intervals to 120 days post-partum. Most binding activity was found in adult rat liver which contained 7 to 10 times that of the adult brain, kidney, spleen or muscle. Binding activity in fetal rat liver was 25-35% of the adult level for either bilirubin or BSP. High

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concentrations of BSP displaced bilirubin from the carrier proteins which indicated common binding sites and a large capacity for adult liver to bind both pigments. The immaturity of a carrier system for bilirubin in the newborn rat may partially explain the physiologic jaundice and hyperbilirubinemia observed in newborn humans.

3096 CHOLESTEROL ABSORPTION FOLLOWING REVERSAL OF THE UPPER AND LOWER HALVES OF THE SMALL INTESTINE. (E.) Gebhard, R. L. (U. Minnesota Med. Sch., Minneapolis) and H. Buchwald. *Surgery* 67(3): 474-477, 1970.

Ten white New Zealand 6 to 8 pound rabbits were prepared by surgically interchanging the distal and proximal halves of small intestine. "Absorptive capacity" (defined as average whole blood cholesterol radioactivity following forced feeding of 10 mg of cholesterol-4-¹⁴C) was 2,272 cpm/ml with the 10 operated animals—essentially identical to the 2,458 count with 10 weight and sex-matched normal control rabbits. The average whole blood cholesterol concentration of the operated animals was 86.9 mg% compared with the control animals at 91.4 mg%, not a statistically significant difference. Thus, reversal of the continuity of jejunal and ileal segments resulted in no change in total cholesterol absorption. There does not appear to be an ileal or jejunal site in the small intestine of the rabbit which is specific or selective for cholesterol absorption. Any relative difference is attributable to the time necessary to prepare cholesterol for absorption, so that whichever segment is distal will be responsible for the major share. Transit time in the small intestine seems to significantly influence quantitative cholesterol absorption.

3097 ON THE *IN VITRO* "ACTIVE TRANSPORT" OF ALDOPENTOSE BY THE RAT JEJUNUM. (E.) Bell, D. J. (U. Med. Sch., Edinburgh, Scotland). *Quart J Exp Physiol* 55(1):59-63, 1970.

Everted jejunal sacs of adult rats were used in this study of 'active transport' of aldopentoses at low concentrations (9 to 40 µg/ml) under *in vitro* aerobic conditions. Using D-xylose, in all jejunal preparations (9) active transport was observed; while in all of 3 experiments the presence of D-glucose in greater amounts (100 µg/ml) than xylose completely prevented the appearance of extra aldopentose on the serosal side of the preparations. No pentose other than xylose was detected chromatographically on the serosal side. In all experiments using L-arabinose (9) and D-ribose (3) no transport was observed.

3098 UPTAKE OF DRUGS BY NORMAL AND DISEASED HUMAN GASTRIC MUCOSA: *IN VITRO* EXPERIMENTS WITH LABELED ACETYSALICYLIC ACID AND THIO-PENTONE. (E.) Jussila, J. (Helsinki U. Central Hosp., Finland), O. Mustala, G. Kvist and M. Siurala. *Arch Int Pharmacodyn* 183(2):270-276, 1970.

The *in vitro* uptake of ¹⁴C-acetylsalicylic acid and

³⁵S-thiopentone by human esophageal, gastric and intestinal biopsy specimens was studied at different pH's of the incubation medium. The uptake of both drugs was significantly higher at pH 3-3.8 than at pH 7-8.4, with a distribution ratio of 2 to 7 at pH 3-3.8 and about one at pH 7-8.4. At pH 3.8 the uptake of ¹⁴C-acetylsalicylic acid by atrophic gastric mucosa was significantly lower than that by a normal mucosa while no corresponding difference between the atrophic and normal gastric mucosa was observed with ³⁵S-thiopentone. In a dissociated form these drugs seemingly are passively taken up by diffusion into the specimens, while at lower pH's and being in lipid-soluble state, the concentration of the drugs in the specimens is higher than that in the medium suggesting the increased metabolic rate or the binding of the drugs to mucosal proteins.

3099 EFFECT OF AGE ON INTESTINAL ABSORPTION OF RIBOFLAVIN IN HUMANS. (E.) Levy, G. (Sch. Med., State U. New York, Buffalo), W. J. Jusko and S. J. Yaffe. *J Pharm Sci* 59(4):487-490, 1970.

Thirteen male and 10 female healthy human subjects (ages 3 months to 40 yr) received a p.o. dose of 150 mg/m² body surface area of riboflavin-5'-phosphate (absorbed specifically in the proximal small intestine). The urinary recovery of the vitamin increased significantly (from 6% to 12% of the dose) over this age range and the ratio of maximum excretion rate to dose and the time of occurrence (of maximum excretion rate) were independent of age. The kinetics of riboflavin elimination also did not show any appreciable change with age. Prompt release of drugs from pharmaceutical dosage forms to assure absorption seemingly is even more important in young children than in adults because of the apparently shorter residence time of such drugs at intestinal absorption sites.

3100 MECHANISM OF BICARBONATE ABSORPTION AND ITS RELATIONSHIP TO SODIUM TRANSPORT IN THE HUMAN JEJUNUM. (E.) Turnberg, L. A. (U. Texas Southwestern Med. Sch., Dallas), J. S. Fordtran, N. W. Carter and F. C. Rector, Jr. *J Clin Invest* 49(3):548-556, 1970.

Sodium and bicarbonate absorption was studied in human subjects by the Ingelfinger triple-lumen constant perfusion technique. The rate of sodium absorption was markedly influenced by bulk water flow; when the net water flow was zero, sodium absorption was zero if there were no concentration gradients between plasma and lumen that favored net NaCl diffusion. The potential difference between abraded skin and jejunal lumen was near zero when saline was perfused and did not change with partial substitution of sulfate or bicarbonate for chloride. The mechanism of the link between bicarbonate and sodium absorption was studied in normal subjects and in 11 patients with pernicious anemia (the latter were chosen because they did not secrete gastric juice which could react with bicarbonate in the jejunal lumen). Bicarbonate absorption occurred against steep electrochemical gradients, did not generate a potential difference between abraded

skin and jejunal lumen, was inhibited by acetazolamide, and generated a high CO_2 tension in jejunal fluid. Bicarbonate absorption seemingly is mediated by active hydrogen secretion, rather than by bicarbonate ion transport per se, and the link between sodium and bicarbonate transport may best be explained by a sodium-hydrogen exchange process.

- 3101 BILIRUBIN ABSORPTION BY THE GALLBLADDER. (E.) Royer, M. (Nat'l. Inst. Hlth., Haedo, Argentina), H. Ortiz, E. Machado and B. Noir. *Scand J Gastroent* 5(1):17-23, 1970.

The absorption of conjugated and unconjugated bilirubin- ^{14}C (with bile) after infusion into the gallbladder or jejunum was studied in dogs with cannulated gallbladder and common bile duct. About 2.9 to 23.5% of a total dose of 41.66 mg of conjugated bilirubin- ^{14}C and 0-0.3 mg% of a total average dose of 7.9 mg of unconjugated bilirubin- ^{14}C were recovered in the cholecystic bile after 8 hr. When labeled bile (from which most of the bilirubin had been precipitated out) was infused into the gallbladder and jejunum, about 27.7% and 2%, resp., of the total radioactivity infused were recovered from the hepatic bile. Small amounts of bilirubin- ^{14}C were consistently found in blood and urine 8 hr after injection of labeled bile into the gallbladder. Both conjugated and unconjugated bilirubin- ^{14}C apparently are absorbed by the gallbladder, transported into the general circulation, and eliminated in the bile and urine, indicating a cholecystohepatic circulation of bilirubin.

- 3102 GASTRIC ABSORPTION AND DISTRIBUTION OF ACETYSALICYLIC ACID AND OTHER ACIDIC COMPOUNDS IN THE RAT. (E.) Morris, C. H. (Sch. Pharm. Pharmacol. Sci., Purdue U., Lafayette, Ind.), J. E. Christian, T. S. Miya and W. G. Hansen. *J Pharm Sci* 59(3):325-329, 1970.

The gastric absorption and distribution of sodium acetylsalicylate- ^{14}C was compared with the absorption and distribution of sodium salts and other weakly acidic compounds from the rat stomach. Acetylsalicylic acid was the one compound tested that produced lesions in the gastric mucosa, although the other compounds tested (radioactive sodium benzoate, sodium acetate, and sodium barbital) had similar absorption patterns. The gross autoradiographs and quantitative data showed that sodium acetylsalicylate, sodium benzoate and sodium barbital concentrations within the corpus of the stomach drop to less than 0.01 $\mu\text{moles/gm}$ of tissue within 2 hr, but remain at relatively high concentrations (0.01 to 0.1 $\mu\text{moles/gm}$ of tissue) in the rumen portion. Autoradiographic localization and tissue analysis showed that sodium acetate rapidly disappears (less than 0.001 $\mu\text{moles/gm}$ of tissue) in 2 hr from both the rumen and corpus. Absorption characteristics of acetylsalicylic acid and its salts may be associated with their ability to cause gastric ulcers.

- 3103 THE SITE OF ABSORPTION OF CHOLESTEROL AND SITOSTEROL IN THE RAT SMALL INTESTINE. (E.) Sylven, C. (Chem. Ctr., Lund, Sweden) and C. Nordstrom. *Scand J Gastroent* 5(1):57-63, 1970.

Cholesterol- ^{14}C and sitosterol- $^{22,23-^3}\text{H}$ were administered intragastrically (in micellar solution) or intraduodenally (dissolved in triolein) to male rats in order to determine the morphological site of uptake of these 2 sterols along the small intestine and in the intestinal villi and crypts. Sterols were uniformly taken up by the proximal (micellar solution) or by the middle part (triolein solution) of the small intestine. The apical halves of the villi contained the major amount of the sterols taken up; the 2 sterols had identical areas of uptake. With the micellar solution, the uptake was maximal after 15 min postadministration; with the triolein solution, absorption was maximal after 6 hr.

- 3104 ABSORPTION OF ACETYSALICYLIC ACID FROM UNBUFFERED AND BUFFERED GASTRIC CONTENTS. (E.) Hunt, J. N. (Guys Hosp. Med. Sch., London, England) and A. R. Cooke. *Amer J Dig Dis* 15(2):95-102, 1970.

The rate of gastric emptying and absorption of acetylsalicylic acid was studied in 19 healthy subjects after the administration of a 200 ml test meal containing 1250 mg/liter of unbuffered acetylsalicylic acid or 3100 mg/liter of buffered acetylsalicylate. The volume of test meal containing unbuffered acetylsalicylic acid was greater than that containing buffered acetylsalicylate at 5 and 10 min after administration in 18/19 subjects. Neither blood clots nor blood staining were observed in the gastric contents after a test meal containing buffered acetylsalicylate or unbuffered acetylsalicylic acid. The mean pH of test meals containing buffered acetylsalicylate before ingestion was 7.0 and for the test meals containing unbuffered acetylsalicylic acid was 2.8. At the end of 10 min, 69% of the buffered and 52% of the unbuffered meal had emptied from the stomach and the mean pH values of the gastric contents after ingestion of the buffered meals at 5, 10, 15, and 20 min were 6.5, 6.3, 5.8, 5.3, resp., and for the unbuffered meals the mean pH of gastric contents after 5 and 10 min was 2.3 and 2.0, resp. The mean percentage absorption of acetylsalicylic acid at 10 min for the buffered solutions (8X) was significantly less than that for the unbuffered solutions (11.6%).

- 3105 THE SODIUM-ALANINE INTERACTION IN RABBIT ILEUM: EFFECT OF SODIUM ON ALANINE FLUXES. (E.) Hajjar, J. J. (Yale U. Sch. Med., New Haven, Conn.), A. S. Lamont and P. F. Curran. *J Gen Physiol* 55(3):277-296, 1970.

The interaction (Model of Curran) between sodium and alanine at the mucosal border of rabbit ileum was tested by examining the efflux of alanine from the cells both directly (with ^{14}C -alanine as tracer) and indirectly (method of Curran, Herrera,

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and Flanigan). As cellular alanine concentration increases (from 0 to 40mM), the efflux tends toward saturation and is influenced by cellular sodium concentration because the "apparent Michaelis constant" (K_t) increases as sodium concentration decreases (K_t increases from 55 to 80 as [Na] decreases from 140mM to 0). The direction of the sodium concentration difference determines the direction of net alanine transfer between the cells and medium: when cell [Na] > medium [Na], the cells extrude alanine against a concentration difference and accumulate it when cell [Na] < medium [Na]. Data support the hypothesis that a transport site combining with and translocating both Na and alanine exists and that a sodium concentration difference between cell and medium provide energy for the active transport of alanine.

3106 THE SODIUM-ALANINE INTERACTION IN RABBIT ILEUM: EFFECT OF ALANINE ON SODIUM FLUXES. (E.) Curran, P. F. (Yale U. Sch. Med., New Haven, Conn.), J. J. Hajjar and I. M. Glynn. *J Gen Physiol* 55(3):297-308, 1970.

The interaction between sodium and alanine transfer across the mucosal border of rabbit ileum was studied by examining the effect of alanine on sodium movement (quantitated by flame photometry and ^{22}Na tracer) in mucosal strips and whole intestinal wall. When mucosal strips were incubated with 40mM alanine and then transferred to an alanine-free medium, cell sodium content decreased (0.6 $\mu\text{Eq}/\text{mg}$) from the control value (0.76 $\mu\text{Eq}/\text{mg}$), but when incubated in alanine-free medium and then transferred to a 40 mM alanine solution, cell sodium concentration increased (0.68 $\mu\text{Eq}/\text{mg}$) from the control value (0.6 $\mu\text{Eq}/\text{mg}$). Sodium efflux from the cells increased by an average of 11% when the cells were loaded with alanine. The relation between the increment in sodium and alanine efflux agrees with the model of Curran for the sodium-alanine interaction at the mucosal border of the cells.

3107 EFFECT OF METOCLOPRAMIDE ON TRANSPORT IN THE SMALL INTESTINE OF THE DOG. (E.) Tinker, J. (Roy. Postgrad. Med. Sch., London, England) and Alan G. Cox. *Gut* 10(12):986-989, 1969.

The dye dilution method described for the simultaneous measurement of flow rate, mean transit time, and volume of the jejunum during the transport of fluid through a segment of the small intestine of the dog is identical in principle to the Stewart-Hamilton technique for measuring cardiac output. The use of a Foley's catheter ensures the required efficiency of collecting samples at the collecting site. The flow rates calculated from the dye dilution curves correlated closely with rates determined independently by the ratio of polyethylene glycol concentration in the infused solution to that in the pooled sample obtained from the jejunal cannula. The technique is only applicable to steady-state conditions, and for this reason a steady perfusion of the small intestine had to be created by

constant infusion of an isotonic electrolyte solution, resulting in satisfactory measurements. In an application of the method, metoclopramide caused a significant decrease in the mean transit time and volume of the perfused segment in comparison with saline in dogs (the mean flow rates were not significantly affected). The dye (bromsulphthalein) dilution curve after the injection of metoclopramide reached an earlier and higher peak than when saline was injected but the areas were almost exactly equal, confirming the similarity of flow rates at the collection site.

3108 THE PHYSIOPATHOLOGICAL FEATURES OF DUODENAL DIGESTION AND ABSORPTION. (It.) Barbara, L. (1st Dept. Spec. Med. Path., Clin. Methodol., U. Bologna, Italy) and G. Fontana. *Minerva Gastroent* 15(3):140-167, 1969.

3109 THE INFLUENCE OF BLOOD FLOW ON WATER AND SOLUTE ABSORPTION IN THE JEJUNUM OF THE RAT. (Ger.) Winne, D. (Pharm. Inst. U. Tubingen, Germany). *Nahrung Schmieberg Arch Pharmacol* 265(5): 425-444, 1970.

3110 IRON EXCRETION INTO GASTRIC JUICE. (E.) Kimura, I. (Okayama U. Med. Sch., Japan). *Jap J Nucl Med* 6(4):413, 1969.

3111 INTESTINAL ABSORPTION OF CALCIUM IN FASTING PATIENTS. (E.) Fromm, G. A. (Surg. Inst., Prov. Buenos Aires, Haedo, Argentina), J. Litvak and O. J. Degrossi. *Lancet* 1(7647):616-617, 1970.

3112 ABSORPTION OF HEMOGLOBIN IRON: THE ROLE OF XANTHINE OXIDASE IN THE INTESTINAL HEME-SPLITTING REACTION. (E.) Dawson, R. B. (Tufts U. Sch. Med., Boston, Mass.), S. Rafal and L. R. Weintaub. *Blood* 35(1):94-103, 1970.

3113 THE ABSORPTION, DISTRIBUTION, AND EXCRETION OF PENTAZOCINE IN MAN AFTER ORAL AND INTRAVENOUS ADMINISTRATION. (E.) Beckett, A. H. (Dept. Pharm., Chelsea Coll., London, England), J. F. Taylor and P. Kourounakis. *J Pharm Pharmacol* 22(2):123-128, 1970.

3114 EFFECT OF RECTAL LUMEN CONCENTRATION ON THE REABSORPTION OF IONS AND WATER BY THE AMERICAN COCKROACH. (E.) Sauer, J. R. (Dept. Entomol., Oklahoma St. U., Stillwater), J. J. Levy, D. W. Smith and R. R. Mills. *Comp Biochem Physiol* 32(4):601-614, 1970.

3115 HEMOGLOBIN UPTAKE BY RAT HEPATOCYTES AND ITS BREAKDOWN WITHIN LYSOSOMES. (E.) Goldfischer, S. (Albert Einstein Coll. Med., Yeshiva U., Bronx, N. Y.), A. B. Novikoff, A. Albala and L. Blempera. *J Cell Biol* 44(3):513-529, 1970.

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- 3116 THE CHEMICAL BOND OF COBALT, ITS ABSORPTION IN THE GASTROINTESTINAL TRACT AND ITS INCORPORATION INTO PROTEIN METAL LIVER COMPLEXES. (Rus.) Merkulova, I. S. (Gorki Med. Inst., Donetsk, USSR), V. R. Soroka and N. Z. Rudenko. *Vop Pitar* 28(6):48-51, 1969.
- 3117 WATER AND SOLUTE UPTAKE BY RECTAL PADS OF *PERIPLANETA AMERICANA*. (E.) Wall, B. J. (Dept. Biol., Case Western Reserve U., Cleveland, Ohio) and J. L. Oschman. *Amer J Physiol* 218(4):1208-1215, 1970.
- 3118 TRANSPORT ACROSS CELL MEMBRANES. (E.) Whittam, R. (Dept. Physiol., U. Leicester, England) and K. P. Wheeler. *Ann Rev Physiol* 32:21-60, 1970.
- 3119 ALCOHOL-INDUCED HYPOGLYCEMIA IN CHILDHOOD. (E.) MacLaren, N. K. (Queen Elizabeth Hosp. Child., London, England), H. B. Valman and E. Levin. *Brit Med J* 1(5691):278-280, 1970.
- 3120 INHIBITION OF SORBITOL OXIDATION BY ETHANOL IN INTACT RATS PRETREATED WITH TRIIODOTHYRONINE OR PROPYL THIOURACIL. (E.) Hillbom, M. E. (Res. Lab., Alko, Helsinki, Finland). *Biochem Pharmacol* 19(2):483-486, 1970.
- 3121 FACTORS AFFECTING GASTROINTESTINAL ABSORPTION OF DRUGS. (E.) Levine, R. R. (Boston U. Med. Ctr., Mass.). *Amer J Dig Dis* 15(2):171-188, 1970.
- 3122 PHARMACOLOGIC ASPECTS OF BILIARY EXCRETION: DOSE DEPENDENCY OF RIBOFLAVIN IN THE RAT. (E.) Nogami, H. (Fac. Pharm. Sci., U. Tokyo, Japan), M. Hanano, S. Awazu and T. Iga. *Chem Pharm Bull* 18(2):228-234, 1970.
- P:Motil (3132)
 - P:Secr:Hepatobil (3163) (3165) (3202)
 - P:Secr:Int (3233)
 - P:Gen (3244) (3245)
 - D:Stomduo (3367)
 - D:Stomduo:Peptulc (3410)
 - D:S.Intest:Malabs (3438) (3439) (3449) (3458)
 - D:Livbil (3545)
 - D:Livbil:Gallb (3664)
 - D:Gen (3698) (3744) (3754)
 - D:Gen:Parasit (3787)

MOTILITY

- 3123 PHARMACOLOGIC IDENTIFICATION OF THE LOWER ESOPHAGEAL SPHINCTER. (E.) Christensen, J. (U. Iowa Coll. Med., Iowa City). *J Clin Invest* 49(4):681-691, 1970.

Both upper and lower (the most distal 1 to 2 cm) esophageal sphincters were demonstrated manometrically in 10 adult male and female opossums. A variety of agonists were used to seek differences between circular muscle from the sphincteric segment and more rostral levels, recording *in vitro* the isometric contractions of strips from the distal 6 cm. Significant differences in threshold concentration occurred for acetylcholine (4 animals), carbachol (3), methacholine (3), nicotine (3), DMPP (1, 1-dimethyl-4-phenylpiperazinium iodide) (3), norepinephrine (4), norepinephrine with propranolol (4); the more distal strips being more sensitive. The gradient of threshold was much steeper for norepinephrine than for the other drugs. Maximal responses did not differ among levels for the choline esters or ganglionic stimulants, but showed proximal diminution for norepinephrine. Responses among the 6 levels of the esophagus were identical (or showed only small differences) when using barium (3 animals), atropine (3), and potassium (3). The sphincter is defined, at least in part, in the esophageal wall rather than in the central nervous system. The greater magnitude

of the difference in sensitivity to norepinephrine than for the other agents suggests that the adrenergic innervation is important in defining the lower esophageal sphincter.

- 3124 ACTION OF CAERULEIN ON THE BILIARY SYSTEM OF THE DOG. (E.) Bertaccini, G. (Inst. Pharmacol., U. Parma, Italy), G. Ballarini, A. Agosti and G. Zannetti. *Arch Int Pharmacodyn* 183(2):261-269, 1970.

The decapeptide caerulein was tested in the dog for activity on the biliary system with a radiographic technique using logglycamic acid as a contrast medium. The threshold doses of caerulein for cholecystokinetic activity by i.v. and s.c. routes were 0.001 and 0.01 $\mu\text{g}/\text{kg}$ resp and spasmogenic effects on the gallbladder with high doses (1 $\mu\text{g}/\text{kg}$) lasted up to 6 to 7 hr. The effect of caerulein on the intra- and extrahepatic bile ducts was documented by the roentgenographic disappearance of these ducts and the spasmogenic activity of caerulein appeared to spare the intraduodenal portion of the choledochus. The observed action of caerulein resembles that of the endogenous hormone cholecystokinin-pancreozymin.

MOTILITY

- 3125 ELECTROMYOGRAPHIC STUDY OF NORMAL HUMAN GASTRIC MOTOR ACTIVITY. (Fr.) Monges, H. (North Hosp., Marseilles, France) and J. Salducci. *Arch Franc Mal Appar Dig* 59(1-2):29-38, 1970.
- 3126 THE pH DEPENDENCE OF HISTAMINE ACTION ON THE GUINEA PIG ILEUM. (E.) Gero, A. (Hahnemann Med. Coll. Hosp., Philadelphia, Pa.) and M. T. Daniele. *Arch Int Pharmacodyn* 183(2):315-319, 1970.
- 3127 GASTRIC PERISTALSIS: A STUDY OF REGIONAL RATES OF CONTRACTION. (E.) Beck, C. S. (Stanford U. Sch. Med., Palo Alto, Calif.) and G. R. Mason. *Amer J Surg* 119(2):217-219, 1970.
- 3128 PHYSICAL FACTORS IN THE STIMULATION OF COLONIC PERISTALSIS. (E.) Hardcastle, J. D. (St. Mark Hosp., London, England) and C. V. Mann. *Gut* 11(1):41-46, 1970.
- 3129 THE EFFECT OF THE INTRINSIC MUCOSAL REFLEX UPON THE PROPAGATION OF INTESTINAL CONTRACTIONS. (E.) Hukahara, T. (Okayama U. Med. Sch., Japan), T. Neya and K. Tsuchiya. *Jap J Physiol* 19(6):824-833, 1969.
- 3130 THE MOTILITY OF THE GASTRO-INTESTINAL TRACT. (E.) Demling, L. (Med. Clin. Polyclin., U. Erlangen-Nuremberg, Germany). *Digestion* 2(6):362-368, 1969.
- 3131 CHOLINERGIC AND HISTAMINERGIC ACTION ON THE GUINEA-PIG ILEUM. (E.) Gero, A. (Hahnemann Med. Coll., Philadelphia, Pa.) and S. Gurland. *Arch Int Pharmacodyn Ther* 183(1):25-27, 1970.
- 3132 MECHANISMS IN INTESTINAL TRANSFER. (E.) Smyth, D. H. (Dept. Physiol., U. Sheffield, England). *J Clin Path* 23(1):1-6, 1970.
- P:Morph (3073)
 - P:Secr:Int (3232) (3238)
 - P:Gen (3258)
 - P:Esoph (3313) (3317)
 - D:Stomduo (3370) (3385)
 - D:L.Intest (3459)
 - D:Livbil:Gallb (3687) (3694)
 - D:Gen (3701) (3744)
 - D:Gen:Parasit (3786)

SECRETION AND METABOLISM

Stomach

- 3133 THE RESPONSE OF THE ISOLATED RAT STOMACH TO ETHANOL. (Fr.) De Saint-Blanquat, G. (I. N. S. E. R. M., Toulouse, France), D. Galliard and R. Derache. *J Physiol Paris* 61(5):435-442, 1969.

The gastric secretory response to 1 or 10% solutions of ethanol, histamine or gastrin was studied in the isolated rat stomach. Free acid secretion (but not total acid) was stimulated by 1% solutions of ethanol, histamine and gastrin while pepsin secretion was stimulated by 1% solutions of ethanol or gastrin and inhibited by 1% solution of histamine. Acid secretion was inhibited and pepsin and lactic acid secretion was stimulated by 10% ethanol. Gastric hyperactivity produced by low concentrations of ethanol seemingly may be due to gastrin stimulation.

- 3134 STUDIES ON THE EFFECT OF 2-PHENYL-2-(2-PYRIDYL)-THIOACETAMIDE (ANTIGASTRIN) ON CANINE GASTRIC ACID SECRETION. (E.) Eisenberg, M. M. (Dept. Surg. U. Minnesota, Minneapolis), J. Isaza, K. Sugawara and R. Tiongco. *Surgery* 67(3):462-467, 1970.

Effects of 2-phenyl-2-(2-pyridyl)-thioacetamide (antigastrin) on gastric acid secretion was studied in 4 dogs with Heidenhain pouches and isolated innervated antrums and 5 dogs with Heidenhain pouches and gastric fistulas. Antigastrin significantly inhibited fundic pouch gastrin secretion with maximal inhibition ranging from 45.2 ± 11% with 10 mg dose to 93.9 ± 1.9% for 160 mg dose of antigastrin. Duration of maximum inhibition was less than 60 min with 10 and 20 mg; 40 mg or greater caused sustained inhibition for 120 to 180 min. In gastric fistula dogs, antigastrin was less effective in inhibiting gastric secretion stimulated by 2-deoxy-D-glucose and histamine; 80 mg of antigastrin significantly inhibited response to 2-deoxy-D-glucose by 40% while 160 mg produced retching. In gastric fistula and denervated fundic pouch dogs, histamine-induced gastric acid secretion was inhibited by antigastrin (40 mg) by 43% and 46% resp. The precise role and specificity of antigastrin in inhibition of nervous- or histamine-stimulated gastric secretion is unclear; interference with histamine- and vagally stimulated gastric juice may seemingly represent inhibition of potentiating background gastrin.

SECRETION AND METABOLISM

Stomach

- 3135 INHIBITORY ACTION OF CHOLECYSTOKININ-PANCREOZYMIN ON GASTRIC PEPTIC SECRETION. (E.) Nakajima, S. (U. Alabama Med. Ctr., Birmingham) and D. F. Magee. *Experientia* 26(2):159, 1970.

The effect of cholecystokinin-pancreozymin on pepsin secretion stimulated by the cholinomimetic agent acetyl- β -methylcholine (mecholy) was studied in six adult mongrel dogs, each with a vagally denervated Heidenhain pouch. Cholecystokinin-pancreozymin (1.0 Ivy dog unit per min i.v.) produced a significant inhibition of gastric pepsin secretion stimulated by mecholy (2 μ g/min). Pepsin inhibition was prompt and was 41% complete within 10 min of the start of cholecystokinin-pancreozymin administration, and 85% complete after 60 min. Pepsin secretion was reduced by cholecystokinin-pancreozymin from a mecholy-stimulated high value of about 100 mg tyrosine per 10 min to a resting value of nearly 25 mg tyrosine per 10 min. Cholecystokinin-pancreozymin significantly inhibits the acid response to gastrin extract, to synthetic peptidase and to endogenously released gastrin and seemingly may be enterogastrone.

- 3136 FACTORS WHICH DETERMINE THE GASTRIC SECRETORY RESPONSE TO 2-DEOXY-D-GLUCOSE. (E.) Himswoth, R. L. (Coll. Physicians Surg., Columbia U., New York, N.Y.) and D. G. Colin-Jones. *Aut* 10(12):1015-1019, 1969.

The minimum amount of 2-deoxy-D-glucose given as a single rapid i.v. injection which would invariably cause a sustained secretion of gastric acid in normoglycemic rats was 25 mg, with the delay in onset (3 to 30 min) being significantly correlated to plasma glucose (delay was longest when the plasma glucose concentration was highest). If the initial plasma glucose concentration was greater than 200 mg/100 ml, this dose of 2-deoxy-D-glucose did not cause an increase in gastric acid output. An established secretion of gastric acid resulting from the administration of 2-deoxy-D-glucose could always be ended by the i.v. infusion of high levels of glucose. A preliminary dose of 90 mg of 3-O-methylglucose prevents the gastric secretory response that should follow injection of 25 mg of 2-deoxy-D-glucose; however, a further dose of 3-O-methylglucose is followed by the typical increase in gastric acid output. Since both glucose and 3-O-methylglucose can prevent 2-deoxy-D-glucose from exciting the gastric secretory center in the brain it appears that the same transport system is used. The use of 2-deoxy-D-glucose for purposes of investigation in man is hazardous because the characteristics of the blood-brain barrier are such that the cells of the brain become progressively more accessible to 2-deoxy-D-glucose as the plasma glucose concentration falls below normal, and the effects of 2-deoxy-D-glucose can be reversed only slowly.

- 3137 EFFECT OF COMBINATION OF HISTAMINE AND PENTAGASTRIN ON GASTRIC SECRETION IN MAN AND DOG. (E.) Grossman, M. I. (VA Ctr., Los Angeles, Cal.), A. M. Brooks and L. R. Johnson. *Gastroenterology* 58(4):470-475, 1970.

Gastric secretion in response to i.v. infusions of histamine and pentagastrin, alone and in combination, was studied in 4 men and in dogs. In man, mean acid outputs stimulated by combinations of histamine and pentagastrin, in doses (0.04 mg/kg/hr and 6.0 μ g/kg/hr, resp.) that produced maximal responses when given alone, were not significantly higher than the maximal observed response to either agent alone and clearly were below the calculated maximal response to histamine. This combination of stimulants did not potentiate pepsin secretion either. In dogs with gastric fistulas, equivalent combinations of histamine and pentagastrin potentiated gastric acid secretion.

- 3138 THE ISOLATION OF GLYCOPROTEIN FROM GASTRIC SECRETION. (Ger.) Kuhn, D. (Med. U. Polyclin. Heidelberg, Germany) and H. Weicker. *Z Klin Chem Klin Biochem* 8(1):80-84, 1970.

- 3139 STUDY OF URINARY PEPINOGEN AND ITS CORRELATION WITH GASTRIC PROTEOLYTIC ENZYME SECRETION. (Fr.) Hirsch-Marie, H. (Hosp. St. Antoine, Paris, France) and M. Conte. *Rev Franc Etud Clin Biol* 14(10):977-983, 1969.

- 3140 QUANTITATIVE MEASUREMENT OF GASTRIC AND URINARY PEPINOGEN AND PEPIN BY LAURELL'S ELECTROPHORETIC IMMUNO-PRECIPIATION. (Fr.) Hirsch-Marie, H. (Hosp. Saint Antoine, Paris, France) and M. Conte. *Arch Franc Mal Appar Dig* 59(1-2):63-70, 1970.

- 3141 THE EFFECTS OF ABOMINE, ACIDINE-PEPSIN AND ACIDINE-MUCOSINE ON THE GASTRIC SECRETION IN DOGS. (Rus.) Chemodanova, D. I. (Dept. Zool., Gorki Pedagog. Inst., Omsk, USSR) *Farmakol Toksik* 32(6):696, 1969.

- 3142 SOME POLYPEPTIDES INFLUENCING GASTRIC-ACID SECRETION. (E.) Gregory, H. (Imperial Chem. Indust., Alderley Park, Macclesfield, England). *Amer J Dig Dis* 15(2):141-148, 1970.

- 3143 THE SECRETORY PATTERN OF THREE STOMACH PREPARATIONS IN THE RAT. (E.) Svensson, S. E. (Inst. Physiol., U. Lund, Sweden). *J Physiol* 207(2):329-350, 1970.

- 3144 THE RELATIONSHIP BETWEEN GASTRIC SECRETION, ELECTROLYTES AND ACID-BASE BALANCE. (It.) Maselli-Campagna, G. (Gen. Clin. Surg. Clin. Therap., U. Bari, Italy), R. Sorace, S. Ferrarese, V. Ronzini and V. Disanto. *Chir Gastroent* 3(3):283-303, 1969.

- 3145 PROTECTION OF THE GASTRIC MUCOSA BY POLY-GALACTOSULPHATE IN EXPERIMENTAL AGGRESSION CONDITIONS. (Fr.) Wegmann, R. (Inst. Med. Histochem., Paris, France) and J. Thomas. *Ann Histochem* 14(3):287-297, 1969.

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3146 HISTAMINE, HISTIDINE DECARBOXYLASE AND GASTRIN IN THE UPPER GASTROINTESTINAL TRACT OF CHICKENS. (Ger.) Ruoff, H. J. (Pharmacol. Inst., U. Tubingen, Germany) and K. F. Sewing. *Naswyn Schmiedeberg Arch Pharmacol* 265(4):301-309, 1970.

3147 STIMULATION OF GASTRIC SECRETION IN TOTAL EXTERNAL PANCREATIC FISTULA. (Sp.) Cipitria, J. C. (Hosp. Ramon Mejia, Buenos Aires, Argentina), G. F. Cualli, C. A. Linares and C. J. Morel. *Rev Argent Cir* 16(5):469-472, 1969.

3148 EFFECTS OF CINCOPIHEN ON GASTRIC MUCOSA SECRETION IN ANTRAL POUCH DOGS. (Jap.) Nakamura, S. (Gunma U. Sch. Med., Maebashi, Japan). *Kitakanto Med J* 19(2):105-111, 1969.

3149 GASTRIC SECRETION AFTER PENTAGASTRIN AND HISTAMINE IN THE BASAL SECRETING FERRET. (E.) Basso, N. (2nd Surg. Clin. Polyclin. Umberto I, Rome, Italy), J. L. A. Roth and C. J. Pfeiffer. *J Surg Res* 10(3):111-115, 1970.

3150 AN IMMUNOLOGICAL ASSAY FOR THE INTRINSIC FACTOR ACTIVITY IN HOG GASTRIC MUCOSAL EXTRACT. (Fr.) Wolff, R. (Fac. Med., Nancy, France), J. P. Nicolas and C. Tamisier. *Ann Biol Clin* 27(10-12):707-713, 1969.

3151 GASTRIN DERIVATIVES INVESTIGATED FOR SECRETORY POTENCY AND FOR CHANGES IN GASTRIC MUCOSAL HISTAMINE FORMATION. (E.) Rosengren, E. (Inst. Physiol. U. Lund, Sweden) and S. E. Svensson. *Brit J Pharmacol* 38(3):473-477, 1970.

- P:Morph (3027) (3033) (3037) (3061) (3073) (3085)
- P:Absorp (3098) (3104) (3110)
- P:Motil (3125)
- P:Gen (3241)
- Diagproc (3266) (3281) (3287) (3293)
- D:Stomduo (3342) (3345) (3353) (3354) (3355) (3361) (3362) (3363) (3367) (3368) (3383)
- D:Stomduo:Peptulc (3389) (3403) (3409)
- D:Gen (3705)

SECRETION AND METABOLISM

Pancreas

3152 RELATIONSHIP BETWEEN PANCREATIC SECRETION AND PANCREATIC BLOOD FLOW. (E.) Goodhead, B. (U. Texas Med. Sch., San Antonio), H. S. HIMAL and J. Zambilowicz. *Gut* 11(1):62-68, 1970.

Pancreatic secretion volume (ml/min), pancreatic blood flow (ml/min), cardiac output (ml/min/kg) and pancreatic perfusion rate (ml/min/100g) were measured in control dogs and dogs infused with secretin, pancreozymin, urecholine or pentagastrin. The values for secretion volume, blood flow, cardiac output and perfusion rate were 0.012, 15.6, 182 and 57, resp., in control dogs and 0.465, 45.8, 240 and 164.2, resp., in response to secretin infusion. Secretion volume, blood flow and perfusion rate were increased by infusion of pancreozymin, urecholine and pentagastrin but to a lesser extent than the increase produced by infusion of secretin. Secretin also increased total blood and perfusion rate to esophagus, stomach, duodenum, gallbladder, pancreas, jejunum, ileum and colon.

3153 A FURTHER PHYSIOLOGICAL ROLE FOR NATURALLY OCCURRING TRYPSIN INHIBITORS: THE EVIDENCE FOR A TROPIC STIMULANT OF THE PANCREATIC ACINAR CELL. (E.) Melmed, R. N. (Middlesex Hosp. Med. Sch., London, England) and I. A. D. Bouchier. *Gut* 10(12):973-979, 1969.

The pancreas of male Sprague-Dawley rats fed a raw soybean supplement (with its naturally occurring heat-labile trypsin inhibitor) was 20 to 40% larger than the pancreas of a control group fed a heated soybean-supplemented diet. Both the specific activity and content of amylase were markedly increased in the pancreas of rats fed a daily supplement of purified trypsin inhibitor from soybean (0.6% w/w), ovomucoid (0.6% w/w) and bovine pancreas (0.043% w/w). Right or left vagotomy did not influence the response of the pancreas to raw soybean-supplemented diet and purified trypsin inhibitor. The primary function of the endogenously secreted pancreatic trypsin inhibitor may be to potentiate enzyme synthesis by the acinar cell thus providing an important stimulus for the repletion of digestive enzymes.

3154 EFFECT OF PRESSURE ON THE INTEGRITY OF THE DUCT-ACINAR SYSTEM OF THE PANCREAS. (E.) Pirola, R. C. (Roy. Free Hosp., London, England) and A. E. Davis. *Gut* 11(1):69-73, 1970.

Tests using India ink introduced into the pancreatic ducts of adult cats show that even in a 15-min period the duct contents can largely escape into the interstitial tissues at pressures below the maximum secretory pressure of the pancreas. There was a close correlation between the pressure in the pancreatic duct and the amount of ink seen in the inter-

stitial tissues, and the escape of ink (which appears to leave through clefts between the acinar cells) was only obvious at pressures of 30 and 40 mm Hg. Stimulated secretory pressure rose from 12 to 15 mm Hg during the control period to peaks of about 47 mm Hg within 10 min. Apart from pressure, other factors such as pancreatitis and the nature of the duct contents, can affect the integrity of the duct-acinar system.

- 3155 THE GASTROINTESTINAL STIMULUS TO INSULIN RELEASE: II. A DUAL ACTION OF SECRETIN. (E.) Kraegen, E. W. (St. Vincent's Hosp., Darlinghurst, New South Wales, Australia), D. J. Chisolm, J. D. Young and L. Lazarus. *J Clin Invest* 49(3): 524-529, 1970.

To further study the role of secretin in insulin release in normal subjects, 2 consecutive 20 min i.v. glucose infusions were administered to 9 healthy male volunteers (aged 18-23 yr) 150 min apart with and without intervening secretin infusion (10 U) given to approximate serum secretin levels seen after oral glucose ingestion. A highly significant potentiation of the insulin response to the post-secretin glucose infusion occurred when secretin was given 7 or 25 min before glucose (in the latter case, serum secretin was undetectable during the glucose infusion). Despite the augmented insulin response, no consistent change in blood glucose variation was observed and this is consistent with the suggestion that the facilitated disposal of an alimentary glucose load is not dependent solely on enhanced insulin secretion.

- 3156 INFLUENCE OF GLUCAGON ON PANCREATIC EXOCRINE SECRETION IN MAN. (E.) Dyck, W. P. (Scott and White Clin., Temple, Texas), E. C. Texter, Jr., J. M. Lasater and N. C. Hightower, Jr. *Gastroenterology* 58(4):532-529, 1970.

The effects of i.v. injection of glucagon (1.0, 5.0, and 10.0 $\mu\text{g}/\text{kg}$) on pancreatic exocrine function

were studied in 7 healthy human subjects during continuous i.v. infusion of secretin (3 U/kg/hr) and pancreozymin (1 U/kg/hr). Glucagon significantly depressed pancreatic secretory flow (without an accompanying reduction in bicarbonate levels) and total protein concentration in all subjects, as maximal inhibition of hormonally stimulated volume and protein concentration always occurred within the first 5 to 10 min and the inhibitory effect lasted no longer than 5 to 20 min for volume and 10 to 30 min for protein concentration. Changes in blood glucose concentration before and after glucagon administration did not follow a consistent pattern and bore no apparent relation to changes in pancreatic secretory volume. Glucagon may have a regulatory role in the control of pancreatic secretion.

- 3157 VAGAL STIMULATION: II. ITS EFFECT ON PANCREATIC SECRETION IN CONSCIOUS DOGS. (E.) White, T. T. (U. Washington Sch. Med., Seattle), J. Bourda, L. A. Robinson and Y. Suda. *Ann Surg* 171(3):357-364, 1970.

- 3158 EFFECT OF LONG-TERM ADMINISTRATION OF SECRETORY SUPPRESSIVES ON RAT PANCREAS. (E.) Lee, Y. S. (Yonsei U. Coll. Med., Seoul, Korea), Y. B. Lee and S. S. Hong. *Yonsei Med J* 10(1):19-24, 1969.

- P:Morph (3038) (3054) (3080) (3090) (3092)
- P:Secr:Int (3232)
- Diagproc (3266) (3289)
- D:Pancreas (3520) (3525)
- D:Pancreas;Pancreat (3534) (3535) (3536)

SECRETION AND METABOLISM

Hepatobiliary Tract

- 3159 THE TOXIC EFFECTS OF DIETHYL ETHER ON LIVER NUCLEIC ACID METABOLISM. (E.) Green, C. D. (U. Virginia Sch. Med., Charlottesville) and W. B. Loomney. *Progress in Anesthesiology: Proceedings of the Fourth World Congress of Anesthesiologists* 910-912, 1968.

The effects of diethyl ether anesthesia on nucleic acid metabolism were studied in regenerating, post-hemihapatctomized rat liver. The relative rate of

DNA synthesis in regenerating liver cells was determined by the grain count per cell nucleus in autoradiographs. The grain count per nucleus after exposure to 60 sec and 60 min of diethyl ether anesthesia was 55.3 ± 5.6 and 38.5 ± 3.4 , resp. Administration of ^{14}C -orotic acid immediately after diethyl ether anesthesia revealed a grain count/min/mg DNA of $11,190 \pm 1618$ after 2 min of anesthesia and $13,882 \pm 1682$ after 30 min. Diethyl ether anesthesia slows the rate of DNA formation.

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3160 METABOLISM OF ETHANOL AND FRUCTOSE IN THE PERFUSED RAT LIVER. (E.) Papenberg, J. (Med. Chem. Inst. U. Berne, Switzerland), J. P. von Wartburg and H. Aepli. *Enzym Biol Clin* 11(3): 237-250, 1970.

The interrelations between ethanol, glucose and fructose metabolism by isolated perfused rat liver were studied by determining the changes in enzyme (alcohol dehydrogenase and catalase) and metabolite (lactate, pyruvate) patterns. The initial concentration (200 mg/100 ml) of ethanol added to the perfusate decreased linearly (62 mg oxidized in the first hr and 52 mg in the second hr) indicating that ethanol utilization by the liver is independent of ethanol concentration. Addition of pyrazol ($3 \times 10^{-3}M$) to the perfusate resulted in a 90% decrease in alcohol dehydrogenase activity and a parallel decrease in ethanol utilization (ethanol oxidation was decreased by 62% in the first hr). Ethanol inhibited the uptake of fructose and its conversion to glucose by perfused liver. Ethanol oxidation was decreased by 25% in the presence of added fructose and fructose uptake was decreased by 21% in the presence of added ethanol. Increased ratios of lactate to pyruvate and α -glycerophosphate to dihydroxyacetone phosphate occurred during ethanol oxidation by isolated perfused liver (these changes were not prevented by pyrazol-induced inhibition of alcohol dehydrogenase).

3161 THE EFFECT OF HEPARIN ON THE METABOLISM OF TRIGLYCERIDES BY THE LIVER. (E.) Heimberg, M. (Vanderbilt U. Sch. Med., Nashville, Tenn.) and D. C. Davis. *Biochem Pharmacol* 19(2): 411-420, 1970.

The effects of heparin on the output of triglycerides, the uptake of chylomicra, the release of lipolytic activity into the perfusate, and the production of glucose, urea and ketone bodies were studied in the isolated, perfused rat liver. The output of triglycerides by the liver was significantly inhibited by crystalline heparin only at the smallest concentrations (0.42 USP units/ml perfusate) and the release of lipolytic activity by the liver was stimulated as the concentration of heparin in the medium increased (the maximal effect occurred at a concentration of 42 USP units/ml perfusate). Paradoxically, as the lipolytic activity in the medium increased, the inhibition of output of triglycerides by heparin diminished. The output of ketone bodies was slightly decreased by heparin but output of glucose and urea were not affected. The uptake and utilization by the liver of chylomicra labeled with palmitic acid $-1-^{14}C$ was accelerated by crystalline heparin. The output of triglyceride into very low density lipoprotein by the liver and the uptake of either chylomicron or very low density lipoprotein triglyceride seemingly occur by different cellular mechanisms.

3162 EFFECT OF L-ASPARAGINASE ON DNA SYNTHESIS IN REGENERATING LIVER AND IN OTHER DIVIDING TISSUES. (E.) Becker, F. F. (New York U. Sch.

Med., New York), R. Baserga and J. D. Broome. *Cancer Res* 30(1):133-137, 1970.

The effect a single submucicidal dose (600 units i.v. or i.p.) of L-asparaginase on DNA synthesis (as measured by tritiated thymidine incorporation) was studied in residual rat hepatocytes following 70% hepatectomy, in continuously dividing rat cells (lining epithelium of the jejunal and ileal crypts, white and red pulp of the spleen and basal layer of the epidermis), and in quiescent mouse and rat parotid and kidney cells stimulated (isoproterenol, folic acid and unilateral nephrectomy) to divide. DNA synthesis in regenerating hepatocytes but not that in continuously dividing cells or cells stimulated to divide was inhibited by L-asparaginase for 10 hr. Regenerating hepatocytes recovered from the inhibitory effect of L-asparaginase 10 to 12 hr after hepatectomy and were resistant to its inhibitory effect if L-asparaginase was administered at that time. Some early phase of biochemical response to 70% hepatectomy may be dependent upon an exogenous source of asparagine, thus implying participation in this response of important, newly-synthesized proteins.

3163 ROLE OF LIVER-CELL POTASSIUM IONS IN SECRETION OF SERUM ALBUMIN AND LIPOPROTEINS. (E.) Judah, J. D. (U. Coll. Hosp. Med. Sch., London, England) and M. R. Nicholls. *Biochem J* 116(4):663-669, 1970.

The role of K^+ in liver cells on protein synthesis (as measured by incorporation of $L-[1-^{14}C]$ leucine) and secretion of serum albumin and lipoprotein was studied *in vitro* in rat liver slices incubated in a medium with 7.7 mM K^+ or depleted of K^+ . If slices were depleted of K^+ , the incorporation of $L-[1-^{14}C]$ leucine into slice proteins and the secretion of serum albumin was reduced and serum albumin accounted for 65% and lipoproteins about 5 to 10% of the labeled protein secreted by the slices. The effect of K^+ depletion in liver slices was reversed by the addition of K^+ to the medium; the amount of serum albumin secreted by slices varied linearly with the K^+ content of the slices; and Rb^+ (but not Ca^{2+} , Li^+ and NH_4^+) could be substituted for K^+ in the medium. Addition of K^+ to the incubation medium promoted K^+ uptake and Na^+ and water efflux from liver slices and these effects were dependent on the K^+ concentration in the medium. The effect of K^+ on secretion of albumin and lipoprotein could be separated from its effect on protein synthesis by the addition of cycloheximide or puromycin to the incubation medium.

3164 THE EFFECT OF ORAL CONTRACEPTIVE STEROIDS ON BILE SECRETION AND BILIRUBIN $2m$ IN RATS. (E.) Heikel, T. A. J. (Dept. Chem. Path., U. Leeds, England) and G. H. Lathé. *Brit J Pharmacol* 38(3): 593-601, 1970.

The effects of estrogens, progestogens and their 17- α -ethinyl derivatives on bile flow, maximum rate of bilirubin secretion ($2m$), and serum and liver bilirubin levels were studied in virgin female Wistar rats. Normal basal bile flow was 8.0 ± 2.1 mg/min

per 100 gm body weight, and during bilirubin infusion was 9.2 ± 2.4 mg/min per 100 gm body weight. Both the 17- α -ethinyl substituted estrogens and progestogens greatly reduced basal bile flow and bile flow during continuous bilirubin infusion by 30 to 45% while the parent compounds, estradiol-17 β and 19-nortestosterone had little or no effect on bile flow. A large dose (40 mg/kg) of progestogens (lynestrenol and norethisterone acetate) reduced basal bile flow to 6.3 ± 1.7 mg/min and bile flow during bilirubin infusion to 6.0 ± 1.15 mg/min while 17- α -ethinylestradiol (25 mg/kg per day for 2 days) reduced basal bile flow to 5.3 ± 1.4 mg/min per 100 gm body weight from a control value of 9.0 ± 2.1 mg/min and bile flow during bilirubin infusion to 5.4 ± 1.9 mg/min from a control value of 9.4 ± 1.8 mg/min. Bilirubin maximum secretion rate (T_m) was affected by only the 3-methyl ether of 17- α -ethinylestradiol (mestranol) (a control value of 81.3 ± 6.9 μ g/min per 100 gm body weight was reduced to a value of 53.1 ± 8.3 μ g/min).

3165 THE ROLE OF THE HEPATIC ENDOPLASMIC RETICULUM IN THE BILIARY EXCRETION OF FOREIGN COMPOUNDS BY THE RAT: THE EFFECT OF PHENOBARBITONE AND SKF 525-A (DIETHYLAMINOETHYL DIPHENYLPROPYLACETATE). (E.) Levine, W. G. (Albert Einstein Coll. Med., Yeshiva U., Bronx, N.Y.), P. Millburn, R. L. Smith and R. T. Williams. *Biochem Pharmacol* 19(1): 235-244, 1970.

The effect of phenobarbitone and SKF 525-A on the biliary excretion of several foreign compounds and the role of the endoplasmic reticulum in this process were studied in female albino Wistar rats. Phenobarbitone pretreatment of rats stimulated the biliary excretion of biphenyl, stilbestrol and phenolphthalein (all of which underwent metabolism prior to excretion in the bile) and did not affect the biliary elimination of stilbestrol glucuronide, phenolphthalein glucuronide, succinylsulphathiazole and indocyanine green (all of which were excreted unchanged). SKF 525-A which inhibited the glucuronide conjugation of stilbestrol and phenolphthalein depressed their excretion in the bile in the form of their O-glucuronides and did not influence the biliary excretion of phenolphthalein glucuronide. The biliary excretion of biphenyl, stilbestrol and phenolphthalein were considered to occur in at least 2 steps: 1) metabolism and 2) transfer of the metabolites to bile. Phenobarbitone and SKF 525-A treatment in rats influenced (1) but not (2). The endoplasmic reticulum seemingly is involved in the metabolism of foreign compounds but it does not appear to play a role in their transfer from liver to bile.

3166 EFFECTS OF CHRONIC ETHANOL FEEDING ON SERUM LIPOPROTEIN METABOLISM IN THE RAT. (E.) Baraona, E. (Mount Sinai Sch. Med., Bronx, New York) and C. S. Lieber. *J Clin Invest* 49(4):769-778, 1970.

In Sprague-Dawley rats, the chronic feeding of ethanol-containing diet (6 ml/100 g body weight) resulted in rapidly increasing levels of blood alcohol, reaching a peak 2 hr after gastric intubation (about

153 mg/100 ml blood), followed by a progressive decline. The incorporation of dietary palmitic acid- 3 H and i.v. injected L-lysine- 14 C into serum lipoproteins was increased. The main increases of total amount, labeling, and specific activity of lipid and protein occurred in the dL1.019 lipoprotein fraction. Fat absorption and the clearance of injected chylomicrons were not affected by ethanol feeding. Blocking of lipoprotein and chylomicron removal with Triton did not prevent the action of ethanol on serum lipids, indicating that the ethanol effect is not likely due to defective removal of lipids from the circulation. Ethanol enhanced the incorporation of chylomicron fatty acids into newly synthesized very low density lipoproteins, as shown by an increased reappearance of the fatty acid label into the lipids of this fraction after injection of palmitate- 14 C/glycerol- 3 H doubly labeled chylomicrons. Alcohol feeding resulted in a progressive accumulation of fat in the liver. The results indicate that alcoholic hyperlipemia is due, at least in part, to an increase in newly synthesized lipoproteins, and that it is unlikely that defective lipoprotein synthesis or secretion represent primary mechanisms for the pathogenesis of the alcoholic fatty liver.

3167 BIOCHEMICAL PATHOLOGY OF FATTY LIVER INDUCED BY INHALED CARBON TETRACHLORIDE, WITH SPECIAL REFERENCE TO ATP AND LIPID METABOLISM IN THE MOUSE LIVER. (E.) Watanabe, S. (Okayama U. Med. Sch., Japan). *Acta Med Okayama* 23(6): 559-567, 1969.

The contents of ATP, triglyceride and total lipid in liver and the P:O ratio of liver mitochondria were determined in mice exposed to inhalation of 800 p.p.m. of carbon tetrachloride for 8 hr and in control mice. Liver ATP content decreased slightly immediately after inhalation, rapidly decreased until 4 hr after inhalation and gradually decreased until 20 hr after inhalation. Total lipid content increased slightly immediately after the exposure to carbon tetrachloride and increased gradually until 20 hr later. Triglyceride content increased at an almost constant rate during and after exposure to carbon tetrachloride. P:O ratio of liver mitochondria did not change immediately after exposure but later kept parallel in relation to decreased ATP content in the liver as revealed by electron microscopy. The decrease in ATP content in the liver after carbon tetrachloride inhalation is attributed mainly to the uncoupling of oxidative phosphorylation of liver mitochondria.

3168 BILE COMPOSITION IN THE CANINE GALLBLADDER AFTER SELECTIVE GASTRIC AND TRUNCAL VAGOTOMY. (E.) Inberg, M. V. (Dept. Surg., U. Turku, Finland), J. Ahonen and T. M. Scheinin. *Ann Chir Gynaec Fenn* 58(4):329-333, 1969.

The composition (cholates, cholesterol and phospholipids) of gallbladder bile was studied successively after pyloroplasty, selective gastric vagotomy, and truncal vagotomy in four dogs. The composition of canine gallbladder bile was not significantly

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altered after selective gastric vagotomy, truncal vagotomy, and pyloroplasty alone, nor was the ratio of cholesterol to cholate. The only difference between selective gastric and truncal vagotomy was the increased resting volume and the great residual volume of the vagotomized gallbladder after its contraction. The association of gallstones with the vagotomized gallbladder is discussed.

- 3169 INHIBITION BY BILE SALTS OF THE JEJUNAL TRANSPORT OF 3-O-METHYL GLUCOSE. (E.) Roy, C. C. (U. Colorado Med. Ctr., Denver), R. S. Dubois and F. Philippon. *Nature* 225(5237): 1055-1056, 1970.

The effects of bile salts on jejunal transport of 3-O-methyl glucose were studied in Sprague-Dawley rats with extracorporeally perfused segments of jejunum removed from their intact circulation. Bile depletion was carried out by use of bile duct fistula with cannula. There was a significant increase of 3-O-methyl glucose absorption in bile-depleted animals (23.2 ± 1.95 %/min vs controls 15.1 ± 1.13 %/min, $p < 0.01$). A marked difference in *in vitro* λ absorption/min of 3-O-methylglucose existed between bile fistula rats perfused *in vivo* with electrolyte solution (33.6 ± 1.86 %/min) and those perfused with either bile (20.6 ± 1.04 %/min) or sodium taurocholate (21.8 ± 1.07 %/min) for 48 hr. There was no correlation between absorptive capacity and metabolic function as assessed by protein, hexokinase, Na^+/K^+ -stimulated ATPase and glucose determinations performed on tissue immediately adjacent to removed jejunal segments. Since there was no apparent relationship between 3-O-methyl glucose absorption and metabolic function in presence or absence of bile salts, it is postulated that bile salts may have a specific effect on the monosaccharide-active transport system localized in plasma membrane of epithelial cell microvilli.

- 3170 BIOLOGICAL ASSAY OF CHOLECYSTOKININ IN GUINEA-PIG GALLBLADDER *IN SITU*. (E.) Ljungberg, S. (Dept. Pharmacol. Stockholm, Sweden). *Acta Pharm Suec* 6(6):599-606, 1969.

A method for the biological assay of cholecystokinin in the guinea pig gallbladder *in situ* is described. Under urethane anesthesia the jugular vein was cannulated, the gallbladder was surgically exposed and a thin silk thread was fastened to its free pole, without perforation. In order to measure the isotonic contractions of the gallbladder, the bile duct was kept intact and the free end of the thread was extended over a pulley, with a 0.5 gm counterweight, and connected to a strain transducer. An analysis of the effect of 5 different dosage levels of cholecystokinin (0.05 to 0.80 Ivy Dog Units/kg) revealed a rectilinear log dose-response line and the weighted mean of the precision index in ten assays was $\lambda = 0.0746 \pm 0.0087$.

- 3171 SOME PHARMACOLOGICAL PROPERTIES OF CHOLECYSTOKININ. (E.) Ljungberg, S. (Dept. Pharmacol., Stockholm, Sweden). *Acta Pharm Suec* 6(6):607-612, 1969.

The pharmacologic properties of purified preparations of cholecystokinin-pancreozymin were investigated in mice, rabbits and guinea pigs. No toxic effects of a single i.v. administration of cholecystokinin (up to 2000 Ivy Dog Units (IDU)/kg) were produced in mice and doses between 0.2 and 32.0 IDU/kg, i.v., had no significant effect on the blood pressure, heart rate, and ventilation in urethane-anesthetized rabbits. A concentration of 0.005 IDU/ml caused an acetylcholine-like contraction in *in vitro* preparation of guinea pig intestine. Moderate doses of 1 IDU/kg gave a significant increase in lymph flow (1.23 ml/hr compared to a control value of 1.01 ml/hr) from the intestinal tract in rats. The cholecystokinin-pancreozymin preparation exhibited a villikin-like activity characterized by stimulating movements of the villi and of intestinal activity.

- 3172 HEPATIC METABOLISM OF FREE FATTY ACIDS IN NORMAL AND DIABETIC DOGS. (E.) Basso, L. V. (U. California San Francisco Med. Ctr.) and R. J. Havel. *J Clin Invest* 49(3):537-547, 1970.

Fasted dogs prepared with catheters in the femoral artery, portal vein, and hepatic vein and infused i.v. with palmitate- 1^{14}C were used to estimate uptake of free fatty acids in liver and their conversion to major metabolic products secreted into hepatic venous blood. Animals were studied under normal conditions; when fat mobilization was increased abruptly by infusing norepinephrine; and when insulin was withdrawn from depancreatized dogs (it was assumed the 80% of hepatic blood flow was derived from the portal vein). Hepatic uptake was proportional to net outflow transport of plasma free fatty acids in the 3 groups and, in each, the hepatic extraction fraction was about 25%. Since the specific activity of the free fatty acids entering and leaving the liver was equal and their composition was closely similar in the 3 sites sampled, apparently palmitate is a representative tracer for free fatty acids entering the liver and the liver apparently does not release free fatty acids into the blood. In norepinephrine-infused dogs, the fraction of free fatty acids secreted in triglycerides (13%) was similar to that of control animals, so that transport of triglycerides was increased. In diabetic dogs no increased transport could be demonstrated since an average of only 2% of free fatty acids was converted to plasma triglyceride fatty acids; the hyperlipemia uniformly observed appeared to result from defective removal of triglycerides from the blood. A similar fraction of free fatty acids was converted to ketones in normal and norepinephrine-infused dogs, was somewhat higher in diabetic animals and, in addition, a substantial quantity of ketones was derived from unlabeled precursors. Fractional conversion of free fatty acids to CO_2 was similar in normal and norepinephrine-infused dogs, but reduced in the diabetics.

- 3173 REDUCTION OF DEHYDROEPIANDROSTERONE SULFATE IN THE LIVER DURING ETHANOL METABOLISM. (E.) Admtrand, W. H. (U. California San Francisco Med. Ctr.), T. Cronholm and J. Sjoval. *Biochim Biophys Acta* 202(2):343-348, 1970.

The influence of the metabolism of ethanol on the reduction of 17-ketosteroid sulfate to 17 β -hydroxysteroid sulfate *in vitro* was studied by gas-liquid chromatography and mass spectrometry in liver slices from female guinea pigs. Superfusion of guinea pig liver slices with a solution containing dihydroepiandrosterone sulfate resulted in the formation of 5-androsterone-3 β ,17 β -diol sulfate and when ethanol (2.2-43.5 mM) was added to superfusion fluid there was a consistent increase of 1.3-4.5 fold in androstenediol sulfate production. The same magnitude of increase occurred during superfusion with 1,1-dideuterioethanol, and there was a prompt incorporation of deuterium into the androstenediol sulfate to a maximum of 42 atom percent excess (in the presence of 4-bromopyrazole, dideuterioethanol did not increase deuterated or nondeuterated androstenediol sulfate production). The increased concentration of NADH during ethanol metabolism apparently caused an increased reduction of the 17-ketosteroid to the 17 β -hydroxysteroid.

- 3174 THE EFFECTS OF QUABAIN ON BILE SECRETION IN THE RABBIT. (Fr.) Erlinger, S. (Hosp. Beaujon, Cligny, France), M. Dumont and J. P. Benhamou. *Rev Franc Etud Clin Biol* 14(10):1007-1009, 1969.
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- 3177 PROTEIN AND LIPID BIOSYNTHESIS IN RABBIT LIVER AFTER PARTIAL HEPATECTOMY. (Ukr.) Zhurbin, G. I. (Inst. Biochem. Acad. Sci., Ukraine, Kiev, USSR), M. F. Guly and N. A. Stogny. *Ukr Biokhim Zh* 41(6):686-690, 1969.
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- 3187 CRITICAL CONSIDERATIONS AND EXPERIMENTAL CONTRIBUTION TO A STUDY OF THE MECHANISM OF THE HEPATOTOXIC ACTION OF CARBON TETRACHLORIDE. (Fr.) Chera, G. (Inst. Med. Res., Rumanian Socialist Republic's Acad.). *Rev Roum Embryol Cytol* 5(2):123-134, 1968.
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- P:Absorp (3095) (3101) (3115) (3116) (3122)
- P:Moril (3124)
- P:Secr:Int (3230)
- P:Gen (3258)
- Di:agpro (3260) (3266) (3301)
- D:S:Intest:Malabs (3451)
- D:L:ivbil (3550) (3558) (3563) (3564) (3565) (3573) (3574) (3577) (3578) (3579) (3580) (3587)
- D:L:ivbil:A:Novv:Hep (3596) (3607) (3609) (3610) (3611) (3615) (3616) (3617) (3619) (3621)
- D:L:ivbil:C:Hep (3645)
- D:L:ivbil:C:irrh (3650) (3658)
- D:L:ivbil:G:allb (3661) (3670)
- D:Gen (3695)

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Intestine

- 3226 VITAMIN D STIMULATION OF CALCIUM-DEPENDENT ADENOSINE TRIPHOSPHATASE IN CHICK INTES-TINAL BRUSH BORDERS. (E.) Melancon, M. J. Jr. (Dept. Biochem., U. Wisconsin, Madison) and H. F. DeLuca. *Biochemistry* 9(8):1658-1664, 1970.

The activity of calcium-dependent ATPase in the brush borders of the small intestine was studied in vitamin D-deficient and -repleted (vitamin D₃, 400 or 500 IU p.o. or i.v.) chicks. ATPase activity in brush borders was increased 72 hr after vitamin D₃ administration. Addition of 10mM calcium ions to the incubation medium did not affect ATPase activity in isolated brush borders from vitamin D-deficient chicks but markedly increased ATPase activity in isolated brush borders from chicks which had received vitamin D₃. The stimulatory effect of calcium on brush border ATPase activity required the presence of Mg²⁺; ATPase activity was markedly increased by Mg²⁺ but not to the extent of the combination of Mg²⁺ and Ca²⁺. When Mg²⁺ was added to the incubation medium in concentrations lower than ATP concentration, ATPase activity in brush borders was markedly decreased. The activity of calcium-dependent ATPase in brush borders was optimal at pH 7.7 and was not affected by either Na⁺/K⁺ ATPase or oxidative phosphorylation both in the presence or absence of Ca²⁺. The time course of the increase of calcium-dependent ATPase activity following p.o. or i.v. administration of vitamin D₃ was positively correlated with the time course of appearance of calcium absorption. Calcium-dependent ATPase activity in intestinal brush borders seemingly may be part of the vitamin D-induced calcium transport system.

- 3227 STEROIDS IN GERMFREE AND CONVENTIONAL RATS: SULPHO- AND GLUCURONOHYDROLASE ACTIVITIES OF CECAL CONTENTS FROM CONVENTIONAL RATS. (E.) Eriksson, H. (Karolinska Inst., Stockholm, Sweden) and J. A. Gustafsson. *Eur J Biochem* 13(1):198-202, 1970.

The cleaving of conjugated steroids by intestinal microflora was investigated by incubating cecal contents in germfree and conventional rats with conjugated steroids (7 α -³H-dehydroepiandrosterone 3-sulfate and 7 α -³H-dehydroepiandrosterone 3-glucuronoside) and identifying the products (Sephadex Chromatography). The steroid sulfate was completely hydrolyzed when incubated with an 800 x g sediment but not with the supernatant of cecal contents from conventional rats, and was not hydrolyzed when incubated with cecal contents or different fractions of intestinal mucosa from the germfree rats. The glucuronoside was completely hydrolyzed in all incubations. Ratios between free and conjugated metabolites (from chromatography of fecal extracts after 4-¹⁴C-corticosterone administration) were 0.1 for females and 0.4 for males (in germfree rats), and 1.2 for females and 1.5 for males (in conventional rats). Glucuronidase seemingly is active even in germfree conditions; whereas, sulfatase activity seemingly is microbial and occurs both *in vitro* and *in vivo*.

- 3228 THE EFFECT OF PURE NATURAL SECRETIN ON THE BICARBONATE SECRETION INTO THE DUODENUM IN MAN. (E.) Petersen, H. (Ullevål Hosp., Oslo, Norway). *Scand J Gastroent* 5(2):105-111, 1970.

The bicarbonate response to 1 U/kg i.v. natural secretin was examined in 26 healthy males and females by collecting the gastric and duodenal contents (using the double-lumened Lagerlof tube) and determining bicarbonate outputs (in mEq) by the gasometric method of Van Slyke). The basal 1 hr secretion varied considerably with no relation to body weight but during the first post-secretion hr outputs of bicarbonate were nearly constant and correlated significantly to body weight (r of 0.39). As graded doses of secretin were administered (0.04, 0.2, 1, and 5 clinical U/kg) both the magnitude and duration of the bicarbonate response increased with the relation linear up to 1U/kg which appears to give a near maximal effect.

- 3229 HOURLY AMYLASURIC FLOW AFTER STIMULATION BY DUODENAL HORMONE. (Fr.) Wettendorff, P. (Hosp. Ixelles, Belgium), C. Hensgens, R. Van Der Hoeden and A. Delcourt. *Arch Frans Mal Appar Dig* 59(1-2):71-76, 1970.

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- 3231 INTESTINAL ACTIN-LIKE PROTEIN. (E.) Yabu, H. (Sapporo Med. Coll., Japan), R. Takahashi and E. Miyazaki. *Jap J Physiol* 19(6):722-738, 1969.

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- 3233 METABOLIC CHANGES OF RAT INTESTINE DURING IRON ABSORPTION. (E.) Hattori, M. (Fac. Med., U. Tokyo, Japan) and Y. Yawata. *Jap J Nucl Med* 6(4):414, 1969.

- 3234 IMMUNOLOGICAL PROBLEMS AND REJECTION RESPONSE IN THE COURSE OF HUMAN SMALL INTESTINAL HOMOTRANSPLANTS. (Fr.) Olivier, Ch. (Surg. Clin. Hotel-Dieu, Paris, France), J. L. Amiel and L. Schwarzenberg. *J Chir* 98(4)385-394, 1969.

- 3235 DIGESTION: INTESTINAL SECRETION. (E.) Hendrix, T. R. (Johns Hopkins U. Sch. Med., Baltimore, Md.) and T. M. Bayless. *Ann Rev Physiol* 32:139-164, 1970.

3236 EFFECT OF TESTOSTERONE ON THE INTESTINAL SECRETION OF DOGS: A PRELIMINARY COMMUNICATION. (E.) Mitra, N. K. (J. N. Med. Coll. A.M.U., Aligarh, India), S. Kumar and D. N. Khanna. *J Ass Physicians India* 17(12):691-694, 1969.

3237 EFFECTS OF ANOXIA AND METABOLIC INHIBITORS ON THE SUGAR-EVOKED POTENTIAL AND DEMONSTRATION OF SUGAR-OUTFLOW POTENTIAL IN TOAD INTESTINE. (E.) Hoshi, T. (Tohoku U. Sch. Med., Sendai, Japan) and Y. Komatsu. *Tohoku J Exp Med* 100(1):47-59, 1970.

3238 THE EFFECT OF DUODENAL AND MID SMALL BOWEL TRANSECTION ON THE FREQUENCY GRADIENT OF THE PACESETTER POTENTIAL IN THE CANINE SMALL INTESTINE. (E.) Code, C. F. (Mayo Grad. Sch. Med., U. Minnesota, Rochester) and J. H. Szurszewski. *J Physiol* 207(2):281-289, 1970.

3239 EFFECT OF VITAMIN D ON TISSUE CALCIUM OF RAT DUODENUM. (E.) Urban, E. (U. Iowa Coll. Med., Iowa City) and H. P. Schedl. *Scand J Gastroent* 5(1):33-37, 1970.

- P:Morph (3024) (3025) (3029) (3031) (3036) (3052) (3086) (3091) (3093)
- P:Absorp (3094) (3099) (3100) (3103) (3105) (3106) (3107) (3108) (3109) (3112)
- P:Motil (3126) (3131)
- P:Gen (3246) (3256) (3258)
- Diagproc (3311)
- D:S.Intest (3419)
- D:L.Intest (3500)
- D:Livbil:A.V.Hep (3636)
- D:Livbil:Gallb (3675)
- D:Gen (3719) (3736)

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3240 EFFECT OF ETHANOL METABOLISM ON REDOX STATE OF STEROID SULPHATES IN MAN. (E.) Cronholm, T. (Karolinska Inst., Stockholm, Sweden) and J. Sjoval. *Europ J Biochem* 13(1):124-131, 1970.

The concentrations of hydroxy- and ketosteroid sulphates in plasma and the incorporation of deuterium in the steroids were determined by gas chromatography in 6 healthy men after the p.o. administration of ethanol (0.1-g/kg). The ratios between the 17 β -hydroxysteroid and the 17-ketosteroid, between the 3-sulphates of 5 α -androstane-3 α , 17 β -diol and androstosterone and between their monosulphates increased after ethanol administration but the levels of 5 α -androstane-3 β , 17 β -diol monosulphate, pregnenolone and 5-pregnene-3 β , 20 α -diol monosulphates could not be established. Oral administration (0.1g/kg) of [1-²H₂]ethanol resulted in rapid incorporation (16-22 atom percent excess) into the sulphates of 17 β -hydroxysteroids, slight incorporation (4 atom percent excess) into the monosulphate of 5-pregnene-3 β , 20 α -diol, and no incorporation into the disulphates. The NADH/NAD⁺ ratio in the liver cell cytoplasm seemingly determines the ratio between 3-sulphates of 17 β -hydroxysteroids and corresponding 17-ketosteroids in plasma but the 3-sulphate of 5-pregnene-3 β , 20 α -diol is not formed at the same site or with the same coenzyme.

3241 GASTRIC MUCOSAL BLOOD FLOW FOLLOWING DAMAGE BY ETHANOL, ACETIC ACID OR ASPIRIN. (E.) Augur, N. A. Jr. (Dept. Physiol. U. Michigan, Ann Arbor). *Gastroenterology* 58(3):311-320, 1970.

The gastric mucosal blood flow in vagally denervated Heidenhain pouches in dogs was estimated by amino-

pyrine clearance in four 30 min periods after irrigations with acid solutions of ethanol, acetic acid and aspirin. Mucosal blood flow increased initially when either ethanol or acetic acid was used and subsequently declined with appearance of evidence for gastric mucosal barrier damage. In spite of similar evidence for gastric mucosal barrier damage, the mucosal blood flow with the aspirin solutions was, by the fourth period, significantly greater than the mucosal blood flow with the acetic acid solutions. Studies with acetic acid and aspirin solutions were repeated in vagally innervated Pavlov pouches and the pattern of mucosal blood flow was similar and (in those experiments with homogeneous base lines) the mucosal blood flow of the aspirin studies in the fourth period was again significantly greater than that of the acetic acid study. Although a greater mucosal blood flow might be considered a beneficial and protective influence, invariable bleeding characterized the fourth period of the aspirin experiments while only inconstant and minimal bleeding was noted in the fourth period of the acetic acid experiments.

3242 TRANSPERITONEAL EXCHANGE: I. PERITONEAL PERMEABILITY STUDIED BY TRANSPERITONEAL PLASMA CLEARANCE OF UREA, PAH, INSULIN AND SERUM ALBUMIN IN RABBITS. (E.) Aune, S. (Ullevål Hosp., Oslo, Norway). *Scand J Gastroent* 5(2):85-97, 1970.

The blood-peritoneal barrier was studied by following the transfer of urea, p-aminohippuric acid, insulin and serum albumin (given in an i.v. infusion) from plasma into the peritoneal cavity (samples drawn through a drain inserted in the lateral part

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of the right iliac fossa) in rabbits. Relative clearance using urea clearance as a reference unit (transperitoneal clearance of test solute/transperitoneal clearance of urea) was not affected by variations throughout the experiment and indicated that p-aminohippuric acid appeared in the peritoneum at a rate of 50% of urea, inulin at a rate 25%, and serum albumin at a rate 4.5% (urea clearance itself averaged 2.75 ml/min). The relative clearance rates are comparable to relative diffusibilities. Solutes apparently pass through the peritoneal membrane either by diffusion alone or by combined diffusion and the solvent drag effect of a convective fluid flow although the blood flow limitation of the plasma-peritoneal exchange of solutes cannot be excluded.

3243 STUDIES ON THE RELEASE OF BRADYKININ BY THE SPLANCHNIC CIRCULATION DURING ENDOTOXIC SHOCK. (E.) Shah, J. P. (Hahnemann Med. Coll., Philadelphia, Pa.), U. S. Shah, H. E. Appert and J. M. Howard. *J Trauma* 10(3):255-259, 1970.

Bradykinin concentrations in the femoral artery, portal and hepatic veins in dogs following endotoxin administration (1.5 mg/kg i.v.) were determined by the method of Brocklehurst and Zeitlin. Endotoxin reduced blood pressure from a normal value of 150 mm Hg to 40 to 60 mm Hg and bradykinin levels in portal and hepatic veins and femoral artery (normal values = 3.3, 3.0 and 2.6 ng/ml, resp.). Although the bradykinin level decrease was not statistically significant, the results are consistent with the concept that splanchnic circulation is important in the activation of the kinin production systems.

3244 TRANSPERITONEAL EXCHANGE: II. PERITONEAL BLOOD FLOW ESTIMATED BY HYDROGEN GAS CLEARANCE. (E.) Aume, S. (Ullevål Hosp., Oslo, Norway). *Scand J Gastroent* 5(2):99-104, 1970.

The peritoneal blood flow was estimated by measuring polarographically the removal of hydrogen gas from a perfusion fluid volume injected i.p. in rabbits. Total clearance of the hydrogen gas from the perfusion fluid was equal to the amount leaving the fluid per unit time and concentration gradient and during total clearance periods, mean arterial blood pressure varied between 96 and 120 mm Hg. On the average, the hydrogen loss through the perfusion tubes corresponded to a clearance of 2.25 ml/min. The blood flow clearance of the peritoneal compartment ranged from 12.4 to 21.6 ml/min, with a mean of 17.04 ml/min. Blood flow was at least large enough not to influence the transperitoneal transport of solutes normally present in the blood (the main restriction to such transport is the permeability of the peritoneal membrane).

3245 EXPERIMENTAL STUDIES ON ACUTE STRANGULATED INTESTINAL OBSTRUCTIONS IN GERM-FREE ANIMALS. (E.) Shirota, A. (Nippon Med. Sch., Tokyo, Japan), H. Yokota, H. Hattori, M. Onda, Y. Kiso, K. Yamashita, T. Shiba, Y. Moriyama, K. Adachi, M. Miyashita and K. Aihara. *Internat Surg* 53(3):223-229, 1970.

Completely germ-free 3-month-old ICR mice and a control group contaminated with *E. coli* were used to determine the role of the intestinal bacterial flora in death from acute intestinal obstructions. The survival time after experimentally-induced acute strangulated small intestinal obstructions, was 5-10 hr in the contaminated and 23-49 hr in the germ-free mice. There was no significant increase in the number of microorganisms in the contents of the closed intestinal loop of the germ-free mice, but in the *E. coli* mice there was an exponential increase. Pronounced histological, and cytological changes (disappearance of microvilli, necrosis, dissociation of desmosomes in the intracellular spaces, swelling of mitochondria and disappearance of endoplasmic reticulum) in the intestinal loop were more evident in the *E. coli* mice. Liberation of lipopolysaccharide endotoxin of *E. coli* into the blood could not be found in the germ-free mice, but was clearly evident in the contaminated mice. Liberation of endotoxin into the blood may be closely related to the level of endotoxin in the intestinal contents.

3246 PLASMA SKIMMING IN THE INTESTINAL WALL. (E.) Jodal, M. (Dept. Physiol. U. Goteborg, Sweden) and O. Lundgren. *Bibliotheca Anat* 10:310-311, 1969.

3247 STUDIES ON IRON METABOLISM WITH A WHOLE BODY COUNTER. (E.) Saito, H. (Nagoya U. Sch. Med., Japan). *Jap J Nucl Med* 6(4):412-413, 1969.

3248 RECEPTOR ACTIVITY FOR PORCINE ENTEROVIRUSES IN PIG TISSUES. (E.) Derbyshire, J. B. (Agric. Res. Council, Compton, Newbury, Berkshire, England) and D. M. Jessett. *J Med Microbiol* 2(4):489-493, 1969.

3249 HEMODYNAMIC STUDIES OF THE ABDOMINAL ORGANS BY THE USE OF ¹³¹IMAA AND ⁸⁵Kr. (E.) Kitani, K. (2nd Dept. Int. Med., U. Tokyo, Japan). *Jap J Nucl Med* 6(4):403, 1969.

3250 PRESSURE PERMEABILITY RELATIONS IN CAPILLARIES OF THE RABBIT OMENTUM. (E.) Intaglietta, M. (Dept. Aerospace Mech. Engin. Sci., U. California, La Jolla). *Bibliotheca Anat* 10:238-240, 1969.

3251 LUMINESCENCE-MICROSCOPIC EVIDENCE FOR THE EXISTENCE OF A GRADIENT OF VASCULAR PERMEABILITY IN THE MESENTERY CAPILLARY BED. (E.) Hauck, G. (Inst. Physiol., U. Wurzburg, Germany). *Bibliotheca Anat* 10:221-224, 1969.

3252 THE EFFECT OF DTPA AND CALCIUM ON THE TRANSLLOCATION OF INTRAPERITONEALLY ADMINISTERED ²³⁹PuO₂ PARTICLES. (E.) Sanders, C. L. (Pacific Northwest Lab., Batelle Mem. Inst., Rich-

land, Wash.) and W. J. Bair. *Health Phys* 18(2):169-173, 1970.

3253 IMMUNOLOGY IN GASTROINTESTINAL RESEARCH AND PATIENT CARE. (E.) McGuigan, J. E. (U. Florida Sch. Med., Gainesville). *Amer J Surg* 119(2):111-117, 1970.

3254 BLOOD AND LYMPH VESSELS AND BODY FLUID FLOW IN THE LIVER. (E.) Misimaru, Y. (Lab. Angiol., Tenno, Kure, Japan). *Hiroshima J Med Sci* 18(2-3):65-93, 1969.

3255 THE EFFECT OF ACETYLCHOLINE AND NOREPINEPHRINE ON NITROGEN METABOLISM IN THE GASTROINTESTINAL TRACT IN SHEEP. (Rus.) Soldatenkov, P. F. (Dept. Normal Path. Physiol., Agric. Inst., Sverdlovsk, USSR) and K. D. Yugayi. *Fiziol Zh SSSR Sechenov* 55(12):1493-1500, 1969.

3256 THE BACTERIAL FLORA AND GAS CONTENT OF THE SMALL INTESTINE. (Nor.) Bystrom, J. (Karolinska Hosp., Stockholm, Sweden). *Lakartidningen* 66(51):5391-5397, 1969.

3257 WATER IN RED BLOOD CELLS AND PLASMA OF MESENTERIC BLOOD. (E.) Nelson, R. A. (Mayo Clin., Rochester, Minn.), E. A. Ernst and H. F. McCorkle. *Amer J Dig Dis* 15(4):343-346, 1970.

3258 THE EFFECTS OF GRADED ELECTRICAL STIMULATION OR REFLEX ACTIVATION OF THE SYMPATHETIC AND THE PARASYMPATHETIC NERVE SUPPLY ON THE REGIONAL BLOOD FLOW IN CAT COLON. (E.) Hulten, L. (Dept. Physiol., U. Goteburg, Sweden), M. Jodal and O. Lundgren. *Bibliotheca Anat* 10:312-315, 1969.

3259 TRANS-HEPATIC VASCULAR RESISTANCE DURING PROLONGED ISOLATED LIVER PERFUSIONS. (E.) Abouna, G. M. (U. Colorado Med. Ctr., Denver, Colo.), T. Ashcroft and J. R. Young. *Brit J Surg* 56(12):921-925, 1969.

- P:Morph (3043) (3064)
- P:Absorp (3119)
- D:Gen (3723)

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3260 THE RELATIONSHIP OF THE SERUM ALKALINE PHOSPHATASE TO URINARY HYDROXYPROLINE EXCRETION IN LIVER AND BONE DISEASES. (E.) Cerda, J. J. (VA Hosp. Philadelphia, Pa.), P. P. Toskes, N. A. Shopa and J. H. Wilkinson. *Clin Chem Acta* 27(3):437-443, 1970.

The value of simultaneous determination of serum alkaline phosphatase activity and 24-hr urinary hydroxyproline excretion in the differential diagnosis of bone versus liver hyperphosphatemia (serum alkaline phosphatase greater than 40 IU/liter) was determined in 32 patients (19 with liver disease, 13 with bone disease). All patients with bone disease demonstrated elevations in both urinary hydroxyproline excretion and serum alkaline phosphatase activity while patients with liver disease (biliary cirrhosis, obstructive jaundice, cholestasis, steatonecrosis, hepatitis, sarcoma of liver, liver metastases) showed elevations only in serum alkaline phosphatase activity. There was an excellent correlation between urinary hydroxyproline excretion and the source (liver or bone) alkaline phosphatase isoenzymes in 4/5 patients with liver disease and 4 patients with bone disease. Urinary hydroxyproline excretion seemingly is a reliable method of selecting those patients whose elevated serum alkaline phosphatase is secondary to bone disease as opposed to liver disease.

3261 THE α -FETOPROTEIN TEST FOR LIVER CANCER. (E.) Shanmugaratnam, K. (no affil), K. L. Chua and C. S. Seah. *Singapore Med J* 10(4):230-232, 1969.

The presence of serum α -fetoprotein was investigated in 120 patients from Singapore (33 cases of hepatocellular carcinoma, 3 cases of embryonal carcinoma of the testis and 84 controls). The α -fetoprotein test was positive in 25 of the 33 (76%) cases of hepatocellular carcinoma, and in 2 of the 3 (66%) cases of embryonal carcinoma of the testis. All of the 84 controls (25 cases of cirrhosis, 2 cases of hepatitis, 2 cases of cholangiocellular carcinoma, 4 cases of secondary liver carcinoma, 24 cases of other cancers, and 27 cases of miscellaneous diseases) gave negative results.

3262 MODIFICATION OF PANCREATIC BLOOD FLOW WITH BALLOON CATHETERS: A NEW APPROACH TO PANCREATIC ANGIOGRAPHY. (E.) Reuter, S. R. (U. Hosp. San Diego, Cal.). *Radiology* 95(1):57-63, 1970.

In order to determine whether or not pancreatic angiography could be improved by using the pancreatic arteries as collateral vessels, 50 occlusive examinations were attempted in 22 patients and 20 superselective angiograms of the gastroduodenal, splenic or dorsal pancreatic arteries were performed in 12 patients. In 46 angiographic examinations, temporary occlusion of the celiac, hepatic, or superior mesenteric arteries with balloon catheters frequently improved visualization of arteries in and around the pancreas by causing pancreatic arteries to participate in the collateral blood supply to the occluded vascular bed. The best visualization of the

entire pancreas resulted from celiac occlusion and superior mesenteric injection while hepatic occlusion and superior mesenteric injection improved visualization only in the head, since the splenic artery received its normal blood supply from the nonoccluded celiac artery. In 8 patients, small branches in the head of the pancreas were demonstrated on occlusive examinations which were not seen on combined study, and visualization was frequently equivalent to that found at gastroduodenal angiography. Studies obtained with hepatic occlusion and celiac injection were much less satisfactory than the combined celiac-superior mesenteric studies. Superselective gastroduodenal injections were performed in 10 cases: celiac occlusion with superior mesenteric injection in 4, superior mesenteric occlusion and celiac injection in 3, and hepatic occlusion and superior mesenteric injection in 3. A comparison of these examinations showed that the visualization was about equal in 5. In the other 5 gastroduodenal angiography was better both because of larger number of branches filled and a higher concentration of contrast medium in the branches in the head of the pancreas.

3263 DIAGNOSIS OF HEPATIC HEMANGIOMA WITH COMBINED SCANNING TECHNIQUE. (E.) Freeman, L. M. (Albert Einstein Coll. Med., Yeshiva U., Bronx, N. Y.), R. C. Bernstein and D. B. Hayt. *Radiology* 95(1):127-128, 1970.

An upper gastrointestinal series performed on a 63-yr-old male presenting with progressive abdominal enlargements of several months duration showed a large left upper quadrant mass displacing the stomach forward, laterally and downward. A liver scan (120 μ C colloidal ^{198}Au) demonstrated a massive hepatomegaly with evidence of a large intrahepatic space-occupying lesion, mainly in the left lobe. Selective celiac angiography with and without previous injection of epinephrine led to a suspected diagnosis of either cavernous hemangioma or hepatoma. A hepatic blood pool scan performed 10 min after i.v. administration of 350 μ C of ^{131}I -human serum albumin showed complete filling-in of the defects seen on the ^{198}Au scan. The diagnosis of hemangioma was then considered to be most possible and was confirmed at surgery. Combined liver-scanning technique may be helpful in differentiating hemangioma from other benign and malignant hepatic masses.

3264 EVALUATION OF THE DOUBLE CONTRAST MEDIA TECHNIQUE FOR ORAL CHOLECYSTOGRAPHY. (E.) Palmer, V. (Portland, Oreg.) and A. Gault. *Radiol Techn* 41(5):284-287, 1970.

The combined use of iopanoic acid (Telepaque), sodium ipodate (Oragrafin Granules) and calcium ipodate (Oragrafin Capsules) as a double-contrast media for cholecystographic examination was tested in 112 patients. A standard dose of three grams telepaque and three grams Oragrafin Granules were administered after a fat-free dinner, about 10 to 14 hr before cholecystographic examination. Three hours before the examination one packet of

Oragrafin Capsules was administered with no more than one-quarter cup of water. Eighty-three gall bladders (80%) were visualized without need for reconcentrations, and seven (6%) were visualized with the use of a fatty meal. Only three patients complained of nausea. The reconcentrations percentage was previously 50% when using only three grams of Telepaque and this percentage dropped to 20% when Telepaque, Oragrafin Capsules and Oragrafin Granules were used in combination.

3265 GASTRIC SECRETION IN DUODENAL ULCER, WITH PARTICULAR REFERENCE TO THE DIAGNOSIS OF ZOLLINGER-ELLISON SYNDROME. (E.) Kaye, M. D. (U. Colorado Med. Ctr., Denver), J. Rhodes and P. Beck. *Gastroenterology* 58(4):476-481, 1970.

Basal and maximal acid secretion were measured in the stomachs of 90 patients with duodenal ulcer and the results analyzed with respect to three criteria (basal acid output, the ratio of basal to stimulated acid concentration, and the ratio of basal to maximal acid output) now used in the diagnosis of Zollinger-Ellison syndrome. A basal acid output greater than 15 mEq per hr, a ratio of basal to stimulated acid output greater than 0.6, and a ratio of basal to maximal acid output greater than 0.6 were found, resp., in approximately 10, 2, and 12% of the patients. Because of the overlap between patients with duodenal ulcer and those with islet cell tumor, no one of these criteria apparently is entirely reliable in the differentiation of these two disorders.

3266 SIMULTANEOUS MEASUREMENTS OF TOTAL PANCREATIC, BILIARY AND GASTRIC OUTPUTS IN MAN USING A PERFUSION TECHNIQUE. (E.) Summerskill, W. H. J. (Mayo Clin. Rochester, Minn.), V. L. W. Go and A. F. Hoffman. *Gastroenterology* 58(3):321-328, 1970.

Perfusion of both gastric and duodenal markers with collections from the stomach and duodenum was used to make simultaneous measurements of total duodenal and gastric secretory outputs in man. Calculations of duodenal reflux into the stomach, of contamination of duodenal contents by gastric contents, and of the amounts recycled between the organs were made, and these values used to establish the application of duodenal perfusion for precise measurements of total secretions into the duodenum. Total pancreatic enzyme (lipase, trypsin, amylase) output after intraduodenal perfusion of essential amino acids was identical with that obtained after a maximally tolerated dose (0.125 and 0.250 Crick Harper Raper units/kg/min for 4 hr) of i.v. administered pancreozymin. Simultaneous intraduodenal and i.v. stimulation, however, caused a pancreatic enzyme output which significantly exceeded either method of stimulation alone, or any previously reported, thereby suggesting that conventional stimuli cannot attain maximal secretory capacity for enzymes. When this technique was applied to the determination of total bilirubin output in the duodenum, a high bilirubin output which was consistent with previous reports was observed.

3267 THE VITAMIN A ABSORPTION TEST: II. STUDIES ON CHILDREN AND ADULTS WITH DISORDERS IN THE ALIMENTARY TRACT. (E.) Kahan, J. (Soders Hosp., Stockholm, Sweden). *Scand J Gastroent* 5(1):5-12, 1970.

Children and adults (221) with alimentary tract disorders were given the vitamin A absorption test of Kahan and the results were compared with those of serum β -lipoprotein determination, butter-fat absorption test, and estimations of fecal fat. The maximum increment of the postabsorptive serum vitamin A level closely resembles the results of the fasting serum β -lipoprotein test and in cases of biliary obstruction (range 7 to 50 for control and 0.1 to 4 for diseased) and of malabsorption syndrome (range 7 to 50 for control and 0.1 to 8 for diseased) the levels were below those of the control groups. In celiac disease, cystic fibrosis pancreatic disorders, and after intestinal resection, pathological values were obtained in half the cases. Consideration of the β -lipoprotein results in the evaluation of the vitamin A test reduced the overlap between control and patient groups (especially in children). The vitamin A test correlated well with the butter-fat absorption test ($r = 0.64$, $p < 0.001$) and with the fecal fat estimations ($r = -0.64$, $p < 0.001$) and seemingly is a rapid screening procedure for the detection of malabsorption states and for the estimation of the efficiency of therapeutic measures.

3268 THE VALUE OF γ -GLUTAMYL TRANSEPTIDASE AS A SCREEN TEST FOR LIVER TUMOR. (E.) Aronsen, K. F. (Malmo Gen. Hosp., Sweden), B. Nosslin and B. Pihl. *Acta Chir Scand* 136(1):17-22, 1970.

In 153 patients with cancer (76 with tumors of the liver verified at operation or post mortem and 77 without demonstrable involvement of the liver) determinations were made of the activities of serum γ -glutamyl transpeptidase, alkaline phosphatase and glutamate-pyruvate-transaminase and serum bilirubin. Various statistical methods (the difference index of Zieve and Hill, the critical value, and the discriminant function of Fisher) were used to evaluate the discriminative effectiveness of each test. Determination of the γ -glutamyl transpeptidase proved better than the other tests and gave a correct diagnosis in 90% of the cases, false positive results in 9% and false negative results in 1%, while combined use of the 3 enzyme reactions gave correct classification in 93%. Measurement of the γ -glutamyl transpeptidase appears to be a useful screen test for liver involvement in cancer patients.

3269 X-RAY TELEVISION INSTALLATION PROVIDED WITH A FULL SIZE ROLL FILM CHANGER FOR MASS SURVEY OF GASTROINTESTINAL DISEASES. (E.) Matsuda, H. (Ctr. Adult Dis., Osaka, Japan), A. Nakai, M. Miyachi, K. Ninomiya, M. Okazaki, Y. Hiura and Y. Sasaki. *Amer J Roentgen* 108(4):835-846, 1970.

A newly developed x-ray television installation, provided with full size roll film changer which was

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especially designed for mass survey of gastroduodenal diseases, is described. The superiority of the direct full size filming under television fluoroscopic control is discussed with regard to more roentgenographic information under less radiation exposure compared with the fluororadiographic methods using mirror or lens cameras and using the filming of an image intensifier output screen. One important alteration in the new device is utilization of plumbicon tube in place of vidicon tube. By use of the plumbicon camera a distinct reduction of patient dose from 4,000 mr per min of conventional fluoroscopy to 700 mr per min on skin is obtained.

- 3270 AN INSTRUMENT FOR TRANSDUODENAL SPHINCTEROTOMY AND BIOPSY OF THE DUODENAL PAPILLA. (E.) Larmi, T. K. I. (Dept. Surg., U. Oulu, Finland). *Ann Chir Gynaec Fenn* 58(4):334-335, 1969.

An instrument is described which simultaneously performs sphincterotomy and takes a biopsy specimen for subsequent histological study. The broadest part of the specimen taken for histological analysis derives from the tip of the papilla and the instrument has proved serviceable in biliary tract surgery, and no adverse effects on the patient have been noted from its use.

- 3271 CLINICAL EVALUATION OF A NEW FIBEROPTIC COLONOSCOPE. (E.) Dean, A. C. B. (Roy. Infirmary, Edinburgh, Scotland) and D. J. C. Shearman. *Lancet* 1(7646):550-552, 1970.

A new diagnostic instrument (colonoscope), based on fiber optics instead of a lens system, was used to investigate 38 patients with intact colon or colostomy. The instrument is 1.3 cm in diameter, can be passed a maximum distance of 70 cm and has a controllable tip of 8 cm long which can be moved at 90° angle up or down in one plane. Examination of the large bowel with this flexible instrument is more extensive and more comfortable than with a rigid sigmoidoscope, especially in patients who have had operations on the colon. Useful information (small adenomas and Crohn's disease of the colon), which could not have been obtained by barium enema or routine sigmoidoscopy, was obtained in 8/40 examinations with this instrument.

- 3272 "FIBERDUODENOSCOPY"-- EARLY DIAGNOSIS OF CANCER OF THE PAPANICOLAOU. (E.) Ohi, I. (Tokyo Women's Med. Coll., Japan), T. Takemoto and K. Nakayama. *Surgery* 67(4):561-565, 1970.
- 3273 ACCIDENTS WITH IODINIZED OPAQUE SUBSTANCES IN BILIARY RADIOLOGY-THEIR PREVENTION. (Fr.) Hamidou, B. (C. H. U. Oran, France), J. Dorstal and M. Taleb. *J Med Chir Prat* 141(2):65-72, 1970.
- 3274 CONTRIBUTION OF SELECTIVE ARTERIOGRAPHY IN DIGESTIVE PATHOLOGY. (It.) Ariano, A. A. (St. Elizabeth Clin., Brussels, Belgium) and G. Vielle. *Chir Gastroent* 3(4):418-442, 1969.

- 3275 GASTRIC ASPIRATION BIOPSY AND MAXIMAL HISTAMINE TEST IN HYPERTHYROID PATIENTS. (Sp.) Duhart, J. E. (Fac. Med. U. Buenos Aires, Argentina), C. E. Cerini, H. Obiglio, R. Ibarra and D. Gottlieb. *Medicina* 29(5):346-354, 1969.

- 3276 THE DIAGNOSTIC VALUE OF β -CAROTENE LOADING CURVES. (It.) Sategna-Guidetti, C. (Dept. Gen. Clin. Med., Med. Ther., U. Turin, Italy), A. Pera, A. Palma and T. Grassi. *Minerva Gastroent* 15(3):132-135, 1969.

- 3277 RADIOLOGIC DIAGNOSIS OF COLONIC DISEASE. (E.) Frederick, P. R. (Latter Day Saints Hosp., Salt Lake City, Utah). *J Abdom Surg* 12(4):50-52, 1970.

- 3278 PARADUODENAL HERNIAS: RADIOLOGIC AND ARTERIOGRAPHIC DIAGNOSIS. (E.) Meyers, M. A. (Flower Fifth Avenue Hosp., N.Y. Med. Coll., New York). *Radiology* 95(1):29-37, 1970.

- 3279 RESIDUAL CONTRAST MEDIUM IN THE INTESTINES AND SIDE EFFECTS DURING CHOLECYSTOGRAPHY: A COMPARISON BETWEEN SOME CONTRAST MEDIUM IN CURRENT USE AND A NEW MEDIUM. (E.) Eriksson, S. (Radiol. Dept., U. Umea, Sweden) and G. F. Saltzman. *Acta Radiol* 10(1):69-75, 1970.

- 3280 LIVER BIOPSY BY THE METHOD OF MENGHINI. (Nor.) Ovlisen, B. (Bispebjerg Hosp., Copenhagen, Denmark) and H. Baden. *Nord Med* 83(10):297-299, 1970.

- 3281 A SPECTROPHOTOMETRIC TECHNIQUE FOR THE ASSAY OF THE IRONBINDING CAPACITY OF GASTRIC JUICE. (It.) Russo, G. (Inst. Clin. Pediat., U. Catania, Italy), S. Musumeci-Tuttobene, S. Musumeci-Belfiore and D. Mazzone. *Pediatria [Naples]* 77(4):493-499, 1969.

- 3282 VALUE AND UTILITY OF DETERMINATIONS OF THE FECAL FAT AND NITROGEN IN CHRONIC PANCREATIC DISEASE. (It.) Bertero, R. (Dept. Med., U. Turin, Italy), C. Sategna-Guidetti and A. Palma. *Minerva Gastroent* 15(3):105-111, 1969.

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- 3296 AN EXPERIMENTAL METHOD FOR DEMONSTRATING THE GASTRIC ANTRUM AND ITS CLINICAL APPLICATION. (E.) Epps, J. (Howard U. Coll. Med., Washington, D. C.), E. B. Chung, N. Rogers, LaS. D. Leffall, J. E. White and B. Syphax. *J Nat Med Ass* 62(2):142-144, 161, 1970.
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- 3299 COMPARISON OF DIAGNOSES OBTAINED WITH A SCANNER AND A GAMMA CAMERA AND THEIR CORRELATION WITH SOME LIVER FUNCTION TESTS IN LIVER SCINTIGRAPHY. (E.) Rissanen, P. M. (U. Central Hosp., Helsinki, Finland) and U. K. Patomaki. *Nucllearnedintn* 8(4):366-374, 1969.
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3308 X-RAY DIAGNOSIS OF GRANULOMATOUS COLITIS (CHRON'S DISEASE OF THE LARGE INTESTINE). (Rus.) Shekhter, I. A. (Moscow Med. Stomatol. Inst., USSR) and N. U. Shniger. *Vestn Rentgen Radiol* 44(6):62-70, 1969.

3309 STUDY OF THE PANCREAS BY MEANS OF A GLYCO-AMYLASE BLOOD TEST. (Fr.) Dupuy, R. (Hosp. Beaujon, Clichy, France), J. Coulbois, J. Vallin and C. Boulard. *Rev Int Hepat* 19(5):315-335, 1969.

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3311 A NEW TECHNIQUE FOR SAMPLING DUODENAL CONTENTS: DEMONSTRATION OF UPPER SMALL-BOWEL PATHOGENS. (E.) Beal, C. B. (Neighborhood Hith. Ctr., East Palo Alto, Calif.), P. Viens, R. G. L. Grant and J. M. Hughes. *Amer J Trop Med Hyg* 19(2):349-352, 1970.

- P:Morph (3086)
- D:Stomduo (3385)
- D:Stomduo:Peptulc (3403)
- D:Pancreas (3517) (3520) (3525)
- D:Livbil (3552) (3588)
- D:Livbil:A.Nonv.Hep (3614)
- D:Livbil:Gallb (3672) (3676)
- D:Gen (3705) (3725)
- D:Gen:Parasit (3768) (3788)

GASTROINTESTINAL DISEASES

ESOPHAGUS

- 3312 MORPHOLOGY OF THE EPITHELIUM OF THE DISTAL ESOPHAGUS IN PATIENTS WITH MIDESOPHAGEAL PEPTIC STRICTURES. (E.) Trier, J. S. (Boston U. Sch. Med., Mass.). *Gastroenterology* 58(4):444-461, 1970.

Multiple esophageal suction biopsies were obtained from 5 patients with midesophageal peptic strictures and studied by light and electron microscopy. All biopsies from above the stricture were lined by squamous epithelium, and all from below were lined by columnar epithelium, with the latter containing three cell types. The most abundant was a columnar epithelial cell which contained many glycoprotein granules, and in which the apical surface consisted of a brush border composed of many microvilli. Many mucus-secreting goblet cells and a few chromaffin cells were also observed but no cells resembling gastric parietal or chief cells. Biopsies from the gastroesophageal junction from 2 normal subjects differed from the distal esophageal epithelium of stricture patients in that surface cells contained only sparse microvilli and more abundant secretory granules and intestinal type goblet cells were absent.

- 3313 PROLONGED pH RECORDING IN THE STUDY OF GASTRO-ESOPHAGEAL REFLUX. (E.) Spencer, J. (Hammersmith Hosp., London, England). *Brit J Surg* 56(12):912-914, 1969.

A method for continuous monitoring of esophageal pH for periods of up to 18 hr was used to record the timing and duration of reflux in 15 patients with symptomatic sliding hiatal hernia, and in 11 control subjects. A gastrointestinal glass pH electrode was positioned to record at the junction of the middle and lower thirds of the esophagus and reflux periods were considered to have occurred if the pH was below 4. In 15 patients, maximal acid output (mEq/hr) was determined by use of i.v. histamine infusion, 0.04 mg/kg/hr, or i.m. pentagastrin 6g/kg. Mean 18-hr reflux periods were significantly longer in the patients with hiatal hernia (266.9 min. \pm 282.3), than in the control group (41.1 min. \pm 17.0) and reflux occurred (on the average) during 25% of the 18-hr recording in the hiatal hernia patients. Nocturnal reflux occurred in the majority of patients with hiatal hernia, but in none of the control subjects. In five control subjects with duodenal ulcer, there was a significant positive correlation between maximal acid output and the duration of reflux, but no such correlation was present in patients with hiatal hernia.

- 3314 BLEEDING ESOPHAGEAL VARICES IN PATIENTS WITH WILSON'S DISEASE. (E.) Sternlieb, I. (Albert Einstein Coll. Med., Bronx, N.Y.), I. H. Scheinberg and J. M. Walshe. *Lancet* 1(7648): 638-641, 1970.

Clinical courses of 24 patients with Wilson's disease with bleeding esophageal varices are reviewed. Of 8 patients in whom portacaval shunts were constructed, 1 died immediately following surgery, 5 died within 33 months, 1 patient died

8 yr following surgery after having experienced slow hepatic deterioration and late neurological disease, and 1 patient is well 2 yr postoperatively. Of the 9 patients receiving splenectomies and spleno-renal shunts, 5 patients died within 2 yr while 4 are still alive. Splenectomy in 1 patient was followed by neurological deterioration, with no recurrence of bleeding and the patient is still alive 6 yr after surgery. One patient with gastric transection and another with porta-azygos disconnection died of recurrent hemorrhage. Of 4 patients who received no surgical treatment, 1 is alive, 2 died of recurrent hemorrhage and 1 died of progressive hepatic and neurological deterioration. Treatment with penicillamine or dimercaprol prevented neither initial bleeding nor postoperative neurological or psychiatric deterioration. Incidence and severity of neurological and emotional deterioration in patients with surgery are both significantly greater than in medically treated patients with Wilson's disease, but without esophageal hemorrhage. Surgical decompression of portal hypertension should seemingly be reserved for patients in whom recurrent and uncontrollable hemorrhage threatens life.

- 3315 EFFECTIVENESS OF RADIATION THERAPY IN THE TREATMENT OF CARCINOMA OF THE ESOPHAGUS: A RETROSPECTIVE STUDY. (E.) Frazier, A. B. (Med. Coll. Virginia, Richmond), S. H. Levitt and L. S. DeGiorgi. *Amer J Roentgen* 108(4):830-834, 1970.

- 3316 ESOPHAGEAL MUCOSAL REGENERATION FOLLOWING EXPERIMENTAL PROSTHETIC REPLACEMENT OF THE ESOPHAGUS. (E.) Leininger, B. J. (VA Edward Hines, Jr. Hosp., Hines, Ill.), H. Peacock and W. E. Neville. *Surgery* 67(3):468-473, 1970.

- 3317 RESPONSE OF THE HUMAN ESOPHAGUS TO D-TUBOCURARINE AND ATROPINE. (E.) Kantrowitz, P. A. (Johns Hopkins U. Sch. Med., Baltimore, Md.), C. I. Siegel, M. J. Strong and T. R. Hendrix. *Gut* 11(1):47-50, 1970.

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ESOPHAGUS

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- 3322 CARCINOMA OF THE ESOPHAGUS ARISING IN PATIENTS WITH ACHALASIA OF THE CARDIA. (E.) Pierce, W. S. (Sch. Med. U. Pennsylvania, Philadelphia), H. MacVaugh III, and J. Johnson. *J Thor Cardiovasc Surg* 59(3):335-339, 1970.
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- 3324 LARYNGOTRACHEAL-ESOPHAGEAL CLEFT. (E.) Geiger, J. P. (Letterman Gen. Hosp., San Francisco, Cal.), T. J. O'Connell Jr., S. C. Carter, A. C. Gomez and E. M. Aronstam. *J Thor Cardiovasc Surg* 59(3):330-334, 1970.
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- 3327 SPLENECTOMY AND CORONARY VEIN LIGATION FOR THE CONTROL OF BLEEDING ESOPHAGEAL VARICES. (E.) Smith, G. W. (U. Virginia Med. Ctr., Charlottesville). *Amer J Surg* 119(2):122-131, 1970.
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- 3329 ESOPHAGEAL RECONSTRUCTION BY COLON INTERPOSITION. (E.) Martini, N. (Mem. Hosp., N. Y., N. Y.), A. El-Domeiri and E. J. Beattie, Jr. *Arch Surg* 100(4):358-362, 1970.
- 3330 ESOPHAGEAL HIATUS HERNIA IN THREE GENERATIONS OF ONE FAMILY. (E.) Carre, I. J. (Inst. Clin. Sci., Belfast, Ireland) and P. Froggatt. *Gut* 11(1):51-54, 1970.
- 3331 ESOPHAGOCARDIAC FISTULA: REPORT OF A CASE. (E.) Laubscher, F. A. (Physicians Consult. Lab., Reno, Nev.). *New Eng J Med* 282(14): 794-795, 1970.
- 3332 SPONTANEOUS RUPTURE OF THE ESOPHAGUS. (E.) Salinas Izaguirre, S. F. (St. Barnabas Hosp., New York, N. Y.), J. T. Haggerty and G. Eckert. *Surgery* 67(4):607-613, 1970.
- 3333 ACHALASIA CARDIA. (E.) Tolia, R. M. (Med. Coll. S.S.G. Hosp., Baroda, India), P. A. Bhatt, B. T. Dave and B. K. Vyas. *J Indian Med Ass* 54(1): 26-27, 1970.
- 3334 TRANSABDOMINAL LIGATION-RESECTION OF THE ESOPHAGUS IN CASES OF BLEEDING ESOPHAGEAL VARICES. (E.) Boerema, I. (Amsterdam, Netherlands), P. J. Kloppe and A. A. Holscher. *Surgery* 67(3): 409-413, 1970.
- 3335 SOME ANATOMICAL CONSIDERATIONS IN SLIDING HIATUS HERNIA. (E.) Melcher, D. H. (St. Thomas Hosp., London, England). *Brit J Surg* 56(12): 904-906, 1969.
- 3336 CARCINOMA OF THE ESOPHAGUS AFTER GASTRIC SURGERY. (E.) Shearman, D. J. C. (Roy. Inf., Edinburgh, Scotland), N. D. C. Findlayson, S. J. Arnott and J. G. Pearson. *Lancet* 1(7647):581-582, 1970.
- 3337 ESOPHAGEAL AND GASTRIC DISORDERS IN DIABETES MELLITUS. (Pr.) Schrub, J. Cl. (Rouen, France), R. Laumonier, B. Hillemand and Y. Clabaut. *Sem Hop* 45(50):3161-3172, 1969.

- D:Livbil:Cirrh (3656)
- D:Gen (3712) (3728)

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3338 HIDDEN GASTRIC AUTOANTIBODIES TO INTRINSIC FACTOR IN PERNICIOUS ANEMIA. (E.)

Goldberg, L. S. (U. California Sch. Med., Los Angeles) and R. Bluestone. *J Lab Clin Med* 75(3): 449-456, 1970.

Sera and gastric juices were analyzed for presence of antibody to intrinsic factor (IF) in 12 patients with pernicious anemia (including one with coexistent agammaglobulinemia). IF content of the eluted peaks was greater than that of concentrated gastric juices, when 5 of gastric juice samples were fractionated by acidic gel filtration. IF was not detected in 8 of 12 unconcentrated gastric juice samples from subjects with pernicious anemia. Four specimens contained 74, 80, 54 and 40 pg. of IF per 0.1 ml resp and when concentrated samples of gastric juice were tested, larger amounts of IF (383 to 660 pg. per 0.1 ml) were present in the 4 specimens but not in the other 8. Blocking antibodies were detected in 6 of 12 concentrated samples of whole gastric juice (875 to 4,840 pg. per 0.1 ml); one of these also contained the binding antibody. Blocking antibody was found in 4 additional specimens only after subjecting concentrated gastric juice to acidic gel filtration. Gastric antibodies were predominantly IgG immunoglobulins, except for one which appeared to be a secretory IgA antibody. Gastric juices of patients with pernicious anemia apparently frequently contain autoantibodies to IF as well as IF and blocking autoantibodies and the IF seemingly exist as an antigen-antibody complex.

3339 EFFECT OF PROLONGED ADMINISTRATION OF PARIETAL CELL ANTIBODIES FROM PATIENTS WITH ATROPHIC GASTRITIS AND PERNICIOUS ANEMIA OF THE PARIETAL CELL MASS AND HYDROCHLORIC ACID OUTPUT IN RATS. (E.) Jerzy Glass, G. B. (New York Med. Coll., New York) and N. Tanaka. *Gastroenterology* 58(4): 482-494, 1970.

Mild atrophic lesions (thinning of the mucosa, decrease of the mucosal volume and significant reduction of parietal cell mass), without signs of inflammation or hypersensitivity, were produced in gastric mucosa of rats injected for 6 to 8 weeks with immunoglobulin G processed from sera of patients with atrophic gastritis and pernicious anemia containing circulating parietal cell antibody. The parallel between the reduction of the parietal cell mass and decrease of the mucosal volume, as well as decrease in the intrinsic factor activity of the gastric juice of rats treated for 8 weeks with parietal cell antibodies containing immunoglobulin G, suggests concomitant reduction of peptic cell mass under these circumstances. Rats treated with parietal cell antibodies also demonstrated a profound decrease of the hydrochloric acid output, which was more pronounced than was warranted by the coexisting reduction of the parietal cell mass. Parietal cell antibodies may play a contributory role in the natural history of gastric atrophic lesions in man by producing the reduction of cell mass and cell output.

3340 STOMACH CANCER AND AIR POLLUTION: AN EXPERIMENTAL STUDY IN A PETROCHEMICAL AREA. (E.) Neal, J. (U. Texas Med. Branch, Galveston) and R. H. Rigdon. *Texas Rep Biol Med* 27(3):787-793, 1969.

Carcinogenic activity of air pollutant particles was observed in stomachs of CFW mice fed (in Purina chow) thermal carbon and lamp black, fiber glass filter and particulate matter obtained from the air in the vicinity of petrochemical plants. There was no significant weight change in mice fed various types of hydrocarbons. Papillomas and squamous cell carcinomas occurred in the squamous portion of the stomach with numbers ranging from 1-3 and small in size, but neoplasms were not present in remainder of gastrointestinal tract. Similar gastric tumors occurred in mice fed a control carbon diet. Carbon pigment was usually present in the gastrointestinal tract of mice fed carbon and lamp blacks but no inflammatory reaction was observed. Pulmonary adenomas were present in experimental and control groups (no significant difference in number between lung tumors in treated and control groups). Papillomas and papillary carcinomas readily occur in squamous portion of stomach of mice fed food pellets with benzo (a) pyrene added. The experimental model for carcinogen study in air pollutants would seemingly be useful in clinical and epidemiologic study of gastric cancer in air polluted areas.

3341 CHYLOUS ASCITES FOLLOWING RESECTION OF AN ABDOMINAL AORTIC ANEURYSM. (E.) Bradham, R. R. (Roper Hosp., Charleston, S.C.), H. B. Gregorie and R. Wilson. *Amer Surg* 36(4):238-240, 1970.

A case report is presented of a 71-yr-old man who developed chylous ascites from a lymphatico-peritoneal fistula caused by resection of an abdominal aortic aneurysm. The course of management initially was that of repeated paracentesis and nutritional support with a high protein diet. Operative correction became necessary, and closure of multiple small leaking lymphatics was successful. Healing and recovery progressed rapidly and the patient had no further difficulty. There was no evidence of recurrent ascites 6 months later.

3342 HISTOCHEMICAL STUDY OF THE MUCOSUBSTANCES IN THE CANINE STOMACH: III. THE EFFECT OF CORTICOSTEROIDS. (E.) Lev, R. (New York Med. Coll., New York), H. I. Siegel and G. B. Jerzy Glass. *Gastroenterology* 58(4):495-508, 1970.

Prednisone (1.5 and 3.0 mg/kg for up to 8 weeks) was administered p.o. to 3 dogs with total gastric fistulas and mild chronic gastritis prior to treatment. Prednisone induced hyperplasia of mucous cells in the fundic and antral surface epithelium and increased synthesis of mucus by these cells and the extent of the hyperplastic response depended upon the dose of the drug and the length of time that it was administered. Prolonged treatment with prednisone resulted in erosions and one ulcer, and there was concomitant histological evidence of widespread mucosal damage such as the

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appearance of regenerative type cuboidal epithelium with reduced cytoplasmic mucus, exfoliation of surface cells, and inflammatory changes. In this experimental model, mucosal damage was preceded by increased rather than depressed mucus formation. It is suggested that the preexisting gastritis may have aggravated these changes and that this must be considered in the evaluation of results from histological and secretory studies using total gastric fistulae.

3343 BACTERIA, BILE, AND THE SMALL BOWEL. (E.) Tabaqchali, S. (Roy. Postgrad. Med. Sch., London, England) and S. L. Gorbach. *Gut* 10(12): 963-972, 1969.

Microbial population and bile salt metabolism at different levels of the alimentary tract were studied in 15 patients with disorders of the stomach and small intestine (4 with poly partial gastrectomy, 3 with single duodenal diverticulum, 4 with multiple jejunal diverticulosis, 2 with lesions of the distal small intestine, and 2 with resection of the distal small intestine). Although many patients had an extensive growth of microorganisms such as coliforms and lactobacilli throughout the small bowel irrespective of the causative lesion, the presence of anaerobic microorganisms and free bile acids was related to local anatomical defects (areas of stagnation). The micro-environment (low oxidation-reduction potential) necessary for growth of microorganisms of the bacteroides group appears to be available in areas of intestinal stasis and this requirement is fulfilled in the colon or terminal ileum of normal subjects and in the stagnant area of small bowel in patients with diverticula, strictures, or blind loops. Treatment of 2 of these patients with lincomycin (specifically effective in eradicating the anaerobic flora) led to a reduction in steatorrhea and disappearance of free bile acids from the intestinal fluid. Vitamin B₁₂ malabsorption appeared to be related to the total number of bacteria colonizing the small bowel rather than to any specific type. In 1 patient, the broad-spectrum antibiotic tetracycline was effective in eradicating an abnormal bacterial flora.

3344 CARCINOMA AND INTESTINAL METAPLASIA OF THE STOMACH IN COLOMBIAN MIGRANTS. (E.) Correa, P. (Sch. Med. U. del Valle, Cali, Columbia), C. Cuello and E. Duque. *J Nat Cancer Inst* 44(2): 297-306, 1970.

3345 PREVENTION OF EXPERIMENTAL GASTRIC ULCER IN RATS BY A SUBSTANCE WHICH INCREASES BIOSYNTHESIS OF ACID MUCOPOLYSACCHARIDES. (E.) Ezer, E. (Gedeon Richter Chem. Works Pharmacol. Lab., Budapest, Hungary) and L. Szporny. *J Pharm Pharmacol* 22(2):143-145, 1970.

3346 PRIMARY GASTRIC AMYLOIDOSIS. (It.) Alagni, C. (Major Hosp. Trieste, Italy), L. A. Marin and M. Romani. *Chir Gastroent* 3(4):514-526, 1969.

3347 ALLERGIC GRANULOMATOSIS WITH MASSIVE GASTRIC INVOLVEMENT. (E.) Abell, M. R. (U. Michigan Med. Ctr., Ann Arbor), R. V. Limond, W. E. Blamey and W. Martel. *New Eng J Med* 282(12):665-668, 1970.

3348 SOME UNUSUAL FEATURES OF GASTRIC ADENOMAS. (E.) Kriss, N. (Geneva Gen. Hosp., N. Y.). *Amer J Dig Dis* 15(2):103-110, 1970.

3349 VAGOTOMY, GASTRIC BLOOD FLOW, AND HEMORRHAGE FROM GASTRITIS. (E.) Olsen, W. R. (U. Michigan Med. Ctr., Ann Arbor), W. J. Foley and M. A. Simon. *Amer J Surg* 119(2):183-190, 1970.

3350 GASTRIC LIPOMA MIMICKING A GASTRIC MALIGNANCY. (E.) Reichbach, E. (Dept. Gastroent., U. Chicago, Ill.) and S. Kobayashi. *Amer J Dig Dis* 15(4):359-363, 1970.

3351 ROLE OF OCCULT BLOOD LOSS IN ANEMIA AFTER PARTIAL GASTRECTOMY. (E.) Baird, I. Mcl. (Alfred Hosp., Melbourne, Australia), D. J. B. St. John and S. S. Nasser. *Gut* 11(1):55-61, 1970.

3352 ACUTE PHLEGMASIA OF THE STOMACH. (E.) Stephenson, S. E. (Duval Med. Ctr., Jacksonville, Fla.), H. Yasrebi, R. Rhatigan and E. R. Woodward. *Amer Surg* 36(4):225-231, 1970.

3353 VAGOTOMY AND HEINECKE MIKULICZ PYLOROPLASTY IN THE TREATMENT OF PYLORIC STENOSIS. (E.) Rachlin, L. (VA Hosp., Livermore, Calif.). *Amer Surg* 36(4):251-253, 1970.

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- 3359 TWO CASES OF GASTRIC LYMPHOSARCOMA. (It.) Vota, L. (Civ. Hosp. Genoa, Italy) and G. Barbaro. *Pathologica* 61(893-894):37-44, 1969.
- 3360 STUDIES ON CELL PROLIFERATION IN EARLY GASTRIC CANCER: COMPARISON OF LABELING INDEX IN EARLY GASTRIC CANCER AND OTHER DISEASES OF THE STOMACH, AS JUDGED BY THYMIDINE H-3 AUTORADIOGRAPH. (Jap.) Kobayashi, J. (Sch. Med. Gumma U., Maebashi, Japan). *Kitakanto Med J* 19(2):112-128, 1969.
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- 3366 MENETRIER'S DISEASE SECONDARY TO SUBACUTE GASTRITIS DUE TO BILIARY REFLUX. (Fr.) Cornet, A. (Hosp. Laennec, Paris, France), L. Leger, G. Lemaigre and G. Terris. *Presse Med* 78(13):595-598, 1970.
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- 3372 DUODENAL CARCINOMA ASSOCIATED WITH LANGERHANS ISLETS TUMORS AND WITH THE ZOLLINGER-ELLISON SYNDROME. (Fr.) Gorin, J. P. (Hosp. Cochin, Paris, France), G. Lemaigre, C. Levy, J. Guerre, M. Roux and L. Leger. *J Chir* 98(5):485-502, 1969.
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- 3381 RESTORING THE HEALTH OF DIGESTIVE FISTULA PATIENTS. (E.) Prodescu, V. (Brancovenesc Hosp., Bucarest, Rumania), R. Florescu, P. Toma and R. Dandescu. *Internat Surg* 53(3):218-222, 1970.
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- 3384 THE CONDITION OF THE STOMACH IN MAJOR CARDIOVASCULAR DISEASES. (Rus.) Grigorian, E. G. (Yerevan Med. Inst., Armenia, USSR). *Ter Arkh* 41(12):8-13, 1969.
- 3385 ELECTROGASTROGRAPHY FOR GASTRIC MOTILITY IN THYROTOXICOSIS. (Rus.) Synovets, A. S. (Pirogov Med. Inst., Odessa, USSR) and G. A. Sorokin. *Vestn Khir* 102(12):31-33, 1969.
- 3386 OPERATIONS ON THE PAPILLA DUODENI MAJOR. (Rus.) Mamantavishvili, D. G. (Tiflis Inst. Postgrad Med. Educ., USSR). *Klin Khir* 52(1):42-43, 1970.
- P:Motil (3127)
 - Diagproc (3272) (3291) (3293) (3296) (3303) (3304)
 - D:Esoph (3336) (3337)
 - D:S.Intest (3420) (3433)
 - D:L.Intest (3468)
 - D:Livbil (3549) (3569)
 - D:Livbil:Galb (3692)

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Peptic Ulcers

- 3387 REDUCTION OF THE ACID RESPONSE TO PENTAGASTRIN BY 1-HYOSCYAMINE IN ULCER PATIENTS. (E.) Borg, I. (Almanna Hosp., Malmo, Sweden) and S. Emas. *Scand J Gastroent* 5(2):149-153, 1970.
- The effect of 1-hyoscyamine (0.4 to 2.8 mg/8 hr p.o.) on the acid response to pentagastrin (6 μ g/kg s.c.) was studied by gastric secretory tests (method of Emas, Lilja and Borg) in 27 gastric and duodenal ulcer patients. Treatment with 1-hyoscyamine reduced the retained acid amount by 68% (from 2.53 to 0.80 mEq), the mean basal acid output by 67% (from 2.14 to 0.17 mEq/30 min), lowered the mean curve for acid output (maximal output 7.60 to 5.14 mEq/15 min, time independent maximal output 9.89 to 7.38 mEq/15 min, and mean peak output 16.30 to 11.58 mEq/30 min), and reduced the acid concentration of the retained gastric juice (47.6%), basal secretion (31.8%), and secretory acid (14.3%).
- 3388 AMINOTRANSFERASES IN CASES OF GASTRIC ULCERS: I. "AMINOTRANSFERASE PATTERN" OF A NATIVE HOMOGENATE AND SUBCELLULAR FRACTIONS OF THE HUMAN GASTRIC MUCOUS MEMBRANE. (E.) Jaroszewicz, L. (Med. Acad. Bialystok, Poland), K. Zwierz and J. Popowicz. *Digestion* 2(6):323-328, 1969.
- The 'aminotransferase pattern' was determined for native homogenate and subcellular fractions prepared from mucosa samples obtained after gastrectomy on gastric ulcer patients. Transaminase activity (measured as μ M glutamic acid/mg protein) in native homogenate was highest for alanine (1.27 \pm 0.64), leucine (0.91 \pm 0.33), aspartic acid (0.85 \pm 0.46), isoleucine (0.77 \pm 0.29) and valine (0.72 \pm 0.27). Transamination rate of methionine was considerably lower (0.21 \pm 0.08) while other amino acids had negligible activity. There were no enzymes found which reacted with histidine in human gastric mucosa.

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In mitochondrial fraction from gastric mucosa, there was a high level of aspartate aminotransferase activity while a somewhat lower activity of alanine, leucine, isoleucine, and valine aminotransferases was observed. Development of methods for determination of alanine, aspartate and branched chain amino acid aminotransferases in human gastric juice is seemingly warranted in order to establish a relation between their activity and presence of pathological states in the stomach wall.

3389 DRUG EFFECTS ON GASTRIC SECRETION AND STRESS GASTRIC HEMORRHAGE IN THE RAT. (E.)

Brodie, D. A. (Merck Inst. Ther. Res., West Point, Penn.), V. J. Lotti and B. G. Bauer. *Amer J Dig Dis* 15(2):111-120, 1970.

The development of a simple rapid technique for placing drugs into male Holtzman rat lateral cerebral ventricle permitted comparison of i.v. and intracerebroventricular drug administration on gastric acid secretion and stress-induced (by cold plus restraint) gastric hemorrhage. The anticholinergic drugs, atropine sulfate and atropine methylbromide, produced inhibition of gastric secretion when administered i.v. or intracerebroventricularly and were more effective in reducing volume than in reducing acidity of gastric secretion. Clonidine (16.0 µg), a centrally acting antihypertensive agent, reduced gastric secretion volume to 0.4 ml after i.v. administration and to 0.8 ml after intracerebroventricular administration from a control value (saline injection) of 4.9 ml for both routes of administration. The antisecretory activity of three CNS depressants, chlorpromazine, chlorthalidone and imipramine, was greater by i.v. than by intracerebroventricular administration. All stomachs of control animals subjected to 2 hr of cold-plus-restraint showed gastric hemorrhage and atropine sulfate and atropine methylbromide effectively reduced stress-induced gastric hemorrhage after i.v. or intracerebroventricular administration. Atropine sulfate (256.0 µg) administered i.v. inhibited 37.5% of stress-induced hemorrhage, while intracerebroventricular administration inhibited gastric hemorrhage by 87.5%.

3390 THE ORIGIN OF IRON CHELATING FACTORS IN GASTRIC JUICE. (E.) Scott, J. M. (Biomed. Res. Lab., Trinity Coll., Dublin, Ireland) and D. G. Weir. *Irish J Med Sci* 2(11):553-558, 1969.

The iron binding capacity (expressed as a ratio to the basal value) of gastric secretion stimulated with a continuous histamine infusion (40 µg/kg/hr) in patients with duodenal peptic ulcers was determined by the method of Morgan, Weir, Gatenby and Scott. The ratios of the first and second post histamine hr (1.14 and 1.14, resp.) were essentially unity, but for a "flushed gastric secretion" obtained by washing the stomach for 3 to 4 min after collecting basal secretion, the ratio was highly significant (1.93). Flushing is known to stimulate mucus secretion and from what is known of the properties of gastric iron binding, this capacity is apparently of mucoid origin.

3391 DUODENAL INHIBITION OF GASTRIC SECRETION BY OSMOTIC AGENTS IN NORMAL SUBJECTS AND PATIENTS WITH DUODENAL ULCER. (E.) Ward, A. S. (Queen Elizabeth Hosp., Birmingham, England), R. A. Wilkins, R. Cocker and C. W. O. Windsor. *Gut* 10(12):1020-1028, 1969.

The effect on gastric secretion of test solutions of saline (0.09 and 3%) and glucose (18.5%) infused into the distal duodenum over a 4 min period after stimulation with pentagastrin (6 µg/kg/hr i.v.) was evaluated by measuring the secretory volume, acid, pepsin and electrolyte concentrations. With the hypotonic saline and the hypertonic glucose, acid output was reduced in both control and ulcer groups but with the hypertonic saline, output was reduced in the ulcer group with no change in the controls. In all cases, the responses were rapid (immediate or within 5 min from the start of the infusion) and the hydrogen ion concentration was constant suggesting that the inhibition of acid was due to the decreased volume of gastric juice. Sodium, chloride and potassium concentrations remained constant in all the groups while pepsin output and concentration were both reduced by all 3 test solutions. Since the responses to varying duodenal osmolarity are similar in control subjects and duodenal ulcer patients, there is no evidence of impaired inhibition in the ulcer group.

3392 EFFECT OF PROTEASE INHIBITORS ON EXPERIMENTAL PEPTIC ULCERATION. (E.) Ellis, C. M. (U. Minnesota Hosp., Minneapolis), J. G. Lumseth and D. M. Nicoloff. *Amer J Surg* 119(2):213-216, 1970.

The effects of various protease inhibitors were studied in 70 adult dogs in which chronic peptic ulceration similar to that seen in man was produced by placing the antrum on the colon as an antiperistaltic diverticulum. In the control group (given gelatin capsules), ulcers developed in 8 of the 10 dogs (6 had perforated ulcers). In the group receiving carrageenan, ulceration developed in 2 of the 10 dogs and both ulcers perforated. When SN-263 (sulfated amylopectin) was given, ulceration developed in 3 of the 10 dogs with perforation developing in 2 dogs. In the group receiving charcoal, ulcers developed in 4 of 10 dogs with perforation in 2 dogs. In the group receiving antacids, 5 dogs had ulcers and all were perforated; the size and numbers of ulcers were the same as the control group. In the group receiving cellulose sulfate, 8 of 10 dogs had ulcers with perforation occurring in 7; the size and number of the ulcers were the same as the control group. All 10 dogs receiving Amberlite IRC-50 showed severe ulceration and perforation and the average number of ulcers per dog was almost three times that of the control group and all of the dogs in this group died within a 2-3 week period. Protease inhibitors may be considered in the treatment of chronic peptic ulceration in man.

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- 3393 ELECTROPHORETIC HETEROGENITY AND RELATIONSHIPS OF PEPSINOGENS IN HUMAN URINE, SERUM AND GASTRIC MUCOSA. (E.) Samloff, I. M. (Harbor Gen. Hosp., Torrance, Calif.) and P. L. Townes. *Gastroenterology* 58(4):462-469, 1970.
- The molecular forms of pepsinogen (Pg) in urine and their relations to six of the seven pepsinogens in gastric mucosa were studied in 180 patients with known renal or peptic ulcer disease by agar-gel electrophoresis. Of these patients, 152 excreted Pg 2, Pg 3, Pg 4, and Pg 5 and 28 excreted only Pg 2, Pg 3, and Pg 4. These two patterns which have been designated A and B, respectively, were absolutely constant among individual patients. Of 23 patients from whom gastric mucosa was available, 19 had Pg 2, Pg 3, Pg 4, and Pg 5 in both their mucosa and urine, while 3 had only Pg 2, Pg 3, and Pg 4. Pg 6 and Pg 7 (or both) were found in the urine of only 8 of the 180 control subjects (5 of whom had proteinuria) and in 13 of 15 patients with renal disease and proteinuria. The demonstration of Pg 6 and Pg 7 in serum and the failure to find an inhibitor of these zymogens in normal urine is due neither to their failure to enter the circulation nor to their inhibition by urine.
- 3394 THE EFFECT OF 1-HYOSCYAMINE ON PENTAGASTRIN-INDUCED SECRETION OF ACID AND PEPSIN IN MAN. (E.) Walan, A. (Sahlgren Hosp., U. Goteborg, Sweden) and G. Dotevall. *Scand J Gastroent* 5(2):135-142, 1970.
- 3395 A COMMENTARY ON PEPTIC ULCER. (E.) Jones, F. A. (no affil). *London Clin Med J* 11(1):13-20, 1970.
- 3396 RESULT AND CONSIDERATIONS ON THE INTRA-OPERATIVE STUDY OF THE GASTRIC SECRETION IN ULCER DISEASE. (It.) Grassi, G. (United Hosp. Rome, Italy), C. Orecchia, I. Cantarelli, E. Fivoli and B. Sbuclz. *Chir Gastroent* 3(4):465-474, 1969.
- 3397 THE EPIDEMIOLOGY OF PEPTIC ULCER IN CHILDHOOD. (E.) Sultz, H. A. (Sch. Med. St. U. New York, Buffalo), E. R. Schlesinger, J. G. Feldman and W. E. Mosher. *Amer J Publ Hlth* 60(3):492-498, 1970.
- 3398 GASTRIC RESECTION FOR DUODENAL ULCER IN WOMEN: A FOLLOW-UP STUDY. (E.) Lauen, O. (Aker Hosp., Oslo, Norway). *J Oslo City Hosp* 20(2):28-31, 1970.
- 3399 SURGICAL MANAGEMENT OF PEPTIC ULCER. (E.) Savage, L. E. (U. South Dakota Sch. Med., Yankton) and C. B. McVay. *Amer J Surg* 119(2):191-196, 1970.
- 3400 CORROSIVE INJURIES OF THE STOMACH. (E.) Allen, R. E. (San Francisco Gen. Hosp., Calif.), M. J. Thoshinsky, R. J. Stallone and T. K. Hunt. *Arch Surg* 100(4):409-413, 1970.
- 3401 EMPHASIS ON SURGICAL TECHNIC AND JUDGMENT IN THE MANAGEMENT OF GASTRIC ULCERS. (E.) Herrington, J. L. Jr. (Vanderbilt U. Med. Ctr., Nashville, Tenn.). *Amer Surg* 36(4):183-197, 1970.
- 3402 SURGERY FOR DUODENAL AND GASTRIC ULCER IN INFANCY AND CHILDHOOD. (E.) Strode, J. E. (Straub Clin, Honolulu, Hawaii) and J. F. Balfour. *Surgery* 67(3):527-535, 1970.
- 3403 CORRELATION BETWEEN RADIOLOGICAL FINDINGS IN THE STOMACH AND DUODENUM AND GASTRIC ACID SECRETION IN PATIENTS WITH PEPTIC ULCER DISEASE. (E.) Andersson, H. (Sahlgren Hosp., U. Goteborg, Sweden), G. Dotevall, H. Lingaas and A. Walan. *Scand J Gastroent* 5(2):123-128, 1970.
- 3404 INFLUENCE OF AGE AND ABO BLOOD GROUPS IN THE PRECIPITATION OF BLEEDING PEPTIC ULCERS. (E.) Berg, M. (Michael Reese Hosp. Med. Ctr., Chicago, Ill.). *Gut* 10(12):1029-1030, 1969.
- 3405 SELECTIVE GASTRIC VAGOTOMY ASSOCIATED WITH ANTRECTOMY IN THE SURGERY OF DUODENAL ULCER: IMMEDIATE RESULTS. (Por.) Chacon, J. P. (Surgical D., Medical School, Sao Paulo, Brazil). *Rev Ass Med Brasil* 15(1):19-25, 1969.
- 3406 RECENT TRENDS IN GASTRO-DUODENAL ULCER SURGERY. (Nor.) Krause, U. (U. Hosp. Uppsala, Sweden). *Nord Med* 83(3):65-73, 1970.
- 3407 SULPIRIDEX AND GASTRO-DUODENAL ULCER SYNDROMES: TRIAL THERAPY IN 48 CASES. (Fr.) Felix, H. (Lyon, France), A. Maillard, M. Legendre and J. Giraud. *Arch Frano Mal Appar Dig* 59(1-2):39-50, 1970.
- 3408 218 PARTIAL GASTRECTOMIES FOR DUODENAL ULCER FOLLOWED BY GASTRO-DUODENAL ANASTOMOSIS. (Fr.) Robert, J. (no affil), A. Tounsi, N. Benyahia, O. Cherkouli, L. Balafrej, P. Desvignes and Robineau. *Montpellier Chir* 15(3):215-219, 1969.
- 3409 DEVELOPMENTS IN NON-CHOLINERGIC ANTI-ULCER AGENTS. (E.) Butler, D. E. (Parke, Davis Co., Ann Arbor, Mich.), R. A. Purdon and P. Bass. *Amer J Dig Dis* 15(2):157-170, 1970.
- 3410 BASAL AND POST HISTAMINE ACID OUTPUTS IN CONTROL SUBJECTS AND PATIENTS WITH DUODENAL ULCER. (E.) Devi, G. S. (Med. Coll. Kurnool, India), A. K. Chari, G. Devasankaraiiah, C. Rao and S. Naidu. *Indian J Med Sci* 23(12):641-647, 1969.
- 3411 GASTRIC RESECTION FOR THE REMOVAL OF DUODENAL ULCER. (Rus.) Fadayev, A. D. (Cherkosk Reg. Hosp., USSR). *Klin Khir* (12):46-47, 1969.

3412 REPEATED OPERATIONS IN GASTRIC AND DUODENAL ULCER. (Rus.) Shor, L. M. (Kaliningrad Reg. Hosp., USSR), L. V. Savich, A. Ya. Danilov and V. A. Kosov. *Klin Khir* (12):47-50, 1969.

3413 THE PATHOGENESIS OF THROMBOEMBOLIA AND HEMORRHAGE IN CANCER AND ULCER OF THE STOMACH AND DUODENUM. (Rus.) Kalchenko, I. I. (Kiev Inst. Postgrad. Med., USSR), P. V. Lys and P. A. Ryabyl. *Klin Khir* (12):18-24, 1969.

3414 GASTRIC SECRETION OF POTASSIUM, SODIUM, CALCIUM, AND PHOSPHORUS FOLLOWING STIMULATION BY HISTAMINE AND PEPTAVLON. (E.) Aagaard, P. (U. Hosp., Copenhagen, Denmark) and J. Christiansen. *Scand J Gastroent* 5(2):155-160, 1970.

- P:Absorp (3102)
- Diagproc (3265) (3270) (3287) (3288) (3294)
- D:Esoph (3313) (3325)
- D:Gen (3712)

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3415 FETAL GASTROINTESTINAL OBSTRUCTION: PRENATAL DIAGNOSIS BASED ON AMNIOTIC FLUID ANALYSIS. (E.) Grimes, L. D. (U. Alabama Med. Ctr., Birmingham) and G. Cassady. *Amer J Obstet Gynec* 106(8):1196-1200, 1970.

The case reports of 4 pregnant women are described in whom the triad of hydramnios, elevated amniotic fluid bilirubin, and fetal small bowel obstruction were confirmed. Hydramnios and Zone II or III amniotic fluid spectral curves led to prenatal suspicion of fetal gastrointestinal obstruction (duodenal atresia in 3 fetuses and ileal atresia in 1) in all 4 patients. Definitive prenatal diagnosis of gastrointestinal obstruction was achieved in 2 patients in whom visualization of contrast media in the gut was not achieved following amniography in active, nonanemic, normocephalic fetuses. Three of the four fetuses were born live and the findings suspicioned by amniotic fluid spectral curves enabled rapid diagnosis and definite management of the intestinal obstruction in the newborn infants.

3416 SMALL BOWEL MORPHOLOGY IN EXPERIMENTAL CANINE CHOLERA: A LIGHT AND ELECTRON MICROSCOPIC STUDY. (E.) Elliott, H. L. (Johns Hopkins U. Sch. Med., Baltimore, Md.), C. C. J. Carpenter, R. B. Sack and J. H. Yardley. *Lab Invest* 22(2):112-120, 1970.

Small bowel morphology in experimental cholera was observed in 8 mongrel dogs undergoing serial full thickness jejunal and ileal biopsies performed prior to peroral infection with live *Vibrio cholerae* (controls were similarly treated). In the absence of treatment (fluid replacement therapy), no dif-

ferences were seen by light or electron microscopy between control biopsies and those during cholera diarrhea, except for minimal acute inflammation around the crypts. During i.v. fluid therapy and maximal stool flows, dilation of capillaries by plasma and edema of lamina propria were seen in villus tips, and heightened goblet cell mucus production and loss were seen in dilated crypts. Results confirm previous demonstrations of epithelial integrity during human cholera diarrhea and the primary target of cholera exotoxin seemingly is the crypt epithelium which represents the chief site of net fluid loss in cholera.

3417 MECONIUM ILEUS AND ITS COMPLICATIONS: A REAPPRAISAL OF PLAIN FILM ROENTGEN DIAGNOSTIC CRITERIA. (E.) Leonidas, J. C. (Mt. Sinai Sch. Med., New York, N. Y.), W. E. Berdon, D. H. Baker and T. V. Santulli. *Amer J Roentgen* 108(3):598-609, 1970.

Sixty patients with documented cystic fibrosis and meconium ileus were reviewed with special emphasis on their clinical and roentgenographic findings. Twenty-four patients had uncomplicated meconium ileus; 9 of these cases had a family history of cystic fibrosis. Roentgenographic examination prior to surgery showed a constant finding of uneven distention of intestinal loops (some were markedly dilated). Two patients were also found with incomplete intestinal obstruction at birth. In the complicated meconium group of 36 patients, complications occurred during prenatal period with characteristic sequelae of bowel obstruction by normal meconium. Nine patients had simple volvulus, whereas 23 had combined volvulus, gangrene, atresia, and perforation. Eleven patients exhibited calcification (mecon-

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ium peritonitis) and small intestinal atresia. Traditional plain film roentgen criteria for meconium ileus (bubbly-granular pattern, absence of air-filled levels) were found absent in many "uncomplicated" cases, while these criteria were confusingly present in some "complicated" cases. In "uncomplicated" cases, major problem was the inability to accurately distinguish small bowel from colon obstruction without barium enema examination, while in "complicated" cases, the major problem was inability to suspect complications unless calcifications or mass effect of volvulus could be seen. The bizarre and broad range of roentgen findings reflects varying prenatal intestinal problems secondary to distal ileal meconium obstruction. Meconium ileus prognosis is grave with only 9 of 24 patients with complete atresia currently alive; 1 month follow-up surgery; 5 patients currently alive. Of the complicated cases, 18 of 36 survived longer than 1 month with only 10 currently alive.

- 3418 EVALUATION OF THE EFFICIENCY OF BILE SALT RECIRCULATION IN PATIENTS WITH TERMINAL ILEOPATHIES BY MEANS OF DEOXYCHOLATE DETERMINATION IN DUODENAL ASPIRATES. (E.) Thaysen, E. H. (Aalborg Munic. Hosp., Denmark), A. Bruusgaard and B. Eriksen. *Scand J Gastroent* 5(1):39-47, 1970.

Deoxycholate concentration (mg/100 ml) in fasting duodenal aspirate following cholecystokinin stimulation (1.00 Ivy Dog Unit/kg i.v.) was determined by the method of Szalkowski and Mader in 6 ilectomized patients, 5 patients with terminal ileitis and 8 controls. The mean maximum deoxycholate concentrations for both the ilectomized group (79) and the terminal ileitis group (148) were significantly below that of the controls (335). The hypothesis that this indicates a compromised intestinal reabsorption of bile salts is further supported by the low serum cholesterol concentrations and the presence of steatorrhea in most of the patients examined.

- 3419 THE INTESTINAL INSULINOTROPIC ACTION AFTER JEJUNO-ILEOSTOMY. (E.) Rehfeld, J. F. (Bispebjerg Hosp., Copenhagen, Denmark), E. Juhl and F. Quaade. *Scand J Gastroent* 5(1):77-80, 1970.

Glucose tolerance tests (p.o. and i.v.) were run on 3 patients before and after undergoing jejunostomy (preserving 37 cm of functioning jejunum and 12 cm of the distal ileum). In the oral glucose tolerance test, preoperatively 2 patients responded normally (1 patient was considered diabetic with a 3 hr value greater than 120 mg%), while postoperatively none of them had a rise and the immunoreactive insulin showed a rise both times (confirmed that the rise is greater after p.o. than after i.v. glucose). Glucose concentrations and insulin responses were almost identical before and after the operation for the i.v. tests. An intestinal β -cell stimulation located in the duodenum and first part of the jejunum apparently does exist.

- 3420 THE SMALL INTESTINE IN VITAMIN D DEPENDENT RICKETS. (E.) Hamilton, R. (Hosp. Sick Child., Toronto, Ontario, Canada), J. Harrison, D. Fraser, I. Radde, R. Morecki and L. Paunier. *Pediatrics* 45(3):364-373, 1970.

Small intestinal function (calcium, phosphorus and magnesium balance studies) and structure (biopsy) were studied in 6 children with vitamin D dependent rickets after vitamin D therapy and in 1 child before treatment. No symptoms of intestinal malabsorption or abnormalities (studied by light and electron microscopy) in the duodenal mucosa were detected in the treated children or in the untreated child. Comparison of data on the child examined before and after therapy revealed a rise in serum calcium (5.7 to 12.2 mg/100 ml), exchangeable pool calcium (2.0 to 6.5 g), accretion to bone (0.22 to 0.84 g), and dietary calcium absorption (0 to 68% of intake), with a decrease in fecal calcium excretion (765 to 254 mg/day). Phosphorus fecal excretion decreased (265 to 34 mg/day) and magnesium intake exceeded the combined urinary and fecal excretion both before and after vitamin D therapy although serum magnesium remained normal throughout the study.

- 3421 CHOLESTYRAMINE AND POLYSORBATE-80 IN THE TREATMENT OF CHOLERHEIC ENTEROPATHY: REPORT OF A CASE. (E.) Shuster, F. (North Miami Beach, Fla.), R. C. Spoto and M. N. Jacobs. *Amer J Dig Dis* 15(4):353-358, 1970.

A case is presented of an 18-yr-old male patient who was treated with cholestyramine (4 g t.i.d., p.o.) and polysorbate-80 for diarrhea and mild transient steatorrhea following subtotal ileectomy. The diarrhea improved remarkably after cholestyramine, an ionic exchange resin sequesterer of ionized bile salts. Because it is nonionic, polysorbate-80 was not sequestered by cholestyramine, and could be administered concurrently. Improvement in fecal-fat excretion and tritolein 131 I absorption was suggested even when polysorbate-80 was administered with cholestyramine, despite the tendency of cholestyramine to worsen these parameters. Together cholestyramine and polysorbate-80 may be useful in treating the diarrhea and steatorrhea of "cholerheic enteropathy".

- 3422 TUMORS OF THE SMALL INTESTINE. (Fr.) Verhaege, M. (no affil.), J. C. Laurent and A. Leqint. *Clinique* 65(662):71-76, 1970.

- 3423 INTERNAL HERNIA THROUGH THE MESENTERY OF A MECKEL'S DIVERTICULUM. (E.) Dalinka, M. K. (Wilford Hall USAF Med. Ctr., Lackland AFB, Texas), J. F. Wunder and R. D. Wolfe. *Radiology* 95(1):39-40, 1970.

- 3424 CROHN'S DISEASE. (Sw.) Rosenqvist, H. (Soder Hosp., Stockholm, Sweden). *Lakar-tidningen* 67(7):741-748, 1970.

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- 3425 BIZARRE LEIOMYOBLASTOMA OF JEJUNUM WITH ALCOHOL-INDUCED PAIN. (E.) Cerda, J. J. (VA Hosp., Philadelphia, Pa.), P. P. Toskes and P. V. Skerrett. *Amer J Dig Dis* 15(2):121-126, 1970.
- 3426 JEJUNAL CARCINOMA AS THE SOURCE OF RE-CURRENT GASTROINTESTINAL HEMORRHAGE. (E.) Cave, R. H. (Naval Hosp., St. Albans, New York) and D. J. Doohen. *Milit Med* 135(3):218-220, 1970.
- 3427 GIANT MECKEL'S DIVERTICULUM IN A PREMATURE INFANT. (E.) Cross, V. F. (St. Peter's Hosp., Albany, N. Y.), A. J. Wendth, J. J. Phelan, H. G. Goussous and D. J. Moriarty. *Amer J Roentgen* 108(3):591-597, 1970.
- 3428 JEJUNOCOLOSTOMY FOR OBESITY. (E.) Wills, C. E., Jr. (Wills Mem. Hosp., Washington, Ga.). *Maryland Med J* 19(3):45-50, 1970.
- 3429 BOWEL HERNIATION THROUGH THE FORAMEN OF WINSLOW. (E.) Cook, J. L. (U. Louisville Sch. Med., Kentucky). *Amer Surg* 36(4):241-247, 1970.
- 3430 UNUSUAL COMPLICATIONS IN PATIENTS WITH MECKEL'S DIVERTICULUM: CASE REPORT. (E.) Hallbook, T. (U. Hosp., Lund, Sweden) and E. Lindstedt. *Acta Chir Scand* 136(1):77-80, 1970.
- 3431 TECHNIQUES OF SMALL BOWEL LOOP INVERSION. (It.) Grassi, G. (Hosp. United, Rome, Italy), E. Fivoli and C. Orecchia. *Chir Gastroent* 3(4):529-534, 1969.
- 3432 A CASE OF JEJUNAL ADENOCARCINOMA. (It.) Vota, L. (Civil Hosp. Genoa, Italy), G. Virdis and G. Barbaro. *Pathologica* 61(893-894):45-49, 1969.
- 3433 MAST-CELL BEHAVIOR IN CROSBY BIOPSY DUODENOJEJUNAL MUCOSA SPECIMENS IN MEGALOBlastic ANEMIA. (It.) Astaldi, G. (City Hosp., Tortona, Italy), J. Krc, V. Krcova, A. A. Astaldi Jr. and P. L. Taverna. *Minerva Med* 61(13):595-603, 1970.
- P:Secr:Int (3234)
 - Diagproc (3278) (3290)
 - D:Stomduo (3368)
 - D:L:Intest (3469)
 - D:L:Intest:Ulccol (3506)
 - D:Gen (3707)

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Regional Enteritis

- 3434 A PSYCHOSOMATIC COMPARISON OF PATIENTS WITH ULCERATIVE COLITIS AND CROHN'S DISEASE. (E.) McKegney, F. P. (Yale U. Sch. Med., New Haven, Conn.), R. O. Gordon and S. M. Levine. *Psychosom Med* 32(2):153-166, 1970.

In Phase 1 of this study the charts of 83 patients with clearly established ulcerative colitis or Crohn's disease (drawn from all cases seen during the preceding 10 yr) were reviewed, and in Phase 2, the charts of a consecutive sampling of 35 outpatients and 5 inpatients with inflammatory bowel disease (21 with ulcerative colitis and 19 with Crohn's disease, representing all patients seen during a 2-month period) were reviewed. Investigation revealed a high incidence of emotional disturbances and life crises prior to the onset of illness in both dis-

eases (e.g. in Phase 2 patients, a serious life crisis occurred during the 6-month period prior to the onset of disease in 86% of the ulcerative colitis patients and in 68% of the Crohn's disease patients). There were no significant differences between patients with the two diseases in a large number of demographic, psychosocial, personality, behavioral, psychiatric, and physical disease characteristics. In both syndromes, there was a highly positive correlation between the severity of emotional disturbance and the seriousness of the physical illness. The results of the study support the theory that similar personality and life event factors contribute to, and may be necessary for, the development and severity of ulcerative colitis and Crohn's disease. The study indicates the need for early identification and treatment of emotional disturbance in both groups of patients.

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3435 SEVERE GROWTH RETARDATION IN CHILDREN WITH INFLAMMATORY BOWEL DISEASE. (E.) McCaffery, T. D. (Dept. Med. U. Chicago, Ill.), K. Nasr, A. M. Lawrence and J. B. Kirsner. *Pediatrics* 45(3):386-393, 1970.

The pathogenesis of severe growth retardation (defined as height below the third percentile) was investigated in 22 children with chronic inflammatory bowel disease (either ulcerative colitis or regional enteritis). Some children exhibited delayed secondary maturation (6), delayed epiphyseal closure (8), at least 1 relative with the bowel disease (9) or another disease (19), personality disorders (11), and varying dietary problems (all 22), including steatorrhea, hypoalbuminemia, anorexia and vomiting. Only 2 out of 20 children showed a percentile growth increment during steroid treatment, while 18 increased slightly in height, and the success noted with intestinal resection could be a result of this steroid treatment or a delayed onset of pubertal growth spurt. Spontaneous growth occurred in only 1 child and androgen therapy in this child brought on secondary sexual maturation without any growth acceleration.

3436 GENETIC TENDENCY IN CROHN'S DISEASE. (E.) Hislop, I. G. (Queen Elizabeth Hosp., Woodville, Australia) and A. K. Grant. *Gut* 10(12): 994-995, 1969.

Remarkable similarity occurred in the course of Crohn's disease in a 27 year old housewife and her monozygotic twin (also a housewife). The difference in time between diagnoses was only 11 months and there was close parallelism in the site, extent, and progress of the disease, although only 1 twin required bowel (terminal ileum) resection. This represents the fifth reported instance of Crohn's disease in identical twins, and, considered together, a multigene focus or possibly a genetic predisposition requiring an environmental factor for its clinical expression may be involved.

- D:Stomduo (3364)
- D:S.Intest (3418)
- D:L.Intest (3462) (3477)
- D:L.Intest:Ulccol (3507)

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Malabsorption

3437 RESPONSE OF THE JEJUNAL MUCOSA IN ADULT CELIAC DISEASE TO ORAL PREDNISOLONE. (E.) Wall, A. J. (Roy. Postgrad. Med. Sch., London, England), A. P. Douglas, C. C. Booth and A. G. E. Pearse. *Gut* 11(1):7-14, 1970.

Histologic, microscopic, histochemical and biochemical changes in the jejunal mucosa in response to treatment with prednisolone (10g p.o. q.i.d. for 4-5 weeks) and a normal diet were studied in 5 patients with adult celiac disease. Cell height improved in all patients, normal cell height (729.3 μ) was reached by 1 patient, and lymphoid infiltrate became less intense in all patients during prednisolone treatment. Within 4 weeks after withdrawal of prednisolone, cell height decreased (but not to pretreatment levels) and lymphoid infiltrate increased. Before treatment, microvilli of surface cells were blunted, fused and reduced in number, mitochondria were swollen and lacking in cristae, and cell nuclei were irregular in shape and position. During prednisolone treatment partial or complete recovery of the microvilli, mitochondria and cell nuclei occurred but following withdrawal of prednisolone, surface cells reverted to their pretreatment appearance. Prednisolone treatment increased the brush border activity of alkaline phosphatase, non-specific esterase, monoamine oxidase and lysosomal acid phosphatase but following prednisolone withdrawal the activities of these enzymes reverted to pretreatment

levels. Prednisolone improved the ability of the jejunal mucosa to digest a gluten peptide solution (as measured by release of proline and glutamic acid) and this improvement reverted to pretreatment level following prednisolone withdrawal. Xylose absorption improved and fecal fat and nitrogen excretion decreased in 4 patients during prednisolone treatment (steatorrhea remitted completely in 1 patient). In 1 patient, prednisolone withdrawal was followed by severe relapse with weight loss, diarrhea and increased steatorrhea.

3438 THE ABSORPTION OF α -TOCOPHEROL IN CONTROL SUBJECTS AND IN PATIENTS WITH INTESTINAL MALABSORPTION. (E.) MacMahon, M. T. (Roy. Postgrad. Med. Sch., London, England) and G. Neale. *Clin Sci* 38(2):197-210, 1970.

Absorption of p.o. doses of 12 and 25 μ C of tritiated DL- α -tocopherol was studied in seven control subjects and 23 patients with malabsorption (celiac disease, tropical sprue, lymphangiectasia, gastrectomy, pancreatic insufficiency, common bile duct obstruction) by measuring radioactivity in plasma, feces and urine. Radioactivity first appeared in the plasma of control subjects between 1 and 3 hr after the α -tocopherol administration and was maximal between 3 and 9 hr (thereafter declining exponentially), with a

mean half-life of 53 hr. Net absorption of tritiated α -tocopherol (calculated by assuming that administered radioactivity not recovered from the feces excreted in 6 days had been absorbed) was 68.6% of the oral dose in control subjects. A mean of 8.2% of the oral dose of α -tocopherol was recovered from the urine within 3 days in control subjects. Radioactivity in plasma of control subjects was almost entirely associated with free α -tocopherol. Net absorption of tritiated α -tocopherol was 11.2% of the oral dose in patients with pancreatic and biliary disease, 29.5% in patients with lymphangiectasia, 42.6% in patients with celiac disease or tropical sprue, and 54.6% in patients with gastrectomy. Mean urinary excretion of radioactivity (% of oral dose) was 0.5 to 4.5% in patients with pancreatic and biliary disease, 4.5% in patients with celiac disease or tropical sprue, 1.8% in patients with lymphangiectasia, and 11.4% in patients with gastrectomy. Malabsorption of tritiated α -tocopherol in patients with celiac disease or tropical sprue was correlated with the degree of steatorrhea and malabsorption of tritiated α -tocopherol was more severe than that of fat in patients with intestinal lymphangiectasia.

3439 RENAL AND INTESTINAL HEXOSE TRANSPORT IN FAMILIAL GLUCOSE-GALACTOSE MALABSORPTION. (E.) Elsas, L. J. (Yale U. Sch. Med., New Haven, Conn.), R. E. Hillman, J. H. Patterson, and L. E. Rosenberg. *J Clin Invest* 49(3):576-585, 1970.

In vitro transport (uptake, efflux) of D-glucose- ^{14}C by biopsy specimens of jejunal mucosa and *in vivo* transport of glucose (titration techniques) by the kidney were studied (by Michaelis-Meutin analysis) in a 3-yr-old girl with congenital glucose-galactose malabsorption, in 4 members of her family, and in 16 normal volunteers. Uptake of D-glucose by normal jejunal mucosa increased with time and was concentrated to levels 14.4 and 17.5 times greater than that in the incubation medium at 30 and 60 min, resp. Accumulation of D-glucose by normal jejunal mucosa was inhibited when incubation was carried out in the absence of sodium ion or in the presence of ouabain, sodium cyanide, 2,4-dinitrophenol and D-galactose. There was no accumulation of D-glucose by the jejunal mucosa of the patient with congenital glucose-galactose malabsorption during a 60-min incubation period and the jejunal mucosa of both of her parents and a half-sister accumulated D-glucose at values intermediate between her own and those of her normal brother. When jejunal mucosa was preincubated with radioactive D-glucose- ^{14}C for 30 min and transferred to an isotope-free medium, there was a progressive increase in radioactivity in the medium and the amount of radioactivity remaining in the tissue decreased with increasing time (no difference was observed between biopsy specimens from normal subjects and patient-family heterozygotes). Renal inulin clearance and glucose reabsorption were 78 ml/min and 187 mg/min, resp., in the patient and 123 ml/min and 291 mg/min, resp., in normal subjects. Familial glucose-galactose malabsorption apparently is an inherited autosomal recessive trait and heterozygotes for this trait demonstrate a reduced capacity for

glucose transport accompanied by a partially impaired renal glucose transport.

3440 NUCLEIC ACID CONTENT OF THE INTESTINAL MUCOSA IN KWASHIORKOR. (E.) Konno, T. (Dept. Child Hth. Med., U. Cape Town, South Africa), D. Becker and J. D. L. Hansen. *S Afr Med J* 43(50):1527-1528, 1969.

The content of RNA, DNA and protein was determined by ultraviolet absorption and optical density analyses of small intestine biopsy specimens taken from 6 children (age 9 to 27 months) with Kwashiorkor during hospital admission and subsequent recovery. There was no significant difference in the amount of DNA, RNA and protein found in the intestinal mucosa during hospital admission and subsequent recovery from Kwashiorkor. The cell composition of the intestinal mucosa (unlike the liver) apparently is not altered in Kwashiorkor.

3441 PEPTIDE HYDROLASE ACTIVITY OF HUMAN INTESTINAL MUCOSA IN ADULT CELIAC DISEASE. (E.) Douglas, A. P. (Roy. Postgrad. Med. Sch., London) and T. J. Peters. *Gut* 11(1):15-17, 1970.

The levels of 2 peptide hydrolases were studied in the intestinal mucosa from normal subjects, patients with untreated celiac disease, and treated (prednisolone, 40 mg/day for 21 to 35 days; p.o. or gluten withdrawal) patients. The mucosa from the untreated patients had significantly reduced activity against glycyl-glycine and leucyl-leucine but no such difference was found for the treated patients. There was a rise in intestinal peptide hydrolase during successful treatment with gluten withdrawal or prednisolone. The reduction in peptidase activity in untreated celiac disease was secondary to the mucosal damage.

3442 A FEW ENZYMIC AND IMMUNOLOGIC RESEARCHES IN CHILDREN WITH CELIAC DISEASE AND OTHER CHRONIC ENTEROPATHIES AND WITH IMMUNOLOGIC DEFICIENCIES. (E.) Nordip, S. (Hosp. Burlo Garofalo, Trieste, Italy), G. Cordone, R. Gatti, A. G. Marchi, P. Moscatelli and P. Vignola. *Helvetica Acta Paediat* 25(1):62-76, 1970.

Metabolic and immunologic studies in children with celiac diseases and other chronic enteropathies with immunologic deficiencies were separately conducted as follows: 1) enzyme activity of intestine; 2) IgG production and secretion in intestinal mucosa; 3) phytohemagglutinin (PHA) reactivity of *in vitro* cultured peripheral-blood lymphocytes. There was a statistically significant increase of lysosome β -glucuronidase of intestine in gluten-intolerance and other chronic enteropathies and enzyme activity was significantly decreased in several diseases with immunologic deficiency. IgG hyperproduction occurred in patients with gluten-intolerance and other chronic enteropathies. There was no relation between blast-transformation and β -glucuronidase increase in PHA-stimulated lymphocytes and PHA-hyposensitivity of lymphocytes (chiefly demonstrated by non-increase of

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β -glucuronidase) was observed in several cases of gluten-intolerance and diseases of immunologic deficiency. Immune reactivity, in most cases of gluten-intolerance and other chronic enteropathies, evaluated by study of lymphocyte PHA-activity, was not impaired (this reactivity is seemingly increased in the malabsorption syndrome).

- 3443 AN EVALUATION OF A TEST USING ^{14}C -LABELED TRIGLYCERIDE IN THE DIAGNOSIS OF STEATORRHEA. (E.) Bhatia, S. K. (Roy. Victoria Hosp., Belfast, Ireland), T. K. Bell, A. H. C. Love and D. A. D. Montgomery. *Irish J Med Sci* 2(11):545-552, 1969.

The diagnostic value of intestinal absorption of ^{14}C -labeled triglycerides (5 μC in 1 g fat/kg p.o.) (determined by measuring exhaled $^{14}\text{CO}_2$) was compared with the standard fecal fat excretion test in 56 patients (with steatorrhea, obesity, uncontrolled thyrotoxicosis, or after gastrointestinal surgery) and healthy controls. Since a majority of the patients (76.7%) had the highest $^{14}\text{CO}_2$ concentrations between 5 and 7 hr after receiving the labeled triglycerides, determining the $^{14}\text{CO}_2$ levels (in %mm) during this interval and referring to fecal fat estimations has provided a method to distinguish between patients with steatorrhea ($^{14}\text{CO}_2$ levels below 25%mm), those suspect of steatorrhea ($^{14}\text{CO}_2$ levels between 25 and 30%mm) and healthy controls ($^{14}\text{CO}_2$ levels above 30%mm). The new technique also parallels fecal fat excretion in patients with previous gastrointestinal operations but is unreliable in the presence of uncontrolled thyrotoxicosis or obesity.

- 3444 A SIMPLE JEJUNOCOLIC "VALVE" FOR RELIEF OF RAPID TRANSIT AND THE SHORT BOWEL SYNDROME. (E.) Waddell, W. R. (U. Colorado Med. Ctr., Denver), F. Kern, Jr., C. G. Halgrimson and J. J. Woodbury. *Arch Surg* 100(4):438-444, 1970.

A method of making valves at the site of the jejunocolic anastomoses is described, in which the procedure essentially amounts to creation of a short segment of reverse intussusception. In 3 cases in which the procedure was performed, 2 benefited from the surgery but the third was obstructed by the valve which was placed 31 cm from the ligation of Treitz. In the first 2 cases following surgery, assessments of absorption and nutrition showed that both were unable to absorb vitamin B₁₂. Electrolyte and water balance were normal in both but one case did require magnesium supplementation and his magnesium level was barely normal. Sugar and carbohydrate absorption were severely impaired in both patients which was felt to be due to the absence of ileum and large portions of jejunum. Fat absorption postoperatively was 20 and 50 gm/day, resp. in the 2 patients. A weight gain of 6.8 kg was achieved in one patient who, however, remains underweight and lacks stamina and is following a sedentary life. The second patient gained 13.2 kg, has achieved an ideal weight and leads a normal life.

- 3445 IMMUNOGLOBULINS IN TROPICAL SPRUE. (E.) Samuel, A. M. (Tata Mem. Hosp., Parel, Bombay, India), B. Singh and S. Jarnum. *Scand J Gastroent* 5(2):129-134, 1970.

Serum levels of the immunoglobulins G, M, and A (g/l determined by the radial diffusion method of Mancini, Vaerman, Carbonara and Heremans) and immunoglobulin-G turnover (by measuring ^{125}I labeled immunoglobulin in blood, urine and feces after 20 μC i.v.) were compared in Danish, British and Indian controls and in patients with tropical sprue. Indian control levels of immunoglobulin-G and -M (13.2 and 1.5 resp.) are significantly higher than for the Danish (10.8 and 0.67) and British (9.5 and 0.94) controls but their immunoglobulin-A values (1.8, 1.86, and 2.48 resp.) are similar. Of the 28 sprue patients studied, some had low, normal, and high levels of immunoglobulin-G (1, 23, and 4 resp.) and of immunoglobulin-M (12, 11, and 5 resp.); 2 patients had no immunoglobulin-A while 17 had normal and 9 had high levels. The mean fractional catabolic rate (% intravascular pool/day) for immunoglobulin-G in controls was 6.1 while in sprue patients 7 were above normal, 3 were below normal, 18 were normal, and the mean synthetic rate (mg/kg/day) for Indian controls was 76, while in sprue patients 2 were high, 4 were low and the remaining were normal.

- 3446 GASTROINTESTINAL DYSFUNCTION IN DERMATITIS HERPETIFORMIS. (E.) Berg, N. O. (U. Hosp. Lund, Sweden), A. Dahlqvist, T. Lindberg, T. Mansson, A. Norden and H. Rorsman. *Acta Dermatovener* 50(1): 42-48, 1970.

Nine patients (8 male and 1 female, aged 25 to 73 yr) who had had dermatitis herpetiformis (difficult to control, or with anemia) for 8 to 28 yr, were studied for intestinal dysfunction. All patients showed signs of hemolysis and a normal Schilling test. Peroral biopsy of small-intestinal mucosa revealed "disappearance" of villi in 6 patients. Disaccharidase activities of the mucosa were abnormal in 5 of 8 patients and dipeptidase activities were abnormal in 6. When one patient had been on a gluten-free diet for 4 months the changes in the intestinal mucosa showed distinct regression with single plump, leaf-shaped villi but still abundant cellular infiltration. All 5 disaccharidases were normalized. After the patient had been on the gluten-free diet for 9 months the histological changes had regressed even more. The dipeptidase activities were, however, still significantly decreased. The patient's skin symptoms were not affected by the diet and still required sulfone treatment as before. In the group of 8 patients studied, only 2 (both of whom had undergone gastric resection) were completely normal.

- 3447 PROTEIN-LOSING ENTEROPATHY IN DERMATITIS HERPETIFORMIS. (E.) Gjone, E. (U. Hosp., Oslo, Norway) and A. Oyril. *Scand J Gastroent* 5(1): 13-15, 1970.

The clinical states of 2 patients with dermatitis herpetiformis and protein-losing enteropathy but

without fat or carbohydrate malabsorption are examined. Both patients had normal fat absorption as shown by the vitamin A absorption test (higher than 800 I.U./100 ml in plasma), carbohydrate absorption as shown by the d-xylose test (more than 4.5 g/5 hr in urine), and one had normal fecal excretion (less than 8 g/day) while the other had a high value (12.5 g/day). Both had low total serum protein levels (4.5 and 5.2 g/100 ml), albumin fractions (2.1 and 1.6 g/100 ml), and increased intestinal protein excretion (more than 1.2%). Intestinal biopsy with Crosby's capsule indicated flat jejunal mucosa in one and leaf-shaped villi with intervillous bridging in the other.

3448 DIGESTION OF GLUTEN PEPTIDES BY NORMAL HUMAN JEJUNAL MUCOSA AND MUCOSA FROM PATIENTS WITH ADULT CELIAC DISEASE. (E.) Douglas, A. P. (Roy. Postgrad. Med. Sch., London, England) and C. C. Booth. *Clin Sci* 38(1):11-25, 1970.

Activity of peptidases concerned in the hydrolysis of a peptic-tryptic digest of gluten in mucosa from 26 patients with untreated adult celiac disease whose jejunal biopsies showed subtotal villous atrophy (9 of them studied also after a gluten-free diet), and 9 other patients with adult celiac disease but normal intestinal mucosa who had been on gluten-free diet for a yr or more was compared with that of 32 histologically normal specimens of jejunal mucosa from subjects without malabsorptive disease. The ability of the jejunal mucosa from the patients with untreated adult celiac disease to liberate amino acids from the gluten peptides was significantly less than that of the mucosa from control subjects; with no difference from normal in mucosa from treated adult celiac disease patients regardless of histological condition. The impairment of jejunal mucosal digestion of gluten in untreated adult celiac disease seemingly is a secondary phenomenon and celiac disease seemingly is not due to the absence from the intestinal mucosa of an enzyme normally concerned in the digestion of gluten.

3449 METABOLIC AND HISTOCHEMICAL CHANGES AFTER SMALL-BOWEL RESECTION IN THE DOG. (E.) Wapnick, S. (Roy. Postgrad. Med. Sch., London, England), J. Landor, L. DeFietas, U. Welsch and A. G. Cox. *Brit J Surg* 56(12):899-903, 1969.

Metabolic and histochemical changes were studied in 16 dogs with 75% proximal or distal excision of small intestine (as a single- or multiple-stage procedure). Dogs with distal resections of the small intestine lost more weight than those with proximal resections (not statistically significant) and weight-loss was statistically ($P < .001$) more severe in animals with 75% small intestine resection in multiple stages than in those with a similar length of small intestine resected in one stage. Calorie balance studies showed some increased loss while nitrogen balance exhibited little change following resection. In the 3-stage operation (proximal resection), there was no change in fecal fat excretion after 25% resection ($3.8 \pm .84$ fecal

content), a small but insignificant increase after 50% resection ($11.1 \pm 10.74\%$ fecal content), and a significant increase after 75% resection ($21.2 \pm 15.20\%$ fecal content); control response before resection was $3.8 \pm 2.15\%$. In distal resection groups there were significant and more marked increases in fecal fat at each stage (control response $4.8 \pm 0.99\%$ fecal content; 25% resection, $10.0 \pm 2.85\%$; 50% resection, $22.4 \pm 10.53\%$; 75% resection, $42.6 \pm 16.48\%$). In the one-stage operation, mean % rise in fecal fat excretion above the preoperative value after distal resection (731 ± 417) was significantly greater than mean % rise after proximal resection (235 ± 130). Fecal fat excretion expressed as percentage of fat intake was more severe after 75% resection in 3-stages than in one stage. In dogs with distal resection, the fecal fat value after 75% resection in 3-stages was significantly greater than in one stage while in dogs with proximal resections, fecal fat value after 75% resection in 3-stages was greater than after 75% resection in one stage (not significant). Mean fecal fat value in all 8 dogs after resection of distal 75% of the small intestine ($31.9 \pm 18.6\%$) was significantly greater than in all 8 dogs after resection of the proximal part of 75% of the small intestine ($12 \pm 4.9\%$). Acetylcholinesterase, normally absent or present in minimal amounts in epithelial cells, was increased after proximal resection but not after distal resection of the small intestine in all dogs. The high concentration of acetylcholinesterase found in ileum after jejunal resection seemingly may explain the mechanism whereby fecal fat excretion was lower after proximal rather than distal resection.

3450 TRIGLYCERIDES WITH MEDIUM-LENGTH CHAINS: A NEW TREATMENT IN THE MALABSORPTION OF LIPIDS. (Fr.) Guy-Grand, B. (no affil) and H. Bour. *Rev Prat* 20(6):829-847, 1970.

3451 THE BILE LIPIDS AND FATTY ACIDS IN NUTRITIONAL FAT DEFICIENCY. (Rus.) Pomerantseva, I. I. (Acad. Med. Nauk, Moscow, USSR), M. M. Levachev and G. K. Shlygin. *Vop Pitan* 28(6):36-40, 1969.

3452 MESENTERIAL BOWEL ABSORPTION IN OBSTRUCTED ALIMENTARY TRANSIT WITH SPECIAL REFERENCE TO THE BLIND LOOP SYNDROME. (It.) Zanella, L. (Inst. Clin. Surg. Ther., U. Bologna, Italy), and F. Farruggia. *Ateneo Parmense* 39(supp. 6):273-287, 1968.

3453 GLUCOSE-GALACTOSE MALABSORPTION: STUDIES ON RENAL GLUCOSURIA. (E.) Meeuwisse, G. W. (Dept. Pediat. U. Lund, Sweden). *Helvetica Pediat Acta* 25(1):13-24, 1970.

3454 NORMAL SERUM AND RED-CELL FOLATE LEVELS IN A CHILD WITH CELIAC DISEASE. (E.) Cook, D. M. (West Middlesex Hosp., Isleworth, England), N. Evans, A. Lloyd and J. S. Stewart. *Lancet* 1(7646):571-572, 1970.

SMALL INTESTINE

Malabsorption

3455 PREVALENCE OF LACTOSE MALABSORPTION IN A FINNISH RURAL POPULATION. (E.) Jussila, J. (Child. Hosp., U. Helsinki, Finland), M. Isokoski and K. Launiala. *Scand J Gastroent* 5(1):49-56, 1970.

3456 EXTERNAL PROGRESSIVE OPTHALMOPLÉGIA ASSOCIATED WITH SENSORY MOTOR NERVE DEGENERATION IN A PATIENT WITH CELIAC DISEASE. (Fr.) Telerman-Toppet, N. (Brugmann Hosp., Free U. Brussels, Belgium), C. Coers and J. J. Desneux. *Rev Neurol* 121(1):57-70, 1969.

3457 MALABSORPTION AND JEJUNAL DIVERTICULOSIS. (Nor.) Lind, I. (Med. Clin. Gavle, Sweden). *Nord Med* 83(10):303-306, 1970.

3458 CARBOHYDRATE MALABSORPTION DUE TO ENZYMIC DEFECTS. (Nor.) Skrede, S. (Inst. Clin. Biochem., U. Oslo, Norway). *T Norsk Laegeforen* 90(2B):245-248, 1970.

- P:Morph (3036)
- Diagproc (3267) (3305)
- D:Stomduo (3343)
- D:Gen:Parasit (3786)

LARGE INTESTINE

3459 PRESSURE ACTIVITY OF THE COLON AND RECTUM IN DIVERTICULAR DISEASE BEFORE AND AFTER SIGMOID MYOTOMY. (E.) Attisha, R. P. (Western Gen. Hosp., Edinburgh, Scotland) and A. N. Smith. *Brit J Surg* 56(12):891-894, 1970.

Intraluminal pressure of the colon and rectum was determined in 29 untreated patients with diverticular disease, 14 patients with sigmoid myotomy (1-6 months after surgery), and 9 normal subjects. There was no significant difference in basal pressure activity (recorded as mean motility index) in the three groups tested (normals, 151; diverticular disease, 343; after sigmoid myotomy, 130). There was an increase of the motor activity of the bowel following ingestion of a meal in all groups and patients with diverticular disease (740) responded more than controls (263). Prostigmine increased both amplitude and frequency with a resulting increase in motility index, both for normals and groups with diverticular disease (normals, mean index, 791; diverticular disease, 2856; after sigmoid myotomy, 1183). Wave amplitudes increased after food and prostigmine, while after myotomy, marked decrease in number of waves occurred. Atropine (0.4-0.6 mg) given to patients under treatment with prostigmine caused a decrease in mean motility index from 2852 to 1400. (In subjects already myotomized, the decrease was from 1260 to 200). Propantheline bromide (3.5 mg) virtually abolished all prostigmine effects in diverticular disease group, before and after surgery. There seemingly is some residual smooth-muscle activity (however weakly present) in the colon or at zones close to myotomy site.

3460 COLONIC ILEUS. (E.) Decker, G. A. G. (Johannesburg Hosp., Union of South Africa) and A. D. Smith. *S Afr J Surg* 7(4):143-147, 1969.

The clinical evaluation, subsequent management, and progress of 11 patients with colonic ileus is presented. The radiological picture was that of large bowel distension, but none of the symptoms or signs were diagnostic. It is suggested that a barium enema be done on admission to confirm the presence of organic stenosis before laparotomy. Although the mechanism of colonic ileus is obscure, the possibility of a spastic segment causing a dilatation of the colon is ruled out in the three patients on whom laparotomies were performed. The 8 patients not operated on responded to intravenous fluids and nasogastric suction.

3461 APPENDICITIS ASSOCIATED WITH SHIGELLA SONNEI INFECTION. (E.) Phillips, T. J. (no affil). *Alaska Med* 11(2):74-76, 1969.

An association between *Shigella sonnei* dysentery and acute appendicitis in two cases which occurred during a recent outbreak of dysentery caused by infection with *Shigella sonnei* is presented. At the time of surgery for case 1, it was felt that the primary problem was *Shigella* dysentery which presented symptoms mimicking appendicitis, and the minimal signs of inflammation reported after biopsy tended to confirm this impression. In the second case, however, actual perforation of the appendix occurred in a child who had received partial treatment for proven *Shigella* dysentery.

3462 CUTANEOUS ULCERATION IN CROHN'S DISEASE. (E.) Mountain, J. C. (Roy. Victoria Hosp., Bournemouth, England). *Gut* 11(1):18-26, 1970.

Seven cases of extensive perineal ulceration (4 of them with cutaneous ulceration elsewhere also) were seen in 207 cases of Crohn's disease. Perineal ulceration was the most common site, and in all of these patients (4 male, ages 32 - 66; 3 female, ages 10 - 69) it was the initial site. Perianal ulceration was present in 2 patients and metastatic in 3. Macroscopically, the ulceration was characterized by florid granulation tissue with marked destruction of the surrounding tissues. The skin edge was edematous and there was a typical dusky cyanosis of the surrounding skin. Though the ulceration is usually associated with severe Crohn's disease of the gastrointestinal tract the condition has to be differentiated from tuberculosis by demonstrating the typical sarcoid granulomatous reaction in the absence of central caseation in a biopsy of the ulceration, together with a normal chest radiograph and a negative Mantoux test to a dilution 1 in 100. The first stage in treatment is usually the removal of the adjacent bowel if it is involved in the disease as the ulceration will never heal when the bowel is still present no matter what local treatment is employed. Treatment including oral zinc sulfate and repeated curettage is recommended.

3463 ABSORPTION AND SECRETION OF WATER AND ELECTROLYTES BY THE INTACT HUMAN COLON IN DIFFUSE UNTREATED PROCTOCOLITIS. (E.) Harris, J. (U. Coll. Hosp., London, England) and R. Shields. *Gut* 11(1):27-33, 1970.

The colonic absorption of sodium, potassium, and water in 4 patients with diffuse untreated proctocolitis (ages 27 - 69 yr, 3 of them male with proctocolitis involving the entire colon) was compared with that of 13 healthy male medical students (ages 19 - 23 yr). The colon was perfused with an isotopically-labeled solution instilled through a tube introduced by mouth. In the 4 patients, the mean rate of absorption of sodium was reduced to 1/3, and of water to 1/7; while potassium was secreted into the colonic lumen at a mean rate of more than 4 times that found in the healthy subjects. Sodium and potassium ions moved more rapidly into the lumen of the ulcerated colon and the rate of movement of sodium out of the colonic lumen was diminished. In patients and healthy subjects alike, the net transport of water was closely correlated with that of sodium. The diarrhea of proctocolitis can be explained in part at least by the impairment of the colon in its ability to absorb the salt and water delivered to it from the ileum and by an increase in the secretory function and a decrease in the absorptive function of the diseased colon.

3464 AN *IN VITRO* SYSTEM FOR STUDYING MUCUS SECRETION AND OTHER PHYSIOLOGICAL ACTIVITIES IN HUMAN INTESTINAL MUCOSA. (E.) Johansen, P. G. (Roy. Child. Hosp. Res. Found., Melbourne, Australia). *Experientia* 26(2) 130-131, 1970.

Human rectal mucosa was obtained by suction biopsy from patients with cystic fibrosis for *in vitro* stud-

ies on the excessively viscous mucous secretions and the electrolyte abnormalities in the serous secretions. Trowell's technique was the most satisfactory culture method, using a media based on 199 or Trowell's T8, containing 4 mg/ml glucose, and usually 10% fetal calf serum. Antibiotics were added to the culture medium, and various additives such as insulin and hydrocortisone were tested and the criterion for satisfactory survival was based on histological examination. Biopsies from 40 patients with cystic fibrosis and from normal controls were compared in this study using histochemical methods and autoradiography for examining mucous production. No consistent histological or chemical differences were demonstrated.

3465 ISCHEMIA AND GANGRENE OF THE COLON FOLLOWING ABDOMINAL AORTIC RESECTION.

(E.) McBurney, R. P. (U. Tennessee Med. Sch., Memphis), H. Howard, R. O. Bicks and G. F. Bale. *Amer Surg* 36(4):205-209, 1970.

The records of 20 patients who suffered from ischemia and gangrene of the colon after they had undergone abdominal aortic resection were examined to determine the etiology of and treatment for these complications. Interruption of the arterial blood supply to the left colon results in ischemia and diarrhea, unexplained toxicity, or hypotension that occurs postoperatively suggests ischemia and immediate treatment (usually colectomy if gangrene is present) is advised. Prophylactic measures include avoiding trauma to the collateral circulation of the colon, implanting the inferior mesenteric artery into the wall of the graft, or insuring patency of the internal iliac vessels.

3466 PERFORATION OF THE COLON AFTER EXCHANGE TRANSFUSION IN THE NEWBORN. (E.) Friedman,

A. B. (Mt. Sinai Hosp., Cleveland, Ohio), R. M. Abellera, I. Lidsky and M. Lubert. *New Eng J Med* 282(14):796-797, 1970.

Perforation of the anterior wall of the ascending colon (at its midpoint) as a complication of exchange transfusion is described in a female infant born at 36 weeks gestation. Abdominal distention, vomiting of bile-stained mucus, and passage of normal meconium stool were the earliest findings and abdominal radiographs suggested the presence of intramural gas in the gut and necrotizing enterocolitis. Repeat abdominal radiographs revealed pneumoperitoneum and the previous diagnosis (of necrotizing enterocolitis) with perforation was confirmed. Following exploration of the abdomen (revealed murky fluid and meconium, necrotic ascending colon with midpoint perforation), an uneventful right hemicolectomy was performed. The pathological specimen (ascending colon, appendix, and a portion of the terminal ileum) was characterized by a necrotic oval perforation of the antimesenteric border of the colon and the surrounding mucosa was edematous, ulcerated, necrotic and covered by bile-stained exudate. Authors believe this to be the first case in the American literature that was diagnosed correctly before operation and successfully treated by surgery.

LARGE INTESTINE

- 3467 ANAL DISORDERS IN DIABETES. (Fr.) Schrub, J. Cl. (Rouen, France), B. Hillemand and Y. Clabaut. *Sem Hop* 45(50):3189-3190, 1969.
- 3468 MORPHOLOGIC ABNORMALITIES OF THE SUBMESO-COLIC DIGESTIVE TRACT IN DIABETICS: ATONIA AND DILATATION OF THE COLON—GASTRIC SECRETORY DEFICIENCY ATONIA AND COLONIC DILATION. (Fr.) Schrub, J. Cl. (Rouen, France), B. Hillemand and Y. Clabaut. *Sem Hop* 45(50):3184-3188, 1969.
- 3469 CHANGES IN THE DUODENAL LOOP SECONDARY TO CARCINOMA OF THE HEPATIC FLEXURE OF THE COLON. (E.) Treitel, H. (New York Med. Coll. Metro. Hosp. Ctr., New York), M. A. Meyers and V. Maza. *Brit J Radiol* 43(507):209-213, 1970.
- 3470 SIGMOID VOLVULUS IN CHILDREN. (E.) Hunter, J. G. (U. Virginia Sch. Med., Charlottesville) and T. E. Keats. *Amer J Roentgen* 108(3):621-623, 1970.
- 3471 VILLOUS ADENOCARCINOMA OF THE RECTUM WITH SEVERE ELECTROLYTE DERANGEMENT. (E.) Ariaratnam, T. (St. Laurence's Hosp., Dublin, Ireland), A. P. Clery and M. Abrahamson. *J Irish Med Ass* 63(392):43-45, 1970.
- 3472 SURGICAL MANAGEMENT OF MULTIPLE POLYPOSIS: THE PROBLEM OF CANCER IN THE RETAINED BOWEL SEGMENT. (E.) Moertel, C. G. (Mayo Clin., Rochester, Minn.), J. R. Hill and M. A. Adson. *Arch Surg* 100(4):521-526, 1970.
- 3473 APPENDICITIS AND FEMALE STERILITY. (Bul.) Tokin, R. (Med. Inst. Sofia, Bulgaria) and Z. Vassilev. *Akush Ginek* 8(5):426-430, 1969.
- 3474 PRIMARY CANCER OF THE DIGESTIVE TRACT: CANCER OF THE LARGE INTESTINE. (Sp.) Zuniga, S. R. (Hosp. Gen. Tegucigalpa, Honduras). *Rev Med Hondurena* 36(3):197-224, 1969.
- 3475 PROGNOSIS AFTER SURGICAL TREATMENT OF CANCER OF THE RIGHT SIDE OF THE COLON. (Nor.) Neilsen, J. (Community Hosp., Copenhagen, Denmark), I. Balslev and H. E. Jensen. *Nord Med* 82(48):1501-1505, 1969.
- 3476 BACTERIOLOGY OF INFANTILE DIARRHEA: OBSERVATIONS OVER TWO YEARS IN THE DAKAR HOSPITAL SERVICE. (Fr.) Le Noc, P. (no affil) and H. Plassart. *Bull Soc Path Exot* 62(3):460-468, 1969.
- 3477 CROHN'S DISEASE OF THE COLON: II. TWO CASES OF PARADOXICAL CROHN'S DISEASE STARTING IN THE ANUS OR RECTUM: ACUTE SPREAD TO THE COLON FOLLOWING MANIPULATION AND LATER TO THE ILEUM. (Fr.) Parturier-Albot, M. (Paris, France), Cl. Olivier, B. Crespon and G. Albot. *Sem Hop Paris* 45(52):3296-3303, 1969.
- 3478 VOLVULUS OF THE SIGMOID COLON. (E.) Gupta, S. (Coll. Med. Sci., Banaras Hindu U., Varanasi, India) and M. P. Vaidya. *Indian J Surg* 31(6):596-602, 1969.
- 3479 MASSIVE MEGACOLON AND MEGAILIUM IN CHILDHOOD DUE TO TUBERCULOUS STENOSIS OF THE ASCENDING COLON. (E.) Patton, J. J. (U. California, Los Angeles—Harbor Gen. Hosp., Torrance) and T. C. Moore. *Surgery* 67(3):513-518, 1970.
- 3480 CONDITIONS ASSOCIATED WITH CONGENITAL MEGACOLON. (E.) Kilcoyne, R. F. (Child. Hosp. Med. Ctr., North California, Oakland) and H. Taybi. *Amer J Roentgen* 108(3):615-620, 1970.
- 3481 THREE CASES OF ECTOPIC ANI. (It.) Ruozi-Beretta, L. (Clin. Obstet. Gynec. U. Bari) and N. Miccolis. *Minerva Ginec* 21(23):1638-1643, 1969.
- 3482 CLINICAL AND MANOMETRIC RESULTS ONE YEAR AFTER SIGMOID MYOTOMY FOR DIVERTICULAR DISEASE. (E.) Smith, A. N. (Western Gen. Hosp., Edinburgh, Scotland), R. P. Attisha and T. Balfour. *Brit J Surg* 56(12):895-899, 1969.
- 3483 CANCER OF THE CECUM: REVIEW OF 139 CASES. (E.) Foti, C. E. (Louisiana St. U. Sch. Med., New Orleans) and I. Cohn, Jr. *Amer Surg* 36(3):129-135, 1970.
- 3484 THE TREATMENT OF CHRONIC FISSURE-IN-ANO: A TRIAL OF METHODS. (E.) Hawley, P. R. (U. California Med. Ctr., San Francisco). *Brit J Surg* 56(12):915-918, 1970.
- 3485 CECAL CARCINOMA CAUSING ACUTE APPENDICITIS: CASE IN A YOUNG WOMAN. (E.) Reece, R. L. (Minneapolis, Minn.). *Minnesota Med* 53(2):127-130, 1970.
- 3486 GARDNER'S SYNDROME: REPORT OF A FAMILY. (E.) Liedberg, G. (Dept. Surg., U. Lund, Sweden), K. Lindholm, E. Lindstedt and G. Lindstedt. *Acta Chir Scand* 136(1):81-84, 1970.
- 3487 APPENDICITIS IN INFANCY. (E.) Sembiring, L. (Med. Sch. U. North Sumatra, Medan, Indonesia), J. K. Tjaij and S. Sosroomldjojo. *Paediat Indonesia* 9(5):231-234, 1969.

LARGE INTESTINE

- 3488 A NEW OUTBREAK OF INFANTILE DIARRHEA CAUSED BY PATHOGENIC *E. COLI*. (E.) Poey, S. H. (Med. Sch. U. Indonesia, Jakarta), J. W. Gautama, M. Maksam and H. Ilahude. *Paediatr Indonesia* 9(6):247-254, 1969.
- 3489 A NEW METHOD FOR TREATMENT OF CARCINOMA OF THE BREASTS AND COLON WITH 5-FLUOROURACIL. (E.) Van Way III, G. W. (Vanderbilt U. Med. Ctr., Nashville, Tenn.) and V. H. Reynolds. *Amer Surg* 36(4):210-218, 1970.
- 3490 RECTAL OBSTRUCTION BY POSTPERFORATED COLONIC ABSCESS. (E.) Dietz, M. W. (Burge-Protestant Hosp., Springfield, Mo.). *Southern Med J* 63(3):327-329, 1970.
- 3491 SURGICAL MANAGEMENT OF TRAUMATIC INJURIES OF THE COLON AND RECTUM. (E.) Ganchrow, M. I. (Evacuation Hosp., S. Vietnam), G. S. Lavenson, Jr. and J. J. McNamara. *Arch Surg* 100(4):515-520, 1970.
- 3492 SECOND-LOOK OPERATION FOR COLON CARCINOMA AFTER FLUOROURACIL THERAPY. (E.) Mackman, S. (U. Wisconsin Med. Ctr., Madison), A. R. Curreri and F. J. Ansfield. *Arch Surg* 100(4):527-531, 1970.
- 3493 LATENT ANOMALIES ASSOCIATED WITH IMPERFORATE ANUS. (E.) Tank, E. S. (U. Michigan Med. Ctr., Ann Arbor). *Arch Surg* 100(4):512-514, 1970.
- 3494 PYLOPHLEBITIS AND LIVER ABSCESSSES FOLLOWING APPENDICITIS. (E.) Till, H. J. (St. Margaret's Hosp., Montgomery, Ala.). *J Med Ass Alabama* 39(9):831-833, 1970.
- 3495 CANCER OF THE RECTUM. (E.) Lawrence, W. Jr. (Richmond, Va.) and J. S. Horsley III. *Virginia Med Month* 97(4):236-237, 1970.
- 3496 GEOGRAPHIC PATTERNS OF LARGE INTESTINE AND RECTAL MALIGNANCY MORTALITY IN VIRGINIA. (E.) Krasnow, S. (Georator Corp., Manassas, Va.). *Virginia Med Month* 97(4):226-227, 1970.
- 3497 MALIGNANT MUCOCELE OF THE APPENDIX WITH THROMBOEMBOLIC MANIFESTATION. (E.) Endlich, H. L. (Granada Hills Commun. Hosp., Calif.) and A. A. Roscher. *Int Surg* 53(3):210-217, 1970.
- 3498 LYMPHOID HYPERPLASIA OF THE LARGE INTESTINE ASSOCIATED WITH HYPERGLOBULINEMIA: REPORT OF A CASE. (E.) Wolfson, J. J. (U. Minnesota Hosp., Minneapolis), G. Goldstein, W. Krivit and R. Hong. *Amer J Roentgen* 108(3):610-614, 1970.
- 3499 PSEUDOMYXOMA PERITONEI COMPLICATING MUCOCELE OF THE APPENDIX. (E.) Jain, S. P. (Irwin Hosp., New Delhi, India). *J Indian Med Ass* 54(2):70-71, 1970.
- 3500 BULLET APPENDICITIS: "A NEW FORM OF LEAD POISONING." (E.) Rydell, W. B. (Southern Nevada Mem. Hosp., Las Vegas). *Rocky Mountain Med J* 67(3):48-50, 1970.
- 3501 MUCOID ADENOCARCINOMA IN ANORECTAL FISTULA. (E.) Lentini, J. (no affil), R. Ortiz and E. Fornells. *Amer J Proct* 21(2):103-112, 1970.
- 3502 A NEW METHOD TO AVOID COLOSTOMY IN OBSTRUCTIONS OF THE COLON DUE TO NON-OPERABLE CARCINOMA. (E.) Sanz, C. (Prov. Hosp., San Sebastian Sp.). *Amer J Proct* 21(2):127-136, 1970.
- 3503 ANORECTAL SURGICAL ANATOMY. (E.) De Los Rios, E. (Red Cross Proctol. Serv., Barcelona, Spain). *Amer J Proctol* 21(2):137-139, 1970.
- 3504 PALLIATIVE RADIATION THERAPY IN PATIENTS WITH CANCER OF THE COLON AND RECTUM. (E.) Whiteley, H. W., Jr. (Mem. Hosp., New York, N. Y.), M. W. Stearns, R. H. Leaming and M. R. Deddish. *Cancer* 25(2):343-346, 1970.
- 3505 BARIUM SULFATE INTO THE HEART FROM EXTRA-PERITONEAL RUPTURE OF THE RECTOSIGMOID. (E.) Noveroske, R. J. (Gibson Gen. Hosp., Princeton, Ind.). *J Indiana Med Ass* 63(1):32-33, 1970.

- P:Morph (3086)
- P:Absorp (3114)
- P:Motil (3128)
- Diagproc (3271) (3277)
- D:S:Intest (3421)
- D:Gen:Parasit (3768) (3769) (3772)

LARGE INTESTINE

Ulcerative Colitis

3506 VITAMIN B₁₂-ABSORPTION IN ILEOSTOMY PATIENTS AFTER OPERATION FOR ULCERATIVE COLITIS. (E.) Hultén, L. (Sahlgren Hosp., U. Goteborg, Sweden), J. Kewenter, E. Persson and C. Ahren. *Scand J Gastroent* 5(2):113-116, 1970.

Vitamin B₁₂ absorption was studied in 22 ileostomy patients at various intervals after operation (with panproctocolectomy) for ulcerative colitis. Low Schilling-test values (5 to 10%) were found in 11 patients and normal values (>10%) in 11 patients. No correlations between lowered vitamin B₁₂ absorption and preoperative length of case-history, and low absorption values and length of resected ileum segment were observed. Low vitamin B₁₂ absorption values were observed in 8 of 10 'short-term ileostomy patients' (tests performed within one yr or less) while low values were found in 3 of 12 'long-term ileostomy patients'. Vitamin B₁₂ was normal (>200 pg/ml) in all 22 patients including those with lowered vitamin B₁₂ absorption (similar results were found in patients observed for more than 3 yr). Folic acid in serum and blood, hemoglobin, serum iron, transferrin, and serum creatinine were at normal levels in all patients. Defective vitamin B₁₂ absorption seemingly is due to bacterial imbalance in the terminal ileum after ileostomy.

3507 AN EPIDEMIOLOGICAL STUDY OF ULCERATIVE COLITIS AND REGIONAL ENTERITIS AMONG ADULTS IN BALTIMORE: III. PSYCHOLOGICAL AND POSSIBLE STRESS-PRECIPITATING FACTORS. (E.) Monk, M. (St. U. New York, Downstate Med. Ctr., Brooklyn), A. I. Mendeloff, C. I. Siegel and A. Lilienfeld. *J Chron Dis* 22(8-9):565-578, 1970.

Possible events considered as emotionally and psychologically disruptive were listed following interview of 158 ulcerative colitis patients and 69 regional enteritis patients (study groups) and 105 irritable colon patients and 735 healthy individuals (comparison groups) in Baltimore. Social and cultural discontinuities, geographic mobility, and job changes were studied, with little difference between groups although the study groups had a significantly different family background (more patients in the study group were only children and generally came from smaller families) than the comparison groups. These findings agree with the results obtained when more intensive psychiatric interviewing was used.

3508 A CASE OF ULCERATIVE COLITIS AND PYOSTOMATITIS VEGETANS IN AN AFRICAN. (E.) Naish, J. M. (Coll. Med., U. Lagos, Nigeria), B. D. Batchvarov and V. L. Lawoyin. *Gut* 11(1):38-40, 1970.

A case of pyostomatitis vegetans and ulcerative colitis in a 26-yr-old African male is described. The colitis, confirmed clinically and radiologically, antedated the development of pyostomatitis. Pred-

nison (40 mg p.o. daily for 7 days) was given in divided dose; after 7 days the dosage was reduced to 20 mg. Within 48 hr of the beginning of treatment, the swelling in the oral mucosa subsided, the pinpoint pustular lesions regressed, the rough and granular appearance of the buccal mucosa changed, and hyperemia was reduced. There was less eversion of the lower lip and also a slight improvement in the bowel condition, with a drop in the daily number of stools to four. After 3 months, the mouth lesions remained healed but the colitis remained slightly active with an average of 4 stools daily. The patient's general condition was good and is maintained only on prednisone (15 mg/day).

3509 CHROMOSOMAL ABERRATIONS IN PATIENTS WITH ULCERATIVE COLITIS. (E.) Konstantinova, B. (Postgrad. Med. Inst., Sofia, Bulgaria) and N. Nedkova-Bratanova. *Digestion* 2(6):329-337, 1969.

Cytogenic examinations were conducted to study chromosomal aberrations in 9 patients suffering from severe ulcero-hemorrhagic colitis. A high degree of aneuploidy (up to 44%) and structural aberrations (up to 17.5%) were observed in all patients and aneuploidy had a pronounced hypodiploid character. Chromosomal structural aberrations affected both adhesions and chromosomes in the form of dicentric chromosomes and adhesions between chromosomes. There was a parallelism between the degree of chromosomal aberrations in somatic cells and severity of disease. Aberrations seemingly are due first of all to mutagen influence of the X-rays which had been received during X-ray examinations, to antibiotics, and to other drugs as well as partially to considerable metabolic aberrations which exist in patients.

3510 IRRITABLE COLON SYNDROME. (E.) Pimparkar, B. D. (K. E. M. Hosp., Bombay, India). *J Indian Med Ass* 54(3):95-103, 1970.

3511 GLUCOCORTICOIDS IN THE TREATMENT OF ULCERATIVE COLITIS. (Ser.) Ljaljevic, J. (Sch. Med. Beograd, Yugoslavia), S. Rodic and J. Burijan. *Srpski Arh Celok Lek* 97(6):601-605, 1969.

3512 CLINICAL COURSE OF ULCERATIVE PROCTOSIGMOIDITIS. (E.) Nugent, F. W. (Lahey Clin. Found., Boston, Mass.) M. C. Veidenheimer, S. Zuberi, M. M. Garabedian and N. K. Parikh. *Amer J Dig Dis* 15(4):321-325, 1970.

3513 MEDICAL THERAPY FOR ULCERATIVE COLITIS. (It.) Barany, F. (St. Eric Hosp., Stockholm, Sweden). *Minerva Med Giuliava* 9(3):129-134, 1969.

3514 BENIGN SOLITARY ULCER OF THE RECTUM--A REPORT OF 5 CASES. (E.) Jalan, K. N. (Western Gen. Hosp., Edinburgh, Scotland), P. W. Brunt, N. Maclean and W. Sircus. *Scand J Gastroent* 5(2):143-147, 1970.

3515 ULCERATIVE COLITIS COMPLICATED BY DIFFUSE CARCINOMAS OF THE COLON. (Nor.) Brylid, C. (Central Hosp., Naestved, Norway). *Ugeskr Laeg* 132(7):337-338, 1970.

• D:S.Intest:Regent (3434) (3435)

PANCREAS

3516 ZINC CONTENT OF PANCREATIC TUMORS OF ISLET CELL ORIGIN. (E.) Tomita, T. (Yokohama City U. Sch. Med., Japan). *J Nat Cancer Inst* 44(2):329-337, 1970.

The quantity of zinc in 5 islet cell tumors of the pancreas was measured by direct chemical analysis, and a histochemical correlation was made in 2 pancreatic islet cell tumors. The zinc content of 4 tumors was within the expected range for normal pancreatic tissue (54 to 96 $\mu\text{g/gm}$ wet weight), but one tumor had a concentration of 169 $\mu\text{g/gm}$ wet weight. The pancreatic tissue immediately surrounding 2 islet cell tumors contained 25 to 50% of the normal concentration. Histochemical studies (zinc detection with dithizon and a modified Voight's sulfide silver procedure) showed only weak staining of zinc in these two tumors. The tissue of the islet cell tumors contained greater concentrations of zinc than tissues from exocrine pancreatic tumors (21 to 29 $\mu\text{g/gm}$ wet weight) and from the pancreas of patients with advanced diabetic mellitus (16 to 110 $\mu\text{g/gm}$ wet weight).

3517 DIAGNOSTIC ERRORS IN THE TREATMENT OF PANCREATIC CYSTS IN CHILDREN. (Rus.) Sitkovsky, N. B. (Kiev Med. Inst., USSR). *Vestn Khir* 102(12):109-111, 1969.

3518 PANCREATIC FISTULA. (E.) Jordan, G. L. Jr. (VA Hosp., Houston, Texas). *Amer J Surg* 119(2):200-207, 1970.

3519 CRYOSURGICAL NECROSIS OF THE HEAD OF THE PANCREAS. (E.) Myers, R. S. (Nat. Cancer Inst., Nat. Inst. Hlth., Bethesda, Md.), W. G. Hammond and A. S. Ketchum. *Ann Surg* 171(3):413-418, 1970.

3520 RECOGNITION AND MANAGEMENT OF THE DIARRHEAL SYNDROME CAUSED BY NONBETA ISLET CELL TUMORS OF THE PANCREAS. (E.) Kraft, A. R. (Ohio St. U. Coll. Med., Columbus), R. K. Tompkins and R. M. Zollinger. *Amer J Surg* 119(2):163-170, 1970.

3521 SYSTEMIC STEATONECROSES OF PANCREATIC ORIGIN. (Fr.) Fournie, A. (Purpan Hosp., Toulouse, France), C. Ayrolles, F. De Maulde and J. Caniac. *Rev Med Toulouse* 5(9):759-774, 1969.

3522 ENZYME SUBSTITUTION FOR SURGICAL INSUFFICIENCY OF THE PANCREAS. (Ger.) Tillander, H. (Ekmanska Hosp., Goteborg, Sweden). *Munchen Med Wochr* 112(9):388-393, 1970.

3523 EXTERNAL PANCREATIC INSUFFICIENCY WITH CHRONIC GRANULOPENIA: RECENT OBSERVATIONS ASSOCIATED WITH BONE ANOMALIES. (Fr.) St-Martin, J. (Hosp. Child. Dis., Paris, France), J.-P. Fournet, J. Charlas, G. Schaison, A. Nodot, B. Meyer and J. Vialatte. *Arch Franc Pédiat* 26(8):861-871, 1969.

3524 STUDY OF THE EXOCRINE PANCREATIC MUCOVISCIDIOSIS. (Fr.) Hermier, M. (Hosp. Renee Sabran, Giens, France), M. Mathieu, M. Fillat, R. Gilly, J. P. Chazalotte and J. Cotte. *Rev Franc Etud Clin Biol* 14(9):867-884, 1969.

3525 COMPARATIVE APPRAISAL OF SOME FUNCTIONAL TESTS IN EXOCRINE PANCREATIC DISEASES. (It.) Nociti, V. (Hosp. S. Gerardo dei Tintori, Monza, Italy), U. D'Alonzo and G. Porta. *Osped Ital Chir* 20(6):493-522, 1969.

3526 PANCREATIC LITHIASIS. (E.) Abraham, P. A. (Med. Coll. Hosp., Trivandrum, India). *Indian J Surg* 31(6):588-596, 1969.

3527 CRYOSURGERY OF PRIMATE PANCREAS. (E.) Hammond, W. G. (Nat'l. Cancer Inst., Nat'l. Inst. Hlth., Bethesda, Md.), R. S. Myers and A. S. Ketchum. *Cancer* 25(2):411-414, 1970.

- F:Morph (3034)
- P:Secr:Hepatobil (3172)
- Diagproc (3262) (3282) (3309)
- D:Stomduo (3372)
- D:S.Intest (3417)
- D:L.Intest (3464)

PANCREAS

Pancreatitis

3528 SERUM INSULIN LEVELS IN PATIENTS WITH CHRONIC PANCREATITIS. (E.) Rogers, J. B. (Hahnemann Med. Coll. Hosp., Philadelphia, Pa.), J. M. Howard and F. W. Pairent. *Amer J Surg* 119(2): 171-176, 1970.

Insulin response was compared in patients with chronic pancreatitis (6 with diabetes, 4 without diabetes) to that in normal subjects (6) and diabetic, non-pancreatitis patients (8). Oral glucose tolerance tests performed in all subjects showed a fasting blood sugar level and serum insulin levels of 69 mg% and 25 μ U/ml, resp., in the controls, 84 mg% and 40 μ U/ml in the nonpancreatic diabetics, 84 mg% and 9 μ U/ml in the pancreatic diabetics, and 64 mg% and 20 μ U/ml in pancreatitis patients without diabetes. These levels peaked 1 hr after glucose to 117 mg% and 166 μ U/ml in the controls, and to 132 mg% and 174 μ U/ml in pancreatitis patients without diabetes. In patients with only diabetes, and in pancreatic diabetics, blood glucose peaked after 1 hr at 198 and 222 mg%, resp., while serum insulin peaked 2 hr after glucose at 321 and 64 μ U/ml, resp. (after 5 hr, all levels returned to normal). The mean serum insulin level was doubled in normal subjects within 5 min after an i.v. injection of secretin. In patients with pancreatic diabetes secretin raised the insulin levels from 11 to 19 μ U/ml (in both controls and pancreatic diabetics these levels returned to normal).

3529 LOW MOLECULAR WEIGHT DEXTRAN IN EXPERIMENTAL PANCREATITIS. (E.) Carey, L. C. (Presbyterian-U. Hosp., Pittsburgh, Penn.). *Amer J Surg* 119(2):197-199, 1970.

Hemorrhagic pancreatitis was produced in 3 groups of 10 animals 8 hr after pancreatic infusion of saline (30 cc/kg), albumin (3 cc/kg) and low molecular weight dextran (7 cc/kg), resp. Death occurred in 9 of 10 animals in both the saline and the albumin groups within 24 hr, while only 4 of the 10 animals receiving dextran died. After 48 hr there was no change in the saline group, all animals in the albumin group died, and 5 in the dextran group died. Average hematocrit in animals receiving saline was 42.3%, in animals receiving albumin 37.6%, and in animals receiving dextran 41.9% for an overall average of 40.6%. In 4 hr, the hematocrit increased an average of 13.2%; there was no significant difference between groups. In the animals surviving 24 hr, the hematocrit had begun to return to normal or had remained nearly unchanged from the 4-hr levels (again there was no significant difference between the 3 groups).

3530 LONG-TERM DEVELOPMENT OF CHRONIC PANCREATITIS IN 113 CASES: I. A STUDY OF SPONTANEOUS EVOLUTION. (Fr.) Levrat, M. (Hosp. Edouard Herriot, Lyon, France), L. Descos, B. Moulinier and J. Pasquier. *Arch Franc Mal Appar Dig* 59(1-2):5-18, 1970.

3531 NUTRITION IN PANCREATITIS. (Fr.) Sarles, H. (no affil.) and A. Gerolami. *Rev Prat* 20(6): 867-871, 1970.

3532 SURGICAL TREATMENT OF CHRONIC PANCREATITIS. (Rus.) Shalimov, A. A. (Kharkov Inst. Gen. Emerg. Surg., USSR) and A. Kh. Shamanov. *Klin Khir* 52(1):6-11, 1970.

3533 DIABETES MELLITUS IN PATIENTS WITH PANCREATITIS. (Rus.) Fomenko, L. I. (Kiev Med. Inst. USSR). *Klin Khir* 52(1):11-17, 1970.

3534 LIPID METABOLISM IN ACUTE PANCREATITIS. (Rus.) Shorluyan, P. M. (Rostov-on-the-Don Med. Inst., USSR), E. K. Alimova, T. M. Tereshchenko and R. F. Kamynina. *Klin Khir* 52(1): 17-22, 1970.

3535 EFFECT OF ANTICOAGULANTS ON THE COURSE OF EXPERIMENTAL ACUTE PANCREATITIS. (Rus.) Synovets, A. S. (Pirogov Inst. Med., Odessa, USSR), A. L. Dekhitar and A. P. Levitsky. *Klin Khir* 52(1):33-36, 1970.

3536 CATIONIC METABOLIC DISORDERS IN ACUTE PANCREATITIS. (Rus.) Geshelin, S. A. (Clin. Hosp., Odessa, USSR) and V. M. Lashchevker. *Klin Khir* 52(1):26-33, 1970.

3537 CALCIFYING PANCREATITIS AND PANCREATIC LITHIASIS. (It.) De Medici, A. (Dept. Gen. Clin. Surg., Surg. Ther., U. Pavia, Italy), P. Colombo and L. Bonandrini. *Minerva Gastroent* 15(3):112-131, 1969.

3538 STUDIES ON SIGNIFICANCE OF AEROBIC AND ANEROBIC BACTERIAL FLORA IN EXPERIMENTAL PANCREATITIS. (Jap.) Onishi, T. (Nagoya City U. Med. Sch.). *Nagoya City Univ Med Ass* 20(3):595-612, 1969.

3539 PORTAL HYPERTENSION IN CHRONIC PANCREATITIS: SPLENOPORTOGRAPHIC STUDY OF 20 CASES. (Por.) Reibschaid, S. (no affil.), M. deP. Vilela, P. Aiberto, De J. Faria, F. Secaf, S. J. Mizsputen, A. J. Ganc and E. J. Larsson. *Rev Ass Med Brasil* 15(10):397-402, 1969.

3540 IS ANURIA RELIEVED BY HEPARIN IN THE COURSE OF INTRAVASCULAR COAGULATION CAUSED BY ACUTE PANCREATITIS? (Fr.) Berquet, J.-C. (C. H. U., Reims, France), J.-C. Pire and B. Lardennois. *Anesth Analg (Paris)* 26(4):609-618, 1969.

3541 ACUTE PANCREATITIS IN SURGERY. (Ger.) Alieff, A. (Surg. Clin. U. Dusseldorf, Germany). *Zbl Chir* 94(51):1743-1747, 1969.

- Diagproc (3283)
- D:Livbil:Gallb (3689)

LIVER AND BILIARY TRACT

3542 MITOCHONDRIAL ANTIBODIES AND SUBCLINICAL LIVER DISEASE. (E.) Walker, J. G. (Central Middlesex Hosp., London, England), D. Doniach and I. Doniach. *Quart J Med* 39(153):31-48, 1970.

Thirty-five patients (6 male, aged 41 to 63; 29 female, 19 to 78) without overt clinical liver disease but whose serum gave positive immunofluorescent reactions for mitochondrial antibodies were evaluated for the presence of hepatic abnormalities. Nineteen suffered from collagenoses or related disorders, 10 others had thyroid or gastroimmune disease—only 3 had unrelated miscellaneous conditions. In 10 of the 35 patients there was evidence of liver abnormality and in 8 where biopsies were available hepatitis was seen on histological examination, its severity being proportional to the degree of biochemical change. This subclinical hepatitis had histological similarities to 'aggressive' hepatitis although usually in milder form, and it is regarded as an expression of an autoimmune condition that will not necessarily progress to florid active chronic hepatitis or to primary biliary or cryptogenic cirrhosis (the only three chronic liver conditions in which the antibodies are regularly found). The mitochondrial antibodies are considered to be one of the markers of an underlying pathogenic process common to these diseases.

3543 CIRRHOSIS AND CARCINOMA OF THE LIVER IN MALE RATS GIVEN SUBCUTANEOUS CARBON TETRACHLORIDE. (E.) Reuber, M. D. (Nat'l. Cancer Inst., Bethesda, Md.) and E. L. Glover. *J Nat Cancer Inst* 44(2):419-427, 1970.

Hepatocellular carcinomas (and hyperplastic nodules and cirrhosis) developed in 8 of 13 Osborne-Mendel and 12 of 15 Japanese male, 12 week old rats surviving for as long as 70-105 weeks on semi-weekly s.c. injections of 1.3 ml/kg of a 50% solution of carbon tetrachloride and corn oil. Average survival weeks in various strains of rats were: Japanese (47), Osborne-Mendel (44), Wistar (33), Sprague-Dawley (13) and Black (11). Well-differentiated carcinomas were observed in Japanese, Osborne-Mendel, and Wistar strains, with less-differentiated carcinomas only in Japanese rats. Carcinomas of the liver developed along with mild or moderate rather than severe cirrhosis (rats with severe cirrhosis died early). Wistar rats surviving up to 68 weeks had smaller carcinomas, nodules of hyperplasia, and moderate-to-severe cirrhosis. One Japanese rat had metastases of the lung and lesions of the spleen, thyroid, and kidney.

3544 THE EFFECTS OF THIOPENTONE ON THE LIVER. A STUDY ON 1030 ANESTHESIAS IN HEPATIC

PATIENTS. (E.) Tudosie, N. (Coletina Hosp., Bucarest, Rumania), N. Cinca and C. Marinescu. *Progress In Anesthesiology: Proceedings of the Fourth World Congress of Anesthesiologists* 1260-1261, 1968.

The postoperative effects of 1030 instances of balanced anesthesia (with thiopentone, hydroxydione, ether or methoxyfluorane) on liver function were

studied in patients with liver or bile duct carcinomas, hydatid cysts, advanced cirrhosis, mechanical jaundice, and pancreatic carcinoma. Methoxyfluorane, thiopentone and hydroxydione were well tolerated and did not affect serum transaminase tests, electrophoresis, the prothrombin index, or liver biopsy. Ether was the worst-tolerated anesthetic and caused delayed recovery from surgery, hypersecretion, and a significant increase in Quick's test.

3545 NORMAL SULFOBROMOPHTHALEIN RETENTION IN ESTABLISHED LIVER DISEASE. (E.)

Schoenfield, L. J. (Mayo Clin., Rochester, Minn.), G. R. Onstad and N. P. Goldstein. *Amer J Dig Dis* 15(4):337-342, 1970.

Several indices of BSP transport and metabolism (fractional clearance, duodenal drainage appearance time, conjugation, relative storage capacity and transport maximum) were measured in normal subjects and in patients with hemochromatosis, Wilson's disease or cirrhosis (all patients had normal BSP retention). Values for fractional clearance (%/min), duodenal drainage appearance time (min), conjugation (%), transport maximum (mg/min) and relative storage capacity (mg/min/100ml) after single i.v. injection of 5 mg/kg of BSP were 11.9, 17.3, 64.4, 8.2 and 60.6, resp., in normal subjects. Fractional clearance and relative storage capacity were decreased and transport maximum and conjugation were normal in all patients. Values for serum bilirubin, glutamic oxalacetic acid, protein electrophoresis and alkaline phosphatase were more abnormal in cirrhotic patients with abnormal BSP retention than in those with normal BSP retention.

3546 INTRAPORTAL INFUSION OF OXYGENATED BLOOD

AS A METHOD OF PREVENTION AND TREATMENT OF ACUTE HEPATIC INSUFFICIENCY DURING ANESTHESIA, OPERATION, AND RESUSCITATION IN CHILDREN. (E.) Manevich, A. Z. (Rusakov Child. Hosp., Moscow, USSR), V. G. Akopian and T. D. Kuznetsova. *Progress in Anesthesiology: Proceedings of the Fourth World Congress of Anesthesiologists*. 927-933, 1968.

Prolonged intraportal infusion (through the catheterized umbilical vein) of oxygenated, freshly citrated blood (1.5-3.0 ml/min) and medicinal agents (glucose-Novocaine solutions) was performed on 33 infants operated on for liver cirrhosis and for portal hypertension in order to eliminate regional hypoxemia and prevent hepatic and to assist the compensatory liver mechanisms. Of 8 cirrhotic patients subjected to intraportal perfusion of oxygenated blood and drugs, 4 recovered from the comatose condition and were successfully operated upon. Four patients who were unconscious for more than 24 hr and were unresponsive to physical stimuli, regained consciousness 2-2½ hr following the infusion of oxygenated blood. In all children where infusion was used during surgery and in the post-operative period, acute hepatic insufficiency was prevented.

LIVER AND BILIARY TRACT

3547 SUPPRESSION OF ERYTHROPOIESIS BY ALCOHOL. (E.) Hourihane, D. O'B. (Trinity Coll. Dublin, Ireland) and D. G. Weir. *Brit Med J* 1(5688): 86-89, 1970.

Changes in iron metabolism were studied in 23 alcoholic patients (well nourished and non-anemic) following cessation of prolonged alcohol intake. Serial studies performed at admission showed serum folate levels from 1.0 to 9.2 ng/ml, mean 3.2 ng (normal range, 2.1 to 9.5 ng/ml, mean 5.1 ng) and serum vitamin-B₁₂ levels from 225 to 850 pg/ml, mean 400 pg (normal range 125 to 1025 pg/ml, mean 472 pg). Serum iron levels varied markedly from 70 to 309 µg/ml, mean 172 µg (normal range 60 to 180 µg/ml) and there was a sustained fall in serum iron (maximum decrease to approximately 100 µg/ml) during the first three days after admission and alcohol cessation (slowly rising back to normal). Serum folate values showed a fall in mean level (approximately 2.5 ng/ml) for the first 48 hr after admission, but serum vitamin-B₁₂ levels did not vary significantly during this period. Five non-alcoholic psychiatric patients admitted at same time and receiving similar diets and sedation showed no comparable fall in serum iron or folate levels. Hemosiderin levels were increased after admission in 19/23 alcoholic patients but repeat examination 2 to 7 days later indicated a return to normal hemosiderin levels within erythroblasts in all patients. Prolonged alcohol consumption seemingly interferes with heme synthesis, most probably by direct effect.

3548 ENCEPHALOPATHY AFTER PORTACAVAL SHUNTING MANAGED WITH LACTULOSE. (E.) Brown, H. (Boston City Hosp., Mass.), C. Trey and W. V. McDermott, Jr. *Amer J Surg* 119(2):132-137, 1970.

Four case reports are presented of patients (3 women, 1 man) with hepatic encephalopathy after portacaval shunting who were treated randomly with either 50% lactulose with 20% sorbitol, or with 70% sorbitol alone, while on a diet providing a reasonable protein intake. Data from blood ammonium levels, EEG tracings, colon pH, and number of hospital admissions required showed that neither sugar was toxic. The underlying liver disease did not appear to be altered although the patients were helped by lactulose and occasionally by sorbitol, suggesting that the cathartic effect of both sugars was beneficial. Lactulose did relieve neurological symptoms and produced a fall in blood ammonium levels; hospital admissions were also reduced.

3549 DNA'S FROM HUMAN HEPATOMA AND GASTRIC CANCER MITOCHONDRIA. (E.) Take, S. (Okayama Med. Sch., Japan). *Acta Med Okayama* 23(6):465-479, 1969.

Livers and hepatomas were sampled three hours after death from individuals who had never received anti-tumor agents or x-ray therapy, and gastric cancers were sampled from tissue immediately after operation and electron microscopic and biochemical analyses performed. Mitochondria isolated from human liver, hepatoma and gastric cancer were found

to contain DNA and the DNA content per mitochondrial protein was about 10 times as much in hepatomas as in normal liver. Circular DNA molecules were found in the mitochondria of normal liver, hepatoma and gastric cancer. Circular DNA's from normal liver and cancer mitochondria were about 5µ in length and the frequency of circular DNA's of multiple or shorter length was higher in cancer mitochondrial DNA.

3550 METABOLISM OF PLASMA LIPIDS IN PARTIALLY HEPATECTOMIZED RATS. (E.) Olivecrona, T. (Dept. Chem., U. Umea, Sweden) and G. Fex. *Biochim Biophys Acta* 202(2):259-268, 1970.

The metabolism of labeled plasma lipids was studied in partially hepatectomized male, Sprague-Dawley rats and controls subjected to laparotomy and handling of liver. Disappearance of i.v. injected [³H] oleic acid chylomicra from circulation was retarded after partial hepatectomy compared to controls. Injected dose of label contained 3.5 x 10⁶ counts/min and the half-lives ± SD for injected label were 4.75 ± 1.06 and 2.79 ± 0.79 min (p < 0.01); 6.64 ± 1.45 and 4.37 ± 0.96 min (p < 0.01); and 6.28 ± 1.34 and 3.00 ± 0.49 min (p < 0.01) for partially hepatectomized and laparotomized rats at 4, 20, and 49 hr after operation resp. With regard to liver uptake, two min after [³H] oleic acid injection, less than 4% of radioactivity remained in blood of laparotomized rats and less than 10% in blood of partially hepatectomized rats. At 20 min after injection, corresponding figures were less than 4% in all laparotomized groups and less than 6, 16 and 13% in partially hepatectomized groups at 4, 20 and 49 hr after operation. Similar results were obtained in experiments with labeled oleic acid. Incorporation of labeled glycerol into liver lipids was also increased at 4 hr following partial hepatectomy. When chylomicra labeled *in vitro* with cholesteryl palmitate were injected, approximately 80% of radioactivity was in the liver 60 min after injection in both groups of rats. The main difference between 2 groups of rats seemingly is that the second part of the disappearance curve was slower in partially hepatectomized rats. Initial radioactivity disappearance seemingly was retarded in partially hepatectomized rats to same degree as disappearance of fatty acid labeled chylomicra.

3551 THE HEPATIC RESPONSE TO ENDOTOXIN SHOCK: HEMODYNAMIC AND ENZYMATIC OBSERVATIONS. (E.) Rangel, D. M. (U. California Los Angeles Sch. Med.), A. Dinbar, G. H. Stevens, R. Cooper and E. W. Fonkalsrud. *J Surg Res* 10(4):181-188, 1970.

The role of the liver in endotoxin shock was evaluated by injecting *Escherichia coli* endotoxin into the femoral artery or portal vein of dogs in which the liver had been excluded from circulation, and in dogs with intact livers. Systemic administration of endotoxin produced a more severe hypotension than does injection into the portal vein, which suggests that endotoxin may be removed from the circulation and detoxified by the hepatic circulation. When the liver was excluded from the circulation, a

- profound hypoglycemia followed administration of endotoxin, and death soon occurred. Circulating SGOT, SGPT and alkaline phosphatase levels increased after administration of endotoxin in dogs with normal hepatic circulation and the blood LDH levels were higher in dogs in which the hepatic inflow was excluded, which suggests an extrahepatic origin of the LDH isoenzymes. The liver seemingly exerts a protective effect during the initial phase of endotoxin shock and with the progression of shock the liver deteriorates and hepatic intracellular metabolites may be released into the circulation to accelerate the irreversibility of shock.
- 3552 MECHANISM AND ANATOMOCLINICAL MEANING OF OPACIFICATION OF THE LIVER DURING LYMPHOGRAPHY. (It.) Bobbio, P. (2nd Dept. Gen. Clin. Surg., Surg. Ther., U. Parma, Italy) and G. Barboso. *Minerva Chir* 25(4):247-255, 1970.
- 3553 ARTHROPATHY AND LIVER DISEASE. (E.) Whelton, M. J. (Wetsern Gen. Hosp., Edinburgh, Scotland). *Brit J Hosp Med* 3(2): 243-247, 1970.
- 3554 IMPAIRED FORMATION OF GLUCURONIC ACID CONJUGATES IN LIVER TISSUES OF DIABETIC RATS. (Ger.) Muleer-Oerlinghausen, Inst. Pharmacol. Toxicol. U. Gottingen). *Naunyn Schmiedeberg Arch Pharmacol* 265(4):372-382, 1970.
- 3555 TREATMENT WITH BARBITURATES IN JAUNDICE CAUSED BY DEFECTIVE BILIRUBIN CONJUGATION. (It.) Ciampolini, M. (Pediatic Clin., U. Florence, Italy). *Minerva Pediat* 21(52):2440-2446, 1970.
- 3556 BLOOD AMMONIUM AND ACID BASE BALANCE DURING ACUTE ATROPHY OF THE LIVER. (Fr.) Opolon, P. (C.H.U. St. Antoine, Paris, France), P. Hadchouel, A. Del Corse and J. Caroli. *Ann Med Intern* 121(1): 1-15, 1970.
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- 3558 BLOOD AMMONIA AND ACID BASE EQUILIBRIUM IN THE COURSE OF ACUTE ATROPHY OF THE LIVER. (Fr.) Hadchouel, P. (no affil), P. Opolon and J. Caroli. *Rev Med Chir Foie* 44(6):291-304, 1969.
- 3559 GEOGRAPHY OF PRIMARY LIVER CANCER. (E.) anonymous. *Brit Med J* 1(5693):381-382, 1970.
- 3560 ANGIOGRAPHY OF LIVER ABSCESS IN GRANULOMATOUS DISEASE OF CHILDHOOD: A CASE REPORT. (E.) Nebesar, R. A. (Harvard Med. Sch., Boston, Mass.), M. Tefft and A. H. Colodny. *Amer J Roentgen* 108(3):628-631, 1970.
- 3561 STUDIES ON RECURRENCE OF TUMORS: II RECURRENCE OF THE ASCITES HEPATOMA AH 130. (Jap.) Irino, H. (Gifu U. Sch. Med., Japan). *Acta Schol Med Univ Gifu* 16(4-5):636-641, 1969.
- 3562 STUDIES ON AMEBOID MOVEMENT IN ASCITES TUMOR CELLS. (Jap.) Shimizu, M. (Gifu U. Sch. Med., Japan). *Acta Schol Med Univ Gifu* 16(4-5):493-502, 1969.
- 3563 TREATMENT OF HEPATIC METASTASES. (Fr.) Cappelaere, P. (no affil), A. Demaille and L. Adenis. *Clinique* 65(662):31-36, 1970.
- 3564 CLINICAL EXPERIENCES WITH A NEW LIVER PROTECTOR, EUSINEX. (It.) Bandini, S. (Trabattoni Hosp., Ronzoni di Seregno, Italy), F. Colzani and D. Sarvello. *Gazz Med Ital* 128(10): 589-591, 1969.
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- 3566 KUPFFER-CELL SARCOMA. (E.) Joske, R. A. (Dept. Med., U. Western Australia, Perth) and J. B. Blackwell. *Amer J Dig Dis* 15(2):133-138, 1970.
- 3567 NUCLEAR tRNA AT DIFFERENT STAGES OF CHEMICALLY INDUCED CANCER OF THE LIVER. (Uk.) Korotkouchko, V. P. (Inst. Exp. Clin. Oncol., Min. Publ. Hlth., Kiev, Ukraine, USSR), O. M. Platonov, A. S. Polishchuk and V. G. Pinchuk. *Ukr Biokhim Zh* 41(6):647-654, 1969.
- 3568 HEPATIC METABOLISM IN PERITONITIS. (Rus.) Neiko, E. M. (Ivan Franko Med. Inst., Moscow, USSR) and A. M. Fedorchuk. *Pat Fiziol Eksp Ter* 13(6):71-72, 1969.
- 3569 LIVER NECROSIS FOLLOWING ACCIDENTAL LIGATION OF THE HEPATIC ARTERY DURING GASTRIC RESECTION. (Rus.) Fedko, S. V. (Nikopol City Hosp., USSR) and R. M. Rudenko. *Klin Khir* 52(1):52-53, 1970.
- 3570 TWO CASES OF PRIMARY CARCINOMA OF THE LIVER IN CHILDREN. (E.) Rutten, A. P. M. (St. Laurentius Hosp., Roermond, Netherlands), P. J. H. Sikkenk and A. T. Ariens. *Arch Chir Neerl* 21(4):267-276, 1969.

LIVER AND BILIARY TRACT

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- 3578 LIVER FUNCTION AND SUGAR METABOLISM DURING TREATMENT WITH 6- α -METHYL-17- α -HYDROXY-PROGESTERONE ACETATE IN ADENOCARCINOMA OF THE BODY OF THE UTERUS. NOTE I. INFLUENCE ON THE PROTEIN ELECTROPHORESIS PICTURE, TRANSAMINASES AND SERUM ALKALINE PHOSPHATASE. (It.) Lanza, A. (Sant'Anna Obstet. Gynec. Hosp., Turin, Italy). *Minerva Ginec* 21(23):1612-1623, 1969.
- 3579 BIOCHEMICAL AND STRUCTURAL CHANGES IN RAT LIVER RESULTING FROM THE PARENTAL ADMINISTRATION OF A LARGE DOSE OF SODIUM SALICYLATE. (E.) Bullock, G. R. (Res. Div., Ciba, Horsham, England), V. B. Delaney, B. C. Sawyer and T. F. Slater. *Biochem Pharmacol* 19(1):245-253, 1970.
- 3580 STIMULATION OF HEPATIC DRUG-METABOLIZING ENZYMES BY CHLOROPHENOTHANE (DDT); THE RELATIONSHIP TO LIVER ENLARGEMENT AND HEPATOTOXICITY IN THE RAT. (E.) Hoffman, D. G. (Lilly Toxicol Lab., Eli Lilly Co., Greenfield, Indiana), H. M. Worth, J. L. Emerson and R. C. Anderson. *Toxic Appl Pharmacol* 16(1):171-178, 1970.
- 3581 ANATOMO-PATHOLOGICAL AND STATISTICAL CONTRIBUTIONS TO THE STUDY OF HEPATIC TUBERCULOSIS. (It.) Vercellino, A. (Hosp. St. Louis Gonzaga, Turin, Italy), B. Emanuele and C. Banaudi. *Minerva Med* 61(9):350-356, 1970.
- 3582 SURGICAL MANAGEMENT OF INTRAHEPATIC HEMATOMAS. (E.) Thomas, C. S., Jr. (Vanderbilt U. Sch. Med., Nashville, Tenn.), R. B. Adkins Jr., V. C. Lanier Jr. and J. H. Foster. *Amer Surg* 36(3):171-176, 1970.
- 3583 PREGNANCY AND EXTRAHEPATIC PORTAL HYPERTENSION. (E.) Hendry, W. F. (Roy. Infir. Glasgow, Scotland) and W. A. Mackey. *Brit J Surg* 56(12):909-912, 1969.
- 3584 HEMOSTASIS DURING LIVER RESECTIONS. (E.) Clark, W. R. Jr. (Moyer Clin., Baraga, Mich.) and R. P. Leather. *Surgery* 67(3):556-557, 1970.
- 3585 CONTROL OF THE HEPATIC PARENCHYMA BY DIRECT COMPRESSION: A NEW INSTRUMENT. (E.) Doty, D. B. (Walter Reed Army Med. Ctr., Washington, D. C.), H. W. Kugler and R. V. Moseley. *Surgery* 67(4):720-724, 1970.
- 3586 TRAUMATIC INTRAHEPATIC HEPATIC ARTERY-PORTAL VEIN FISTULA WITH ASSOCIATED HEMOBILIA. (E.) Cleveland, R. J. (Harbor Gen. Hosp., Torrance, Cal.), B. M. Jackson, P. H. Newman and R. J. Nelson. *Ann Surg* 171(3):451-454, 1970.
- 3587 STUDIES ON IRON METABOLISM IN HEPATIC DISORDERS. (E.) Daimon, S. (Kyoto U. Sch. Med., Japan). *Jap J Nucl Med* 6(4):415-416, 1969.
- 3588 HISTOLOGIC CLASSIFICATION OF LIVER-CELL CARCINOMA IN INFANCY AND CHILDHOOD AND ITS CLINICAL EVALUATION: A STUDY OF 70 CASES COLLECTED IN JAPAN. (E.) Kasai, M. (Tohoku U. Sch. Med., Sendai, Japan) and I. Watanabe. *Cancer* 25(3):551-563, 1970.
- 3589 MASSIVE EXCHANGE TRANSFUSIONS IN HEPATIC COMA WITH RECOVERY. (E.) Gelfand, M. L. (New York, N. Y.), L. Sussman, R. Lavarias and C. Florita. *Amer J Dig Dis* 15(4):373-382, 1970.
- 3590 CHANGES IN THE NUCLEOTIDE COMPOSITIONS OF NUCLEOLAR 45 S RNA OF AZO DYE-INDUCED HEPATOMA. (E.) Matsuhisa, T. (Osaka U. Med. Sch., Japan), K. Higashi, S. Gotoh and Y. Sakamoto. *Cancer Res* 30(1):162-166, 1970.

- P:Morph (3042) (3046) (3068)
- P:Secr:Hepatob11 (3208) (3213) (3221)
- Diagproc (3260) (3261) (3263) (3268) (3280) (3284) (3297) (3299) (3300) (3301) (3302)
- D:Esoph (3314)
- D:Gen (3703) (3733)
- D:Gen:Parasit (3767) (3787)

LIVER AND BILIARY TRACT

Acute Nonviral Hepatitis and Hepatic Injury

- 3591 FATAL MASSIVE NECROSIS OF THE LIVER AFTER REPEATED EXPOSURE TO METHOXYFLURANE. (E.) Stefanini, M. (St. Elizabeth Hosp., Danville, Ill.), A. Herland and E. P. Kosyak. *Anesthesiology* 32(4): 374-378, 1970.

The pathology of a case of fatal massive necrosis of the liver following a second administration of methoxyflurane (Penthrane) is discussed on the basis of the case report and postmortem findings. Anatomic and histologic diagnosis was acute massive necrosis with multiple hemorrhages related to acute hepatic failure and acute pulmonary edema, with infection, congestive heart failure and shock as well as acute infectious hepatitis ruled out. In parallel to a mechanism of sensitization responsible for acute hepatic damage following repeated use of halothane, a similar mechanism may be responsible for the necrosis produced by methoxyflurane.

- 3592 ELECTRON-MICROSCOPIC INVESTIGATION OF THE HEPATOTOXIC EFFECTS FOLLOWING THE REPEATED USE OF VARIOUS INHALATION ANESTHETIC AGENTS. (E.) Inamoto, A. (Kyoto U. Hosp., Japan), T. Okamoto and Y. Matsuo. *Progress in Anesthesiology: Proceedings of the Fourth World Congress of Anesthesiologists* 913-918, 1968.

Adult inbred mice and albino rabbits were exposed to repeated doses of inhalation anesthetics (diethyl ether, cyclopropane, halothane, methoxyflurane and chloroform) and liver specimens were taken by biopsy after anesthesia on the third day, on the seventh day and one week after recovery and prepared for electron-microscopic and histopathologic examination. Diethyl ether (4%) and cyclopropane (18%) were almost harmless to the liver cell, even if repeated anesthesia was given for one week and did not reach the clinical level. Halothane (1%) and methoxyflurane (0.5%) were non-toxic when used with sufficient oxygen but dilation of the endoplasmic reticulum by halothane and methoxyflurane suggest transient disturbances in utilization of lipoprotein by the liver cell. Chloroform (0.7%) was definitely hepatotoxic, even if given with a high oxygen concentration, and was most destructive to hepatocytes under hypoxic conditions.

- 3593 HALOTHANE AND LIVER DAMAGE. (E.) Skulberg, A. (Ullevål Hosp., Oslo, Norway), G. K. M. Endresen and I. Lund. *J Oslo City Hosp* 20(1): 3-16, 1970.

Incidence of liver damage caused by halothane anesthesia was investigated by retrospective literature searching and clinical observation in 8 surgical patients. Incidence of acute parenchymatous liver damage following halothane compared to other general anesthetics is as follows: Slater et al (1964), 1:4895 (halothane), 1:4605 (other anesthetics); Dykes et al (1965), 1:1836 (halothane), 1:3224 (other anesthetics); and National Halothane Study, 0.88:10,000 (halothane), 0.73:10,000 (other anesthetics). Retrospective data and observation of 8 surgical patients indicate that hepatic damage due to halothane seemingly is an allergic

relation with low incidence (four surgical patients with previous halothane anesthesia) and the condition is often accompanied by fever, chills, rash, arthralgia, and eosinophilia, with damage occurring most frequently after multiple halothane administrations. Before halothane anesthesia is employed, patients should be questioned about possible previous jaundice attacks and their relation to operation and anesthesia. Unexplainable temperature increase and/or jaundice following halothane administration should discourage use of this anesthetic.

- 3594 INTRAVASCULAR COAGULATION IN ACUTE HEPATIC NECROSIS. (E.) Rake, M. O. (King's Coll. Hosp., London, England), P. T. Flute, G. Pannell and R. Williams. *Lancet* 1(7646):533-537, 1970.

Tests for coagulation and fibrinolysis, the intravascular survival of ^{125}I -labeled fibrinogen, and the influence of different forms of therapy were studied in thirteen patients with acute hepatic necrosis. In all patients, there was evidence of abnormalities in red-blood-cell morphology, with target cells, mild pancytosis and occasional nucleated red blood cells. Two patients had fragmented red blood cells with polychromasia and signs of microangiopathic hemolytic anemia. In all patients prothrombin times and partial thromboplastin times were prolonged, plasminogen levels were low (below 2 casein units per ml), and fibrinolysis was increased as reflected by the abnormally rapid fall of circulating radioactivity of labeled fibrinogen. The half-life of fibrinogen in 6 patients with hepatic necrosis (range: 28-45 hr) was consistently less than that of 5 patients with compensated cirrhosis (range: 63-95 hrs) whose values fell within the normal range. Severe necrosis of liver cells apparently causes increased intravascular coagulation.

- 3595 A POSSIBLE PATHWAY FOR ETHANOL-INDUCED FATTY LIVER AND MODIFICATION OF LIVER INJURY BY ANTIOXIDANTS. (E.) Pennington, S. N. (Cancer Res. Ctr., Columbia, Mo.), S. K. Chattopadhyay and H. D. Brown. *Quart J Stud Alcohol* 31(1):13-19, 1970.

The interaction of cytochrome P-450 (of the mixed-function oxidase system) with ethanol metabolism and role of an antioxidant in this system were studied in isolated microsomes from calf or rat livers. Amount of NADPH or $\text{Na}_2\text{S}_2\text{O}_8$ necessary to reduce totally the available P-450 was approximately 0.5-0.6 mg/3 ml. When various concentrations of ethanol were added to P-450 content of 105,000 x g fraction, ethanol had only a small effect on P-450 content and the observed effect was attributed to acetaldehyde formation. The addition of acetaldehyde had a marked inhibitory effect on P-450 concentration and α -tocopherol acetate effectively inhibited the decrease in P-450 content induced by acetaldehyde addition. Since P-450 content was decreased, mechanism suggested for effect of mixed-function oxidase system in

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- fatty liver development is one whereby mixed-function oxidation fails to metabolize fatty acids which it would ordinarily handle by ω -hydroxylation and this mechanism is inhibited due to ethanol ingestion, i.e., the formation of acetaldehyde which oxidizes reduced P-450.
- 3596 ORGANELLE PATHOLOGY OF THE LIVER: THE ENDOPLASMIC RETICULUM. (E.) Stenger, R. J. (New York Med. Coll., New York). *Gastroenterology* 58(4):554-574, 1970.
- 3597 SEVERE ICTERUS CAUSED BY ACUTE HEPATIC NECROSIS. (Fr.) Opolon, P. (no affil.), Y. Hecht, G. Theodoropoulos, P. Hadchouel, A. Grynblat and J. Caroli. *Rev Med Chir Foie* 44(6): 251-290, 1969.
- 3598 HISTOLOGICAL ASPECTS OF SEVERE ACUTE CYTOLYTIC HEPATITIS: RESULTS OF LIVER BIOPSY. (Fr.) Paliard, P. (Hosp. Edward Herriot, Lyon, France), J. Motin, C. Grimaud and M. Cuhe. *Rev Int Hepat* 19(5):261-271, 1969.
- 3599 SEVERE METHYL ALCOHOL POISONING (A CASE REPORT). (E.) Singh, S. V. (R. N. T. Med. Coll., Udaipur, Rajasthan, India), D. R. Shah, O. P. Kulshrestha, S. Mendiratta and I. L. Jain. *Indian J Med Sci* 23(12):661-664, 1969.
- 3600 EFFECT OF INGESTED MONURON ON THE LIVER. (Rus.) Rubenchik, B. L. (Kiev Inst. Nutr. Hyg., USSR), A. S. Petrun, M. B. Pliss and G. P. Shipko. *Vop Pitani* 28(6):13-18, 1969.
- 3601 CLINICAL FINDINGS IN PATIENTS WITH HEPATITIS AND ABNORMAL BILE DUCT EPITHELIUM. (E.) Christoffersen, P. (Commun. Hosp., Copenhagen, Denmark), H. Poulsen and K. Winkler. *Scand J Gastroent* 5(2):117-121, 1970.
- 3602 HALOGEN SENSITIZATION OF THE LIVER: A CLINICAL SYNDROME WITH TWO CASE REPORTS. (E.) Keown, K. K. (U. Missouri Med. Ctr., Columbia) and H. G. Bingham. *Anest Analg* 48(5):710-714, 1969.
- 3603 EFFECT OF HALOTHANE IN THE LIVER OF DOGS: EXPERIMENTAL HISTOCHEMICAL AND HISTOLOGIC STUDY WITH AN ELECTRON MICROSCOPE. (Sp.) Trevino Garcia Manzo, N. (Natl. Med. Ctr., Mexico), R. Muzquiz Soberon, J. Aguirre Garcia and M. Guerrero Alcazar. *Prensa Med Mexicana* 34(9-10):324-330, 1969.
- 3604 THE LYMPHOCYTE SYSTEM IN ACUTE AND CHRONIC HEPATITIS. (It.) Ascione, A. (Physiology Clin. U. Rome, Italy). *Epatologia* 15(1):17-75, 1969.
- 3605 BACTERIOLOGY OF PERIHEPATIC AND INTRA-HEPATIC ABSCESS. (E.) Gillespie, W. A. (U. Bristol Med. Sch., England). *Proc Roy Soc Med* 63(3):322-323, 1970.
- 3606 HEPATIC VEIN THROMBOSIS: INCREASED INCIDENCE IN RATS GIVEN METHYLCHOLANTHRENE AND CARBON TETRACHLORIDE. (E.) Reuber, M. D. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.). *Arch Environ Hlth* 20(4):458-461, 1970.
- 3607 ENHANCEMENT AND SUPPRESSION OF HEPATO-TOXICITY OF CHLOROFORM BY DRUGS. (Ger.) Scholler, K. L. (Surg. U. Clin., Freiburg, Germany), E. Muller and U. Von Plehwe. *Arzneimittelforschung* 20(2):289-291, 1970.
- 3608 STUDIES ON FRUCTOSE PHOSPHATE ALDOLASE IN EXPERIMENTAL LIVER DAMAGE IN RATS: III. LIVER DAMAGE BY CARBON TETRACHLORIDE. (Ger.) Dikow, A. L. (Oncol. Invest. Inst. Sofia, Bulgaria) and D. Hadjiolov. *Z Klin Chem Klin Biochem* 8(1):35-37, 1970.
- 3609 IMPORTANCE OF SOME AMINOACIDS IN HEPATIC DETOXIFICATION PROCESSES. (It.) Pellegrini, R. (Alexander Fleming Res. Inst., Milan, Italy) and P. A. Vertova. *Gazz Med Ital* 128(10): 602-605, 1969.
- 3610 INFLUENCE OF AMMONIUM INTOXICATION AND ACUTE LIVER DAMAGE ON BRAIN GAMMA AMINO-BUTYRIC ACID IN RATS. (Sp.) Ugarte, G. (Fac. Med. U. Chile, Valparaiso), T. Peneda and A. Vallega. *Arch Biol Med Exp* 5(1-2-3):1-3, 1968.
- 3611 PREVENTION BY ETHYL ALCOHOL OF HEPATIC LESIONS INDUCED BY ALLYL FORMATE. (E.) Schwarzmann, V. (I. N. S. E. R. M. Paris, France), R. Infante, D. Petit and N. Berthaux. *Rev Franc Etud Clin Biol* 14(10):1014-1017, 1969.
- 3612 HALOTHANE AND LIVER FAILURE. (E.) Aach, R. (Washington U. Sch. Med., St. Louis, Mo.). *JAMA* 211(13):2145-2147, 1970.
- 3613 HETEROLOGOUS BOVINE LIVER PERFUSION THERAPY OF ACUTE HEPATIC FAILURE. (E.) Condon, R. E. (U. Illinois Coll. Med., Chicago), C. T. N. Bombeck and F. Steigmann. *Amer J Surg* 119(2):147-154, 1970.
- 3614 RADIOLOGY IN DIAGNOSIS AND CONTROL OF SURGICAL TREATMENT OF SUBPHRENIC AND LIVER ABSCESSSES. (E.) Harley, H. R. S. (Sully Hosp., Penarth, Glamorgan, Scotland). *Proc Roy Soc Med* 63(3):319-322, 1970.

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- 3615 ON THE UNIMPARABLE RESISTANCE OF THE GUINEA PIG TO DIETARY AMINO AZO DYE HEPATOCARCINOGENESIS. (E.) Gosch, H. H. (U. Michigan Med. Sch., Ann Arbor), J. C. Arcos and M. F. Argus. *Z Krebsforsch* 73(3):215-217, 1970.
- 3616 THE ANABOLIC EFFECTS OF ESTROGENS ON MOUSE-LIVER AND THEIR INHIBITION BY CLOMIPHENE. (E.) Schwarzlose, W. (Inst. Pharmacol., U. Erlangen-Nuremberg, Germany) and F. Heim. *Biochem Pharmacol* 19(1):23-26, 1970.
- 3617 β -GLUCURONIDASE ACTIVITY IN THE SERUM AND LIVER OF RATS TREATED WITH PARATHION. (E.) Williams, C. H. (Div. Pharmacol. Toxicol., FDA, Washington, D. C.). *Toxicol Appl Pharmacol* 16(2):533-539, 1970.
- 3618 ACUTE ALCOHOLIC HYPOLYCEMIA IN TWO 4-YEAR-OLDS. (E.) Heggarty, H. J. (Northern Gen. Hosp., Sheffield, England). *Brit Med J* 1(5691):280, 1970.
- 3619 COMPARATIVE MORPHOLOGIC AND FUNCTIONAL STUDIES OF NEPTUNIUM-INDUCED FATTY LIVERS IN RATS. (E.) Berlin, J. D. (Battelle Mem. Inst., Richland, Wash.) and D. D. Mahlum. *Lab Invest* 22(3):252-259, 1970.
- 3620 POLYRIBOSOME DISAGGREGATION IN RAT LIVER FOLLOWING ADMINISTRATION OF TANNIC ACID. (E.) Reddy, J. K. (U. Kansas Med. Ctr., Kansas City), M. Chiga, C. C. Harris and D. J. Svoboda. *Cancer Res* 30(1):58-65, 1970.
- 3621 SELECTED ENZYMES OF PYRIMIDINE NUCLEOTIDE METABOLISM IN LIVERS FROM RATS FED α -NAPHTHYLSIOTHIOCYANATE. (E.) Sneider, T. W. (Med. Sch. U. Wisconsin, Madison), E. L. Krawitt and V. R. Potter. *Cancer Res* 30(1):44-47, 1970.
- 3622 HISTOCHEMICAL STUDIES ON THE ACTION OF AFLATOXINS: I. A CYTOLOGICAL AND CYTOCHEMICAL STUDY OF THE LIVER OF RATS FED A DIET CONTAMINATED WITH *ASPERGILLUS FLAVUS*. (E.) Mietkiewski, K. (Med. Acad. Poznan, Poland), J. Janicki, L. Malendowicz, M. Urbanowicz and B. Filipiak. *Folia Histochem Cytochem* 7(4):379-406, 1969.
- 3623 LIVER CHANGES RESEMBLING THOSE SEEN IN ACUTE PHOSPHORUS POISONING IN A PATIENT RECEIVING CYTOTOXIC DRUGS. (E.) Cochran, A. J. (Western Inf. Glasgow, Scotland) and A. A. Watson. *Med Sci Law* 9(3):202-204, 1969.
- P:Morph (3058) (3081) (3083)
 - P:Secr:Hepatobil (3167) (3211)
 - D:L:Intest (3494)
 - D:L:vb11 (3543)
 - D:Gen:Parasit (3782)

LIVER AND BILIARY TRACT

Acute Viral Hepatitis

- 3624 VIRUS-LIKE PARTICLES IN SERUM OF PATIENTS WITH AUSTRALIA-ANTIGEN-ASSOCIATED HEPATITIS. (E.) Dane, D. S. (Middlesex Hosp., London, England), C. H. Cameron and M. Briggs. *Lancet* 2 (7649):695-698, 1970.
- Serum samples from 16 hepatitis patients positive for Australia-antigen by the agar-gel diffusion test were examined by immune electron microscopy using negative-staining techniques. The small round forms of Australia-antigen were present in all samples and the long forms in some samples while in the sera from 3 patients, there were also a few larger forms approximately 42 m μ in diameter, and when these were penetrated by negative stain a complex structure was revealed. The large particles were often seen in clumps with the small and long forms suggesting that they had been aggregated by the antiserum which had been added before centrifugation. These particles may be complete hepatitis virus and the much more numerous 22 nm particles and long forms of Australia-antigen may be surplus virus-coat material.
- 3625 STUDIES OF AUSTRALIA-SH ANTIGEN IN SPORADIC VIRAL HEPATITIS IN LONDON. (E.) Cossart, Y. E. (Virus Reference Lab., London, England) and J. Vahrman. *Brit Med J* 1(5693):403-405, 1970.
- Sera from 87 patients with acute sporadic viral hepatitis were tested for presence of the Australia-

LIVER AND BILIARY TRACT

Ilan-SH antigen (Au-SH antigen). Of the sera, (first specimen) 51% were negative, 27% were positive by both gel-diffusion, and complement-fixation test, and 22% were positive by complement-fixation test only. Sera with high titers in the complement-fixation test generally reacted positively in the gel-diffusion test, 90% of those producing lines in gel-diffusion test having titers 1/64 or higher, compared with 30% of those which did not. There were, however, 4 cases of high titers in the complement-fixation test which failed to react in the gel-diffusion test. Following testing of a second serum specimen from 13 patients with previous serum antigen, 11 were found negative in the gel-diffusion test, but 9 still contained antigen detectable by complement fixation. There was no correlation between time after onset, return of serum transaminase to normal, and loss of antigen from serum. When patients were divided into clinical categories of infectious hepatitis, serum hepatitis or undetermined (both types), 30% were positive by both gel-diffusion and complement-fixation tests, 20% were positive by complement-fixation alone, and 50% were negative. Cases divided into Au-SH antigen-positive and antigen-negative groups showed that antigen-positive group contained more males than females (4.5 to 1), while antigen-negative were similar (1 to 1). Serum aspartate aminotransferase levels remained raised longer with more fluctuation in the antigen-positive patients. Antigen-positive and antigen-negative hepatitis seemingly may be two distinct clinical entities and that subdivision into these types may be more realistic clinically and epidemiologically than division of viral hepatitis into infectious and serum types.

3626 EXPERIMENTAL ACUTE AND CHRONIC VIRAL HEPATITIS: EFFECT OF ANTITHYMOCYTE GLOBULIN. (E.) Gitnick, G. L. (Mayo Clin., Rochester, Minn.), R. G. Shorter and L. J. Schoenfeld. *Gastroenterology* 58(4):516-523, 1970.

The effect of rabbit antimouse thymocyte globulin was studied in mice with experimental acute viral hepatitis due to reovirus type 3 or murine hepatitis virus type 3 infection. Antithymocyte globulin significantly increased the mortality of these mice and in other experiments in converted a subclinical hepatitis to an overt illness with significant mortality. The clinical course of experimental chronic hepatitis induced by reovirus type 3 was not influenced by the administration of antithymocyte globulin. Bilirubinuria was detected throughout the acute and chronic phases both in antithymocyte globulin-treated and untreated mice. The livers of mice receiving antithymocyte globulin during acute hepatitis showed more extensive hepatocellular necrosis and mononuclear cell infiltration than those receiving virus without antithymocyte globulin while in chronic hepatitis, the degree of hepatocellular necrosis and inflammatory reaction in the livers of mice was not altered by antithymocyte globulin. Fibrosis, but not cirrhosis, was found in the chronic phase of viral hepatitis and viral isolation attempts were successful throughout the acute phase but not in the chronic phase. Complement-fixation, immunodiffusion, and immunoelectrophoretic techniques

failed to demonstrate evidence of circulating anti-liver antibody in the sera of mice having chronic hepatitis.

- 3627 HEPATITIS AND APLASTIC ANEMIA. (Dut.) Timmermans, U. (Mil. Hosp. Antwerp, Belgium) and P. Waumans. *Nederl T Geneesk* 114(7): 286-290, 1970.
- 3628 SERUM HEPATITIS IN THE GREATER NEW ORLEANS AREA. (E.) Larson, D. L. (Louisiana St. Med. Sch., New Orleans), J. Blondin, M. B. Seshul, R. J. Campeau and P. A. LeCour. *J Louisiana Med Soc* 122(3):69-76, 1970.
- 3629 AUSTRALIA ANTIGEN AND HEPATITIS. (E.) anonymous. *Brit Med J* 1(5691):247-248, 1970.
- 3630 PREGNANCY IN INFECTIVE HEPATITIS AND CONTROL EXAMINATIONS OF NEWBORN INFANTS. (Ser.) Perisic, Z. (Sch. Med. Beograd, Yugoslavia), N. Lah and V. Ilic. *Srpski Arh Celok Lek* 97(6): 617-623, 1969.
- 3631 EPIDEMIOLOGY AND CYTOLOGY IN THE DETECTION OF VIRAL HEPATITIS CARRIERS AMONG BLOOD DONORS. (Rus.) Belikova, V. P. (Ivanovsky Virol. Inst., Acad. Med. Nauk, USSR, Podolsk, Ukraine), I. F. Barinsky, I. V. Dementiev and E. P. Filatov. *Zh Mikrobiol* 46(12):43-50, 1969.
- 3632 ADAPTATION TO INFECTIOUS DISEASE: AUSTRALIA ANTIGEN AND HEPATITIS. (E.) Blumberg, B. S. (Inst. Cancer Res., Philadelphia, Pa.). *Amer J Phys Anthropol* 32(2):305-308, 1970.
- 3633 SERUM CHOLINESTERASE IN INFECTIVE HEPATITIS AND HEPATIC COMA. (E.) Achari, A. N. (Darbhanga Med. Coll. Laheriasarai, India) and S. M. Ghose. *J Indian Med Ass* 54(1):1-5, 1970.
- 3634 DOWN'S SYNDROME AND INFECTIOUS HEPATITIS. (E.) Krucera, J. (Teratology Unit, U. P. M. D., Prague, Czechoslovakia). *Lancet* 1(7646): 569-570, 1970.
- 3635 SOME PROBLEMS OF VIRAL HEPATITIS. (E.) Sherlock, S. (Roy. Free Hosp., London, England). *Practitioner* 204(1220):271-272, 1970.
- 3636 DISACCHARIDASE CONTENT IN THE SMALL-INTESTINAL MUCOSA OF NORMAL MOUSE AND OF MOUSE WITH VIRAL MHV-3 HEPATITIS. (E.) Filosa, E. (Clin. Infect. Dis. U. Naples), G. G. Balestrieri, G. Ruggiero and F. Piccinino. *Enzym Biol Clin* 11(3):231-236, 1970.

3637 STUDY OF LIPID DIGESTION IN PATIENTS WITH VIRAL HEPATITIS. (E.) Modai, M. (Tel-Hashomer Hosp., Tel-Aviv, Israel) and E. Theodor. *Proc Tel-Hashomer Hosp* 8(2-3):48-49, 1969.

3638 SOME OBSERVATIONS ON AN OUTBREAK OF INFECTIOUS HEPATITIS OCCURRING IN A LARGE PRIMARY SCHOOL. (E.) Rogers, P. S. (Coburg, Victoria, Australia) and F. Ford. *Med J Aust* 57(7):316-319, 1970.

3639 APPLICATION OF PREVENTIVE HEALTH MEASURES TO CURTAIL CHIMPANZEE-ASSOCIATED INFECTIOUS HEPATITIS IN HANDLERS. (E.) Krushak, D. H. (Nat'l. Communicable Dis. Ctr., Phoenix, Ariz.). *Lab Anim Care* 20(1):52-56, 1970.

3640 HEPATITIS IN MARMOSETS. (E.) Deinhardt, F. (Presbyterian-St. Luke's Hosp., Chicago, Ill.), A. W. Holmes and L. G. Wolfe. (With response from Melnick, J. L. (Baylor Coll. Med., Houston, Texas) and W. P. Parks.) *J Infect Dis* 121(3):351-354, 1970.

- P:Morph (3084)
- D:Livbil:C.Hep (3604) (3642)
- D:Livbil:Cirrh (3648)

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Chronic Hepatitis

3641 AUSTRALIA ANTIGEN IN CHRONIC HEPATITIS IN AUSTRALIA. (E.) Mathews, J. D. (Roy. Melbourne Hosp., Australia) and I. R. Mackay. *Brit Med J* 1(5691):259-261, 1970.

Sera from patients with lupoid hepatitis, active chronic hepatitis, and other hepatic and autoimmune diseases were tested for Australian antigen (Au(1)). Antibody to Au(1) was found in 2 of 102 patients who had received numerous transfusions while the sera of two out of 53 patients with active chronic and lupoid hepatitis and 7 out of 20 patients with clinically atypical acute hepatitis were positive for Au(1). Au(1) was not found in 20 typical cases of infectious hepatitis in young people and in 86 patients with other diseases. Au(1)-positive cases of chronic hepatitis seemingly come from a subpopulation of older patients and active chronic hepatitis may be attributable to initial infection with or breakdown of immunological tolerance to Au(1)-positive (long-incubation-period) hepatitis virus; in younger patients, active chronic hepatitis may follow infection with Au(1)-negative (short-incubation-period) hepatitis virus which has not yet been determined serologically.

3642 PRESENCE OF PARTICLES OTHER THAN THE AUSTRALIA-SH ANTIGEN IN A CASE OF CHRONIC ACTIVE HEPATITIS WITH CIRRHOSIS. (E.) Zuckerman, A. J. (London Sch. Hyg. Trop. Med., England), P. E. Taylor and J. D. Almeida. *Brit Med J* 1(5691):262-264, 1970.

Examination of serum specimens from a middle-aged man with chronic active hepatitis and cirrhosis proved negative for Australian-SH antigen by immunodiffusion and complement fixation. Serum

samples (complete fixation) showed anticomplementary activity up to and at a 1:8 dilution and subsequent electron microscopy revealed virus-like structures similar to coronavirus group (a mouse hepatitis virus was found to belong to the same coronavirus group). Serum samples containing MS-1 agent (infectious hepatitis variety) was found negative for Australia-SH antigen when tested by immunodiffusion, complement fixation, and electron microscopy. Antibody response seemingly is due to a hitherto undescribed human virus generically related to mouse hepatitis viruses (human counterpart with serological relationship). Negative findings with MS-1 pool indicate possible immunological differences between serum hepatitis and infectious hepatitis.

3643 METABOLISM OF ^{131}I GAMMA GLOBULINS IN PATIENTS WITH CHRONIC LIVER DISEASE. (E.) Hirayama, C. (Fac. Med. Kyushu U., Fukuoka, Japan), T. Fukuda and T. Toda. *Clin Chem Acta* 27(3):409-413, 1970.

The metabolism of ^{131}I -labeled γ -globulins (γG , γA , γM) (50-100 μC , i.v.) was studied by scintillation counting in 17 patients with chronic non-alcoholic liver disease (chronic hepatitis and cirrhosis) and 15 normal subjects. Patients with chronic active hepatitis and liver cirrhosis showed a significant decrease in half-life of γG (9.4 ± 2.0 and 10.1 ± 1.7 days resp, compared to 14.1 ± 2.7 days for controls) and a significant increase in the synthesis rate (102 ± 29 mg/kg/day and 123 ± 25 mg/kg/day resp, compared to 52 ± 5 mg/kg/day for controls). Following treatment with 20-30 mg of prednisolone (daily, 3-4 weeks), the synthesis rate decreased significantly in patients with liver cirrhosis (70 ± 10 mg/kg/day compared to 52.5

LIVER AND BILIARY TRACT

Chronic Hepatitis

mg/kg/day for controls); no significant change occurred in chronic active hepatitis. Serum concentrations of γ A (7.5 ± 2.1 mg/ml) and γ M (2.8 ± 0.7 mg/ml) in liver cirrhosis patients were significantly increased compared to controls (2.9 ± 1.0 mg/ml and 0.9 ± 0.1 mg/ml, resp.). Synthetic rate of γ A increased in all liver cirrhosis patients (108 ± 52 mg/kg/day compared to 29.4 ± 4 mg/kg/day in controls), while the synthetic rate of γ M was increased in liver cirrhosis patients (19 ± 5.6 mg/kg/day compared to 6 ± 0.6 mg/kg/day in controls); significant prolongation of half-life (8.0 ± 0.7 days compared to 6.0 ± 0.7 days for controls) was observed with γ M. Concentrations of serum γ C seemingly are regulated by a feedback control mechanism and increased synthesis of γ A and γ M are apparently the major contributing factors to their elevated serum levels.

3644 THE DETERMINATION OF THE α_2 -GLOBULIN CONCENTRATION IN PROTRACTED AND CHRONIC FORMS OF INFECTIOUS HEPATITIS. (Rus.) Safonova, L. G. (Lugan Med. Inst. USSR) and R. P. Dorofeeva. *Ter Arkh* 41(12):46-49, 1969.

3645 LIPID METABOLISM IN PATIENTS WITH CHRONIC POSTINFECTIOUS HEPATITIS TREATED BY USING FAT ENRICHED DIETS. (Rus.) Sadyk-Zade, K. S. (Inst. Nutr., Acad. Med. Nauk, USSR, Moscow). *Vop Pitani* 28(6):41-44, 1969.

3646 DUBIN-JOHNSON SYNDROME. (E.) Muhammad, S. (Med. Sch. U. Indonesia, Jakarta) and S. Darmawan. *Pediatr Indonesia* 9(6):280-285, 1969.

3647 WIDESPREAD ARTERIAL SPIDERS IN A CASE OF LATENT HEPATITIS, WITH RESOLUTION AFTER THERAPY. (E.) Whiting, D. A. (Johannesburg, S. Africa), J. C. Kallmeyer and I. W. Simpson. *Brit J Derm* 82(1):32-36, 1970.

- D:Livbil:A.Nonv.Hep (3604)
- D:Livbil:A.V.Hep (3626)

LIVER AND BILIARY TRACT

Cirrhosis

3648 IMMUNOLOGICAL PICTURE IN INDIAN CHILDHOOD CIRRHOSIS. (E.) Chandra, R. K. (All India Inst. Med. Sci., New Delhi). *Lancet* 1(7646):537-540, 1970.

Serum transaminases (SGOT, SGPT), immunoglobulins (IgG, IgA and IgM) and complement component (β_{1C}) were determined in 30 healthy children and 30 patients with Indian childhood cirrhosis, 6 with acute viral hepatitis, 5 with extrahepatic biliary atresia, 6 with fatty liver and 5 with thalassemia. Values for SGOT and SGPT, IgG, IgA and IgM, and β_{1C} in normal children were 0.80 μ mole/ml/hr and 0.95 μ mole/ml/hr, 117%, 85% and 144%, and 103%, resp. Serum IgG, IgA and IgM levels were significantly increased in patients with Indian childhood cirrhosis and acute viral hepatitis with the greatest increase occurring in IgM levels. Serum β_{1C} levels were markedly decreased in all patients and in 22/30 patients with Indian childhood cirrhosis, a qualitatively different complement component was detected by immunoelectrophoresis. Hepatitis-associated antigen was detected in the serum of 6/30 patients with Indian childhood cirrhosis and the presence of this antigen was not

specifically related to the levels of serum immunoglobulins, transaminases or complement or the clinical grading of the severity of hepatic damage. Hepatitis-associated antigen was also detected in the serum of 4/6 children with acute viral hepatitis. Smooth muscle antibodies were detected in 9/11 sera test from patients with Indian childhood cirrhosis and in two patients, these antibodies were present in dilutions up to 1/20 using both anti-IgG and anti-IgM conjugates. Indian childhood cirrhosis may constitute an infection with a hepatitis-associated antigen in early life in a genetically-disposed infant, resulting in liver cell damage possibly perpetuated by secondary immunological mechanisms.

3649 LIVER IN FELTY'S SYNDROME. (E.) Blendis, L. M. (King's Coll. Hosp. Med. Sch., London, England), I. D. Ansell, K. L. Jones, E. Hamilton and R. Williams. *Brit Med J* 1(5689):131-135, 1970.

Liver function, histology, and hematological changes were studied in 12 patients with Felty's syndrome.

All patients demonstrated neutropenia during illness (less than 2,000/cu mm), 2 patients had a platelet count below 100,000/cu mm (neither of them suffering from purpura) and 6 patients were anemic, with hemoglobin concentrations of 7 to 11 g/100 ml. Total red cell mass in 6 anemic patients was either normal or in one patient, increased at 35.8 ml/kg (normal range 22 to 34 ml/kg). In 5 of these patients, anemia was due to increased plasma volume from 61.8 to 111.1 ml/kg (normal range 34 to 48 ml/kg) and eventual red cell mass dilution. Two patients had increased hemolysis (hemoglobin dropped from 12 to 9.4 g/100 ml) associated with red cell sequestration by enlarged spleens. Eight out of 12 patients showed abnormal liver function tests while in 5 patients, liver histology showed lymphocytic infiltration of sinusoids and portal tracts together with portal tract cirrhosis. Macronodular cirrhosis was eventually found in one of these patients, while another patient showed nodules without true cirrhosis (observed in 2 additional patients with Felty's syndrome). Increased splenic blood flow was present in 2 patients with values of 712 and 1060 ml/min (normal range 100 to 300 ml/min).

3650 TRANSFER OF MEDIUM CHAIN FATTY ACIDS FROM BLOOD TO SPINAL FLUID IN PATIENTS WITH CIRRHOSIS. (E.) Linscheer, W. G. (Lemuel Shattuck Hosp., Boston, Mass.), A. L. Blum and R. R. Platt. *Gastroenterology* 58(4):509-515, 1970.

A test meal of medium chain triglycerides (C6-C12; 0.5 g/kg p.o.) was administered to 12 patients with advanced alcoholic cirrhosis and to 12 noncirrhotic control subjects and the concentration of medium chain fatty acids in serum, serum ultrafiltrates, and spinal fluid were measured. Serum octanoic acid concentrations were 2 times higher in the cirrhotic patients than in the control subjects due to its impaired clearance from the portal venous circulation. Spinal fluid octanoic acid levels were 4 to 5 times higher in the cirrhotic patients as compared with the controls. Serum ultrafiltrates of cirrhotic patients demonstrated decreased protein binding of octanoic acid in serum at higher levels of serum octanoic acid than in control subjects. *In vitro*, spinal fluid concentrations were approximated from the serum octanoic acid concentrations. A passive diffusion of octanoic acid into the cerebrospinal fluid probably occurs in advanced alcoholic cirrhosis.

3651 EFFECTS OF DOPAMINE ON RENAL FUNCTION IN PATIENTS WITH CIRRHOSIS. (E.) Barnardo, D. E. (Mayo Clin., Rochester, Minn.), W. P. Balduz and F. T. Maher. *Gastroenterology* 58(4):524-531, 1970.

The effects of dopamine (mean dose of 1.9 µg/kg/min for 179 min, i.v.) on renal function were studied in 10 patients with cirrhosis and various degrees of impairment of renal function. Dopamine caused a consistent increase in effective renal plasma flow but little change in glomerular filtration rate or sodium and water excretion. Cardiac output was not altered by the dopamine injections. The hemodynamic change was attributed to a direct effect of dopamine

on the renal vasculature, resulting in a reduction in both preglomerular and postglomerular resistance.

3652 IMMUNE REACTIONS IN CIRRHOTIC PATIENTS: STATISTICAL ANALYSIS OF 106 OBSERVATIONS. (Fr.) Nakache, J. P. (Fac. Med. Pitie Salpetriere, France), D. Salmon, F. Gremy, A. Gerbal, J. C. Homberg, Ch. Salmon, H. Rochant, Y. Hecht and J. Caroli. *Rev Europ Etud Clin Biol* 15(1):71-80, 1970.

3653 UNSTABLE HYPERLIPEMIA IN ALCOHOLICS WITH ZIEVE'S SYNDROME: STUDY OF THREE CASES. (Fr.) Moretti, G. (Bordeaux, France), J. Staefien and J. Beylot. *Bordeaux Med* 2(11):2379-2392, 1969.

3654 DENERVATION OF THE COMMON HEPATIC ARTERY IN CIRRHOSIS OF THE LIVER. (Rus.) Efimishin, N. S. (Grodzinsk Med. Inst., USSR). *Vestn Khir* 102(12):20-23, 1969.

3655 CIRRHOSIS: A GROWING THREAT TO LIFE. (E.) Carper, J. (no affil). *Today's Health* 48(2):26-27, 67-68, 1970.

3656 SIGNIFICANCE OF SPLENOMEGALY IN PATIENTS WITH HEPATIC CIRRHOSIS AND BLEEDING ESOPHAGEAL VARICES. (E.) Dumont, A. E. (New York U. Sch. Med., New York), E. Amorosi and W. M. Stahl. *Ann Surg* 171(4):522-526, 1970.

3657 EMERGENCY PORTOCAVAL ANASTOMOSIS IN CIRRHOTICS: WITH REFERENCE TO 61 OBSERVATIONS. (Fr.) Maillard, J. N. (no affil), P. Capelle, R. Giuli and B. Goyer. *Vie Med* 50(36):4489, 4491, 4493, 4495, 1969.

3658 EFFECTS OF DIENESTROL ON THE THYROXINE BINDING CAPACITY OF ALPHA-GLOBULIN IN HEPATIC CIRRHOSIS. (Sp.) Zaminovich, A. (Hosp. Sch. Jose de San Martin, Buenos Aires, Argentina), S. El Tamer, O. Degrossi and H. Gotta. *Medicina* 29(5):355-358, 1969.

3659 BILIARY CIRRHOSIS SECONDARY TO EXTRAPULMONARY PARAGONIMIASIS. (E.) Okuda, K. (Kurume U. Sch. Med., Japan), S. Kuratomi, M. Moriyama and A. Mae. *Digestion* 2(6):347-353, 1969.

3660 THE EFFECT OF BENZOBROMARONUM ON GOUT, DIABETES MELLITUS, HYPERLIPEMIA, FATTY LIVER AND HYPERTENSION. (E.) Mertz, D. P. (Med. Polyclin. U. Frieberg, Germany), I. Sulzberger and M. Klopfer. *Munchen Med Wschr* 112(6):241-247, 1970.

- D:Livbil (3545) (3546)
- D:Livbil:C.Hep (3643)
- D:Gen (3752)

LIVER AND BILIARY TRACT

Gallbladder and Biliary Tract Diseases

3661 INDUCTION OF RAT LIVER ALKALINE PHOSPHATASE: THE MECHANISM OF THE SERUM ELEVATION IN BILE DUCT OBSTRUCTION. (E.) Kaplan, M. M. (Tufts-New England Med. Ctr., Boston, Mass.) and A. Righetti. *J Clin Invest* 49(3):508-516, 1970.

The mechanism of the elevation in serum alkaline phosphatase activity produced after bile duct obstruction (double ligation) was studied in rats by assaying alkaline phosphatase activity in liver and serum, by measurements of *de novo* protein synthesis, and by identification of alkaline phosphatase isozymes. Within 12 hr after bile duct obstruction, there was a 2.5-fold increase in serum alkaline phosphatase activity (normal value = 0.15 IU/ml) and a 7-fold increase in liver alkaline phosphatase activity (normal value = 1 IU/g) and the increased activity lasted for 5 days. The increase in serum alkaline phosphatase activity was accompanied by the appearance of a new isozyme with the same electrophoretic mobility, Michaelis constants, pH optima and heat of denaturation as liver alkaline phosphatase. Rats with bile duct fistulas excreted into the bile approximately 0.025 IU of alkaline phosphatase/g liver/12 hr and the increase in liver alkaline phosphatase activity resulting from bile duct ligation in these rats was 6.0 IU/g liver. Cyclohexamide, 100 µg/100 g i.m. 1 hr before bile duct ligation, inhibited protein synthesis by 68%, the increase in liver phosphatase activity by 98% and that in serum phosphatase activity by 80%. Cycloheximide did not affect the increase in serum glutamic pyruvic transaminase activity and the decrease in liver activity produced by bile duct ligation. Elevated serum phosphatase activity in bile duct obstruction seemingly originates in the liver and is dependent on *de novo* protein synthesis.

3662 BILE PERITONITIS: AN EXPERIMENTAL AND CLINICAL STUDY. (E.) Conn, J. H. (U. Mississippi Sch. Med., Jackson), C. M. Chavez and W. R. Fain. *Amer Surg* 36(4):219-224, 1970.

Bile peritonitis produced by creating an internal biliary fistula resulted in death within 60 hr in 10 of 15 dogs; replacement of circulating plasma volume (dextran, 500 ml over 4 hr period) in 5 of the 10 dogs did not significantly increase longevity. At autopsy the peritoneal fluid of these dogs contained various pathogenic bacteria. When penicillin (1,200,000 U) was given to 5 additional dogs immediately following an internal biliary fistula, there were no deaths and although these animals collected up to 5,000 ml of biliary ascitic fluid, cultures were negative except in 2 dogs. A study of patients with internal biliary fistula showed that they had minimal symptomatology, with large quantities of biliary ascitic fluid and negative bacterial cultures. The difference in response between man and dog might be due to a pre-existing peritoneal bacterial flora in the dog.

3663 ANGIOGRAPHIC FINDINGS IN HYPERPLASTIC CHOLECYSTOSES. (E.) Elfving, G. (U. Central Hosp., Helsinki, Finland), H. Myllärmiemi and P. Peltohallio. *Ann Chir Gynaec Fenn* 58(4):322-325, 1969.

Eleven hyperplastic cholecystotic gallbladders were examined by the technique of microangiography and the results compared with a gallbladder wall in which nothing abnormal was seen either grossly or microscopically. The veins followed the cystic artery and its branches from the neck of the gallbladder to its fundus, and in all hyperplastic cholecystotic gallbladders and the vasculature was distinctly more profuse and more stratified than in normal controls. Vasculization displaying smaller networks and more numerous rami was typical in the hyperplastic gallbladders. Vascular changes encountered in different hyperplastic cholecystoses seemingly are secondary occurrences since the hyperplastic mucosa which provides the gallbladder with a larger resorption surface naturally requires a correspondingly increased blood supply.

3664 IRON IN HUMAN BILE. (E.) Mekel, R. C. P. M. (Natl. Nutr. Res. Inst., Pretoria, South Africa), C. J. Van Der Merwe, E. J. P. De Bruin and C. R. Jansen. *S Afr Med J* 44(3):56-58, 1970.

The excretion in the bile (collected by a T-drain) of a tracer dose of i.v. administered ⁵⁹Fe was studied in 2 female patients who had undergone bile-duct operations. The results obtained for the two cases were almost identical. Following an initial rapid rise of ⁵⁹Fe concentration in the bile during the first 60 to 75 min. after injection, a constant level of excretion through the T-drain was 0.0017% and 0.0012%, resp., of the dose administered (21,200 nC and 17,200 nC) in the two cases. About 25 to 33% of the body iron excreted via the gastrointestinal tract apparently comes from the bile and reabsorption of a portion of the biliary iron is probable, although the rate of reabsorption is not known.

3665 HEMOBILIA AND HEMOCHOLECYST DUE TO CHOLECYSTITIS WITHOUT STONES: REPORT OF A CASE. (E.) Silvennoinen, E. (U. Central Hosp., Helsinki, Finland) and V. Makela. *Ann Chir Gynaec Fenn* 58(4):336-338, 1969.

3666 EXPERIMENTAL BILIARY LITHIASIS IN DOGS CAUSED BY A SLOWLY INDUCED STENOSIS OF THE TERMINAL COMMON BILE DUCT. (It.) Mattiolo, F. (Inst. Clin. Surg. Gen., Surg. Ther., U. Genoa, Italy) and G. C. Torre. *Pathologica* 61(893-894):17-23, 1969.

3667 THE DECEIVING GALLBLADDER. (E.) Picarra, B. J. (Long Island U., Greenvale, New York). *J Abdom Surg* 12(3):37-40, 1970.

3668 FATAL GASTROINTESTINAL TRACT HEMORRHAGE: A COMPLICATION OF ULCERATIVE CHOLECYSTITIS, CHOLELITHIASIS AND CHOLECYSTODUODENAL FISTULA. (E.) Schenken, J. R. (Nebraska Methodist Hosp., Omaha) and J. R. Adamson. *Amer J Clin Path* 53(3):423-424, 1970.

- 3669 CLOSTRIDIAL INFECTION FOLLOWING CHOLECYSTECTOMY. (Dut.) Bornhaupt, C. L. (Militt. Hosp. A. Mathijssen, Utrecht, Netherlands). *Nederl Milit Geneesk T* 22(6):329-333, 1969.
- 3670 PATHOGENESIS OF POSTHEPATIC HYPERBILIRUBINEMIA. FUNCTIONAL AND ULTRASTRUCTURAL STUDIES. (It.) Gentilini, P. (Inst. Spl. Path. Med. Clin. Method., U. Study, Firenze, Italy), C. Surrenti, A. C. Tommasi and R. Camilloni. *Arch Ital Mal Appar Dig* 35(6):553-562, 1969.
- 3671 SURGICAL TREATMENT OF CHOLELITHIASIS. (Rus.) Romanov, P. K. (Dzhanelidze Emerg. Res. Inst., Leningrad, USSR) and N. S. Triumfara. *Vestn Khir* 103(2):14-17, 1970.
- 3672 RADIOISOTOPE SCANNING OF THE LIVER IN DIAGNOSIS OF OBSTRUCTIVE JAUNDICE IN ALVEOCOCCOSIS. (Rus.) Sheffer, R. Ya. (Altai Med. Inst., USSR) and S. L. Pribylovsky. *Vestn Khir* 102(12):17-19, 1969.
- 3673 DUODENAL CATHETERIZATION IN PATIENTS AFTER BILE DUCT SURGERY. (Rus.) Makhov, N. I. (Vladimirovskiy Reg. Clin. Res. Inst., Moscow, USSR) and Ju. A. Travkin. *Vestn Khir* 102(12):23-25, 1969.
- 3674 BIOCHEMICAL BLOOD SERUM PARAMETERS AND LIVER MORPHOLOGICAL DATA IN OBSTRUCTIVE JAUNDICE. (Rus.) Strutchkov, V. I. (Sechenov Med. Inst., Acad. Med. Nauk USSR, Moscow), V. S. Vasilliev, V. A. Smoliar and N. K. Bogdanovich. *Ter Arkh* 41(12):40-44, 1969.
- 3675 INTESTINAL ALKALINE PHOSPHATASE IN CHRONIC HEPATO-BILIARY DISEASE. (Rus.) Bakhadynov, K. B. (Atakhanov Pediat. Inst., Tashkent, USSR), K. K. Kakharbekov, E. A. Beil and Z. F. Cherenok. *Ter Arkh* 41(12):44-46, 1969.
- 3676 IMPORTANCE OF PUNCTURE BIOPSY OF THE PANCREAS FOR THE ASSESSMENT OF OBSTRUCTIVE JAUNDICE. (Rus.) Lobko, A. F. (Pirogov Med. Inst., Odessa, USSR). *Klin Khir* 52(1):22-26, 1970.
- 3677 SPONTANEOUS BILE DUCT PERFORATION IN AN INFANT. (E.) Van De Stadt, F. R. (Groningen U. Surg. Clin., Netherlands). *Arch Chir Neerland* 21(4):313-318, 1969.
- 3678 GAS GANGRENE OF THE GALLBLADDER OR GANGRENOUS PNEUMOCHOLECYSTITIS. (E.) Lemmens, H. A. J. (St. Annadal Hosp., Maastricht, Netherlands) and J. Louyest. *Arch Chir Neerland* 21(4):333-342, 1969.
- 3679 BETA LIPOPROTEINS IN OBSTRUCTIVE JAUNDICE. MEASUREMENT OF 2 IMMUNOLOGICALLY DISTINCT FRACTIONS. (Fr.) Burstein, M. (Nat. Ctr. Blood Transfus., Paris, France) and J. Caroli. *Rev Med* 14(1):68-71, 1969.
- 3680 PAINS OF THE BILIARY TYPE AND HYPERPLASTIC STATES OF THE GALLBLADDER MUCOSA. (Fr.) Leonard, P. (157 Brand Whitlock Blvd., Brussels, Belgium). *Acta Gastroent Belg* 32(10):739-760, 1969.
- 3681 A PATIENT WITH ICTERUS GRAVIDARUM. (Dut.) De Bruijne, H. (Militt. Hosp. Dr. A. Mathijssen, Utrecht, Netherlands). *Nederl Milit Geneesk T* 22(6):338-342, 1969.
- 3682 BENIGN TUMORS OF CHOLECYSTITIS: DESCRIPTION OF CASES OF PAPANILLOMA, ADENOMA, AND LIPOMA. (It.) Bonandrini, L. (Dept. Gen. Clin. Surg., Surg. Ther., U. Pavia, Italy), E. Mantellini, P. Colombo and L. Scarabelli. *Minerva Chir* 25(4):297-312, 1970.
- 3683 POTASSIUM IN THE MANAGEMENT OF CARDIAC EMERGENCIES PRESENTING IN THE POST-OPERATIVE COURSE OF DIGESTIVE SYSTEM (PARTICULARLY BILIARY) SURGERY. (It.) Verga, L. (Orzinuovi Hosp., Italy) and A. V. Bo. *Gazz Med Ital* 128(11):630-644, 1970.
- 3684 PRIMARY MALIGNANT TUMORS OF THE GALLBLADDER: REPORT OF 43 CASES. (E.) Tanga, M. R. (Ottawa Gen. Hosp., Ontario, Canada) and J. B. Ewing. *Surgery* 67(3):418-426, 1970.
- 3685 HISTOCHEMICAL AZO-COUPLING REACTIONS OF THE PIGMENTS OF OBSTRUCTIVE ICTERUS AND OF HEMATOIDIN: II. EFFECT OF BLOCKADE, BLEACHING AND EXTRACTION PROCEDURES ON THE PIGMENTS AND THEIR AZO-DERIVATIVES. (E.) Lillie, R. D. (Louisiana State U. Sch. Med., New Orleans) and P. Pizzolato. *J Histochem Cytochem* 18(2):75-79, 1970.
- 3686 POLYARTERITIS NODOSA OF THE GALLBLADDER. (E.) Remigio, P. (Mary Immaculate Hosp. Div. Catholic Med. Ctr., Jamaica, N. Y.) and E. Zaino. *Surgery* 67(3):427-431, 1970.
- 3687 CONTRACTIONS OF THE GALLBLADDER AND THE FORMATION OF GALLSTONES: III. (E.) Hulten, O. (U. Hosp. Uppsala, Sweden). *Acta Chir Scand* 136(1):53-56, 1970.
- 3688 REMOVAL OF RESIDUAL BILIARY TRACT CALCULI WITHOUT REOPERATION. (E.) Mazzariello, R. (Rivadavia, Buenos Aires, Argentina). *Surgery* 67(4):566-573, 1970.

LIVER AND BILIARY TRACT

3689 CHOLECYSTITIS, PANCREATITIS AND PERICARDI-TIS. (E.) Nolin, L. E. (Waterville, Me.) and J. F. Reynolds. *J Maine Med Ass* 61(2):42-43, 1970.

3690 PRIMARY STONE IN COMMON DUCT ASSOCIATED WITH HYPOGENETIC GALLBLADDER: A CASE REPORT. (E.) Polak, T. (Mem. Hosp. Southern California, Culver City). *J Abdom Surg* 12(3):41-42, 1970.

3691 POST-TRAUMATIC ACALCULOUS CHOLECYSTITIS IN YOUNG MALES. (E.) Shaw, R. C. (Brooke Gen. Hosp., Fort Sam Houston, Texas). *Milit Med* 135(3):210-214, 1970.

3692 FILLING DEFECT IN THE DUODENUM DUE TO STONES IN THE BILIARY TRACT. (E.) Shahin, N. (Tel-Hashomer Hosp., Tel Aviv, Israel). *Proc Tel-Hashomer Hosp* 8(2-3):53-55, 1969.

3695 POSTOPERATIVE CHANGES OF ORNITHINE CARBAMOYL TRANSFERASE ACTIVITY IN SERUM (S-OCT) RELATED TO OXYGEN SATURATION IN HEPATIC VEIN BLOOD DURING OPERATIONS IN MAN. (E.) Gillquist, J. (Karolinska Hosp., Stockholm, Sweden), L. Kaijser and S. O. Liljedahl. *Acta Chir Scand* 136(1):9-16, 1970.

The relation between variations in oxygen saturation of the hepatic vein blood (SO_2) during surgery to postoperative changes in serum ornithine carbamoyl transferase activity (measured as n-moles $^{14}CO_2$ /(ml x hr)) was analyzed in 19 patients prior to surgery for fracture of the lower extremity. There was a significant correlation between the early postoperative increase in serum ornithine carbamoyl transferase activity (normal value = <4 n-moles/(ml x hr)) and the low oxygen saturation ($p < 0.001$) of hepatic vein blood during operation. The degree and duration of the fall in oxygen saturation influenced the magnitude of the increase in serum ornithine carbamoyl transferase activity. An early increase in serum ornithine carbamoyl transferase activity seemingly may be caused by ischemia of the liver during operation.

3696 DIARRHEA ASSOCIATED WITH MEDULLARY CARCINOMA OF THE THYROID. (E.) Berneir, J. J. (Hosp. St. Lazare, Paris, France), J. C. Rambaud, D. Cattani and A. Frost. *Act* 10(12):980-985, 1969.

Excessive diarrhea associated with medullary carcinoma of the thyroid is described in 5 patients who were euthyroid and without clinical or laboratory signs of pheochromocytoma. Radiological studies

Gallbladder and Biliary Tract Diseases

3693 A RADIOLOGICALLY DEMONSTRATED FISTULA BETWEEN THE COMMON BILE DUCT AND THE RIGHT RENAL PELVIS. (E.) Op Den Orth, J. O. (Princess Irene Hosp., Almelo, Netherlands). *Radiol Clin Biol* 38(4):402-405, 1970.

3694 PATHOPHYSIOLOGY OF CHOLESTASIS. (E.) Popper, H. (Mt. Sinai Sch. Med. City U. New York) and F. Schaffner. *Human Path* 1(1):1-24, 1970.

- P:Secr:Hepatobil (3182)
- Diagproc (3264) (3273) (3279) (3295) (3298) (3306) (3310)
- D:Stomduo (3366)
- D:S:Intest (3421)
- D:Livbil:A.Nonv.Hep (3601)

GENERAL

with barium meal revealed hypermotility of the small and large intestine and peroral biopsies showed a normal or mildly impaired (villous atrophy, inflammation) small intestinal mucosa in 3/5 patients. The main components of the excessive diarrhea were water and electrolytes. Steatorrhea was mild or absent and xyllose and Schilling tests were normal in the 3 patients with hypermotility. Blood and urine levels of vasoactive excitomotor substances (5-hydroxyindoleacetic acid, serotonin, bradykinin, prostaglandins) and serum albumin and proteins and blood electrolytes, lipids, total cholesterol and hemoglobin were all within normal limits in these patients.

3697 EXPERIENCE WITH CELIAC AXIS COMPRESSION SYNDROME. (E.) Edwards, A. J. (St. Bartholomew Hosp., London, England), J. D. Hamilton, W. D. Nichol, G. W. Taylor and A. M. Dawson. *Brit Med J* 1(5692):342-345, 1970.

A report is made of 7 cases (5 women, 2 men; 18- to 50-yr-old) with celiac axis compression syndrome characterized by epigastric bruits that prompted angiographic study by percutaneous transfemoral retrograde aortography, with selective catheterization of the superior mesenteric artery. The dominant symptom was epigastric pain or discomfort that was related more to posture and activity than to food and was relieved by recumbency. Aortography showed compression of the celiac axis and superior mesenteric arteriograms showed good collateral flow in the celiac axis branches via the pancreaticoduodenal vessels. Laparotomy was performed in 5 cases; the celiac axis was found to be compressed

by fibromuscular tissue associated with the median arcuate ligament of the diaphragm and intermingled with strands of the celiac plexus. The celiac artery was freed from constriction by incision along its ventral aspect and no attempt at celiac neurectomy or ganglionectomy was made. Only 2 patients were symptom-free as a result of the surgery. A survey of 200 healthy adults (100 men, 100 women, 17- to 30-yr-old) showed epigastric bruits in 6.5%; only one of these had dyspepsia, though dyspepsia was present in 12.5% overall.

3698 JEJUNAL TRANSPORT OF ELECTROLYTES AND WATER IN INTESTINAL DISEASE. (E.) Phillips, S. F. (Mayo Clin. Found., Rochester, Minn) and W. C. Schmid. *Gut* 10(12):990-993, 1969.

Decreased absorption of electrolytes (sodium, potassium, chloride, and bicarbonate) and water by the jejunum (from a 20-cm segment) as related to the pathogenesis of diarrhea was examined in patients with intestinal scleroderma (2), ileocolitis (4), gastric hypersecretion (1), and extensive ileal resection (3). Four of the patients were male and 6 were female, with ages ranging from 19 to 69; the 6 healthy control subjects were 22 to 51 yr of age, all of whom absorbed electrolytes and water. Both patients with scleroderma had abnormal absorption (secretion was demonstrated in one of them). Absorption of each electrolyte and water was decreased in ileocolitis in a segment of jejunum that was apparently free of the disease. The patient with islet-cell tumor and gastric hypersecretion also had markedly abnormal absorption. Despite the severe diarrhea in the 3 patients with extensive ileal resection, jejunal absorption was normal. Excretion of fecal fat was excessive in all patients tested.

3699 GASTROINTESTINAL COMPLICATIONS OF THE EHLERS-DANLOS SYNDROME. (E.) Beighton, P. H. (St. Thomas Hosp., London, England), J. L. Murdoch and T. Votteler. *Gut* 10(12):1004-1008, 1969.

Gastrointestinal complications of 125 patients from England, the USA and Canada with Ehlers-Danlos syndrome were examined. The most serious but infrequent complications which occurred were intestinal perforation and hemorrhage (2 patients) and less dangerous abnormalities included external hernia, hiatus hernia, eversion of diaphragm, intestinal diverticula, and rectal prolapse. Surgery was difficult in affected patients due to fragility of tissues and bleeding tendency and in the post-operative period, tearing out of sutures and wound dehiscence occurred. Although structural abnormalities of the gastrointestinal tract are common occurrences in Ehlers-Danlos syndrome, few patients seemingly have any serious complications.

3700 THE PRESENCE OF N₂-FIXING BACTERIA IN THE INTESTINES OF MAN AND ANIMALS. (E.)

Bergersen, F. J. (C. S. I. R. O., Canberra, Australia) and E. H. Hipsley. *J Gen Microbiol* 60(1): 61-65, 1970.

Cultures of N₂-fixing bacteria have been isolated from the feces of man and the intestinal contents of pigs and guinea-pigs. Acetylene-reduction tests indicate that N₂-fixation occurs in the intestine and the best N₂-fixation culture activity was shown by *Klebsiella (K.) aerogenes*. The *K. aerogenes* culture produced H₂ and CO₂ in the ratio of 1:2 when grown anaerobically with glucose as energy source in a shaken liquid culture in which 11.7 µg N/ml culture was fixed in 48 hr. All cultures fixed more N₂ anaerobically than aerobically, but some fixation occurred when 20% O₂ was present.

3701 THE EFFECTS OF ANALGESIC DRUGS ON GASTRO-INTESTINAL MOTILITY IN MAN. (E.) Neely, J. (St. Bartholomew's Hosp., London, England). *Brit J Surg* 56(12):925-929, 1969.

The effects of morphine and pethidine on gastrointestinal motility were studied by use of pressure-sensitive radio-telemetering capsules sutured into either stomach, duodenum or colon in 15 patients undergoing abdominal operations. Only 2 of 15 patients showed any return of spontaneous gut activity before analgesic injection and both patients had undergone vagotomy (in one patient the pressure capsule had been sewn into gastric antrum, while in another it was placed into caecum). Gut activity returned early in remaining 13 patients, but it was related to either morphine or pethidine injections. A motility response always occurred in gut section where pressure capsule was situated following injection of either drug. Highest luminal pressures were obtained in colon following morphine (15mg). Caution in the interpretation of records of gastrointestinal activity after surgery is suggested, and motility tracing must be carefully correlated with injections of analgesics.

3702 THE TREATMENT OF *GIARDIA LAMBLIA* INFECTION WITH MEPACRINE, METRONIDAZOLE AND FURAZOLIDONE. (E.) Bassily, S. (U.S. Naval Med. Res. Unit #3, Cairo, Egypt), Z. Farid, J. W. Mikhail, D. C. Kent and J. S. Lehman, Jr. *J Trop Med Hyg* 73(1): 15-18, 1970.

Results of treatment of *Giardia (G.) lamblia* with mepacrine (100 mg BID-TID, for 5 days), metronidazole (250 mg UID-BID, for 10 days), and furazolidone (100 mg BID-QID, for 7 days) were evaluated in 80 patients (3-52 years old). All 20 patients treated with mepacrine were cured (100%), 19 of 20 patients receiving metronidazole were cured (95%), and 16 of 20 patients treated with furazolidone were cured (80%). All 20 patients receiving placebo continued to be infected to end of 5 week follow-up study. These drugs did not cure patients with other intestinal protozoal infections. Severe nausea and vomiting occurred in 2 patients treated with mepacrine while yellow skin coloration was observed in a third patient. No side-effects were noted in patients receiving metronidazole or furazolidone. Tolerance and lack of side-effects would seemingly make metronidazole (Flagyl) the drug of choice for *G. lamblia* infection.

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- 3703 HEPATIC AMEBIASIS AND ITS TREATMENT WITH METRONIDAZOLE. (E.) Chhetri, M. K. (Inst. Postgrad Med. Educ. Res., Calcutta, India), N. C. Chakravorty, C. Neelakantan, B. Bhattacharya and S. K. Sarkar. *J Ass Physicians India* 17(11): 681-688, 1969.

Clinical courses of hepatic amebiasis and treatment was observed in 60 patients (50 cases of liver abscess and 10 with hepatitis). No age group was immune to complications while complications were found only in males. Forty-three of 60 patients (71%) with disease belonged to poor classes and abscess formation was 3 times more common in patients from poorer social status. History or presence of disposing factor was detected in 43 cases (60%) with liver abscess and in 4 cases (40%) with amebic hepatitis; past history of amebiasis was present in only 20% of patients with liver abscess or hepatitis (10 and 2 patients each). Poor nutritional status appeared to be predisposing condition in this group and pain in the right hypochondrium, tender hepatomegaly, intercostal tenderness, and pyrexia were commonest clinical features. Aspiration of pus was direct confirmatory evidence of liver abscess and a high erythrocyte sedimentation rate and leucocytosis were present in most cases. A positive indirect hemagglutination test was indirect evidence of amebiasis and useful adjunct to diagnosis; radiological findings aided in diagnosis confirmation. Complications due to abscess rupture occurred in 10 patients, with rupture into peritoneal cavity being fatal in 4 cases. Metronidazole administration was successful in 33 of 34 liver abscess cases (97%) and all patients in the hepatitis group (100%); effective dose was 1200 mg/for 5 days or 2400 mg for 2 days. No adverse side effects were observed. Metronidazole is recommended as drug of choice in adults and children in all forms of amebiasis.

- 3704 MEASUREMENT OF GASTROINTESTINAL TRANSMURAL ELECTRIC POTENTIAL DIFFERENCE IN MAN. (E.) Geall, M. G. (Mayo Clin., Rochester, Minn.), C. F. Code, D. C. McClirath and W. H. J. Summerskill. *Gut* 11(1):34-37, 1970.

Measurement in 11 patients undergoing abdominal operations of the electrical potential difference between venous blood and the mucosal surface of the gastrointestinal tract showed a highly significant correlation upon comparison. In 6 of these patients, no measurable difference in potential existed between peripheral blood and the serosa of the colon, small intestine, stomach or parietal peritoneum. In healthy persons, the difference between skin-mucosal and blood-mucosal potential difference approximated the potential difference between skin and blood. Both the skin and the gastrointestinal mucosa were negative with respect to blood. Skin-mucosal potential difference did not become stable until about 5 min and varied greatly among different subjects, whereas blood-mucosal potential difference did not change significantly. Skin-blood potential difference was reduced by skin injury and was lower if recorded from regions of the body other than the fingers. No difference in the potential difference

was found when flowing KCl and agar-KCl electrolyte bridges were used.

- 3705 PROFILE OF GASTRIC POTENTIAL DIFFERENCE IN MAN: EFFECTS OF ASPIRIN, ALCOHOL, BILE AND ENDOGENOUS ACID. (E.) Geall, M. G. (Mayo Clin., Rochester, Minnesota), S. F. Phillips and W. H. J. Summerskill. *Gastroenterology* 58(4):437-444, 1970.

Transmural potential difference of the human stomach was measured in 9 healthy male volunteers and 2 patients with the Zollinger-Ellison syndrome using a reference electrode placed in a peripheral vein. Potential difference was higher in the body of the stomach than in the antrum. Stimulation of gastric acid secretion by betazole caused only a slight and temporary decrease in potential difference below the basal value, the decrease occurring shortly after betazole was injected and prior to the onset of peak acid output. The administration of acetosalicylic acid, alcohol, or duodenal contents rich in bile and pancreatic enzymes all caused rapid and profound reductions in gastric potential difference. Maintenance of gastric potential difference may be a sensitive indicator of mucosal integrity in man.

- 3706 SEROLOGICAL EVIDENCE FOR THE IDENTITY OF THE VASCULAR PERMEABILITY FACTOR AND ILEAL LOOP TOXIN OF *VIBRIO CHOLERAE*. (E.) Mosley, W. H. (Pakistan-SEATO Cholera Res. Lab., Dacca), K. M. S. Aziz and A. Ahmed. *J Infect Dis* 121(3):243-250, 1970.

The toxin-antitoxin titration procedures for the measurement of neutralizing antibody to vascular permeability factor (in rabbit skin) and to cholera toxin (in rabbit ileal loop) were modified to permit a direct comparison of the antibody titers (antitoxin units/ml) by both assays on sera from patients with cholera (range 4 to over 1000) and from hyperimmunized horses, rabbits, and a goat (range 40 to 8000). Two sera from the patients gave identical titers in both assays, 7 sera showed no more than a 30% difference (with the higher values always in the ileal loop test), 2 showed a two-fold difference, 1 a three-fold, and 1 had no detectable titer in either assay. Five of the 6 sera from the animals gave identical titers in both tests with the goat serum showing a 1-fold difference possibly reflecting test variation. Two different toxin preparations (NIH Lot 001 and TX-C-IV-8 DL) from other laboratories were compared to toxin A4 of this study and neutralization curves for each gave identical end points in their respective skin and loop tests. These 2 tests appear to measure a single antigen-antibody reaction suggesting that ileal loop toxin and vascular permeability factor are identical.

- 3707 NUTRITIONAL FOLIC ACID DEFICIENCY WITH MEGALOBlastic CHANGES IN THE SMALL-BOWEL EPITHELIUM. (E.) Rosensweig, N. S. (St. Luke's Hosp. Ctr., New York, N. Y.), A. Bianchi, D. W. Chipman and A. Dreskin. *New Eng J Med* 282(15): 859-861, 1970.

A case of severe prolonged nutritional folic acid deficiency with megaloblastic changes in the small bowel mucosa is reported in a 52-year-old man. The patient was admitted with a long-standing history of chronic alcoholism, several months of poor dietary intake, diarrhea, and megaloblastic anemia. A peroral duodenal biopsy revealed shortened villi, megaloblastic nuclei in the crypt epithelial cells and the villus epithelial cells and an infiltration of mononuclear cells in the lamina propria. After treatment with folic acid, 5 mg t.i.d., the megaloblastic changes in the bone marrow and duodenum returned to normal and the diarrhea disappeared.

3708 UNUSUAL *SPHAEROPHORUS* SPECIES FROM THE LARGE INTESTINE OF MAN. (E.) Pearson, T. A. (Oak Ridge Ass. U. Tennessee) and E. Balish. *Appl Microbiol* 19(3):458-462, 1970.

The levels of *Sphaerophorus* (designated as isolate 6-13-68) and other anaerobic microorganisms in the feces of two cancer patients (chronic myelogenous leukemia and idiopathic thrombocytopenia) were determined by culturing on sheep blood-agar before, and for several weeks after, cobalt irradiation therapy. Isolate 6-13-68 showed extreme polymorphism (rods, filaments, and spheroids) and was a major component of the anaerobic fecal microflora. The levels of isolate 6-13-68 as well as of *Bacteroides* and *Clostridium perfringens* declined during the third week after irradiation treatment in one patient and could not be detected for 4 weeks, but after a second irradiation treatment, isolate 6-13-68 (at concentrations of 10^5 to 10^3) was again a predominant component of the anaerobic microflora. In the second patient, the levels remained fairly constant (10^6 to 10^{10} viable cells/gm feces). Isolate 6-13-68 most closely resembles *Sphaerophorus ridiculosus* in its biochemical (produces gas, foul odor, hydrogen sulfide; is β -hemolytic; and hemagglutinates sheep erythrocytes) and morphologic characteristics.

3709 ALTERATIONS IN HUMAN INTESTINAL MICROFLORA DURING EXPERIMENTAL DIARRHEA. (E.) Gorbach, S. L. (Roy. Postgrad. Med. Sch., London, England), G. Neale, R. Levitan and G. W. Hepner. *Gut* 11(1):1-6, 1970.

Large quantities of fluid (1500 to 2400 ml of sterile, isotonic electrolyte solution) administered through an intestinal tube caused alterations in small bowel bacteriology in 4 of 7 subjects. In 2 normal individuals, colonic bacteria were found in areas of the small bowel which previously had none after fluid infusion. The fecal microflora were also altered in fluid purge: anaerobes were reduced in some subjects and large numbers of *Enterobacter* species emerged in others. In patients with pancreatic insufficiency and diarrhea, the concentration of *Enterobacter* in the feces was directly related to the number of bowel motions per day and treatment with pancreatic enzymes (Cotazym) curtailed the diarrhea and markedly reduced these organisms. Intubation showed that *Enterobacter* occurred in the small intestine and were reduced in the large bowel

during periods of normal bowel action. Diarrhea caused by pancreatic enzyme withdrawal or fluid purgation removed the colonic inhibition and allowed these organisms to appear in the feces. Acidic diarrhea induced by lactose feeding to 3 hypolactasic patients caused decreases in the number of *E. coli* in the feces and increases in the number of *Enterobacter* (bacteroides also declined in one subject). Certain alterations in small and large bowel bacteriology observed in these forms of experimental diarrhea have also been described in naturally occurring diarrhea of diverse etiologies.

3710 ACUTE DIARRHEA IN CHILDREN: A STUDY OF 177 POSTMORTEM CASES. (E.) Mukherji, S. (Grant Med. Coll., Bombay, India). *J Indian Med Ass* 54(3):109-111, 1970.

3711 BACTERIOLOGY OF DIARRHEA IN NEONATES WITH SPECIAL REFERENCE TO ENTEROPATHOGENIC COLI. (E.) Nandi, R. L. (G. R. Med. Coll., Owalior, India). *J Indian Med Ass* 54(3):103-107, 1970.

3712 CLINICAL EXPERIENCE WITH SELECTIVE AND TOTAL ABDOMINAL VAGOTOMY: SPECIAL REFERENCE TO INSULIN TEST AND POSTVAGOTOMY DIARRHEA. (E.) Inberg, M. V. (Dept. Surg., U. Turku, Finland). *Ann Chir Gynae Fenn* 58(supp. 165):3-68, 1969.

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3714 DELAYED INTESTINAL OBSTRUCTION FOLLOWING TREATMENT FOR CANCER. (E.) Ketchum, A. S. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.), R. C. Hoye, Y. H. Pilch and D. L. Morton. *Cancer* 25(2):406-410, 1970.

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3716 POTASSIUM THERAPY AND GASTROINTESTINAL LESIONS. (E.) Emerson, D. N. (Mead Johnson Res. Ctr., Evansville, Indiana). *J Indiana Med Ass* 63(3):228-232, 1970.

3717 COMPARATIVE TRIAL OF FURAZOLIDONE AND CHLORAMPHENICOL IN SYSTEMIC SALMONELLOSIS. (E) Krishna Das, K. V. (Med. Coll. Hosp. Yriyandrum, India). *Indian Pract* 22(11):631-636, 1969.

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3763 *IN VITRO* AND *IN VIVO* STUDIES OF STREPTOMYCIN-DEPENDENT *CHOLERA VIBRIOS*. (E.) Felsenfeld, O. (Delta Primate Res. Ctr., Tulane U. Covington, La.), A. Stegherr-Barrios, E. Aldova, J. Holmes and M. W. Parrott. *Appl Microbiol* 19(3):463-469, 1970.

3764 INCIDENCE OF *SALMONELLAE* IN MEAT IMPORTED FROM THE REPUBLIC OF IRELAND. (E.) Thomas, K. L. (Publ. Hlth. Lab., Conway, England) and A. M. Jones. *Med Officer* 123(2):19-20, 1970.

3765 ALLOGENIC HEPATIC EXTRACORPOREAL ASSISTED ACUTE LIVER FAILURE: AN EXPERIMENTAL STUDY. (E.) DeMaria, A. (Inst. Semeiotic Surg. U. Catania, Italy), V. Rocchi, S. Libra and G. Giuffrida. *Int Surg* 53(3):206-209, 1970.

3766 THE UNMASKING OF TYPHOID FEVER. (E.) Woodward, T. E. (U. Maryland Sch. Med., Baltimore). *S Afr Med J* 44(5):99-106, 1970.

- P:Absorp (3119)
- P:Secr:Hepatobil (3210)
- P:Gen (3253)
- Diagproc (3265) (3267) (3285) (3286) (3292)
- D:Stomduo (3349) (3351) (3358) (3369) (3371) (3372) (3376)
- D:S.Intest (3421)
- D:L.Intest (3461) (3494) (3497) (3505)
- D:Pancreas (3520)
- D:Livbil (3546) (3547)
- D:Livbil:A.V.Hep (3627)
- D:Livbil:C.Hep (3647)
- D:Livbil:Gallb (3663) (3668) (3683)
- D:Gen:Parasit (3767)

GENERAL

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3767 THORACIC DUCT CHANGES IN SCHISTOSOMAL HEPATIC FIBROSIS. (E.) Sadek, A. M. (Dept. Surg., U. Alexandria, UAR), A. Aboul-Enein, E. Hassenein and A. Ismail. *Gut* 11(1):74-78, 1970.

Changes in abdomino-thoracic lymphatics were studied in 20 patients with schistosomal hepatic fibrosis (10 with ascites), 6 patients with heart failure, and 10 control subjects. Dilatation of thoracic duct occurred in patients with schistosomal hepatic fibrosis while thoracic dilatation with tortuosity, an increase (2- to 8-fold) in thoracic duct volume, and dilated and tortuous abdominal lymphatic occurred in patients with schistosomal hepatic fibrosis with ascites. Increased lymph flow rate and pressure (2 to 4 times greater than normal) occurred in patients with thoracic fistulas. Increased amounts of lymph seemingly are formed in schistosomal hepatic fibrosis, thereby perpetuating or initiating ascites formation.

3768 RECTAL BLEEDING DUE TO *TRICHURIS TRICHIURA*. (E.) Fisher, R. M. (Red Cross War Mem. Child. Hosp., Cape Town, Union South Africa) and B. J. Cremin. *Brit J Radiol* 43(507):214-215, 1970.

Trichuris trichiura (whipworm) infestation causing rectal bleeding was diagnosed in 3 children (age 4

to 5) by double-contrast enemas (originally given to exclude polyps as a cause of the bleeding). The parasite was characterized by two typical appearances: first, by wavy linear translucencies in barium relief against the air-diluted barium coated bowel and second, by a coil-whip or pin-wheel appearance. The parasites were distributed throughout the whole of the large bowel and the translucencies were due to the free-hanging tail of the parasite. The radiological diagnosis of *Trichuris trichiura* infestation was confirmed at sigmoidoscopy and on stool examination.

3769 CHAGAS DISEASE OF THE COLON AND RECTUM. (E.) Todd, I. P. (St. Mark's Hosp., London, England), N. H. Porter, B. C. Morson, B. Smith, C. A. Friedmann and R. A. Neal. *Gut* 10(12):1009-1014, 1969.

An unusual case of Chagas disease (a rare condition in patients anywhere but in Central and Latin America) was found in a white 57-yr-old woman born in Britain, who had spent only a short time in an area where the disease is endemic (thus representing perhaps the first case of Chagas disease to be treated in Britain). The patient suffered increasing dysphagia, constipation and abdominal distension over

- a 6-year period and exhibited mega-esophagus, megacolon, megasigmoid, and megarectum. Sphincteric responses had been considerably weakened by straining to relieve constipation. Successful treatment included resection of the dilated sigmoid and upper rectum and anastomosis of the descending colon to the extraperitoneal rectum. Treatment with Compound 349C59 (8-[6-N'-(3-hydroxybutyl) piperazinohexylamino]-6-methoxyquinoline dihydrogen maleate), 45 mg p.o., showed some effect on the parasites by an immediate drop in titer; however, the sera remained positive during a follow-up period of 7 months.
- 3770 EVIDENCE OF TRANSPLENTAL PASSAGE OF SPECIFIC ANTIBODY IN SCHISTOSOMIASIS MANSONI IN MAN. (E.) Hillyer, G. V. (Dept. Microbiol., U. Chicago, Illinois), R. Menendez-Corrada, R. Lluberes and F. Hernandez-Morales. *Amer J Trop Med Hyg* 19(2):289-291, 1970.
- Transplacental passage of specific antibodies in *Schistosoma mansoni* infection was demonstrated in mother-infant pairs. Eighteen of 22 mother-infant pairs demonstrated (circumoval precipitin method) a direct correspondence in titer (1+ to 4+); one matched pair revealed a greater reaction in mother than in child (4+ vs 1+). In three instances, the mother was weakly positive (1+), with 3 children exhibiting negative reactions. Five normal controls were negative for both mother and child. Five of 7 matched samples with titers of 2 to 3+ revealed (cercarial slide-flocculation method) similar antibody titer in both mother and child; mother exhibited higher titers than child in 2 instances. Seven of 19 matched samples demonstrated immunoprecipitins to adult worm extracts (Ouchterlony double-diffusion method) while 10 matched samples exhibited immunoprecipitins to cercarial extracts. Using simple radial immunodiffusion, levels of immunoglobulin G of mother and child were similar (16.00 ± 3.49 mg/ml vs 15.00 ± 3.65 mg/ml resp., immunoglobulin A levels in mothers averaged 2.71 ± 0.90 mg/ml (immunoglobulin A was not observed in infant cord blood) and immunoglobulin M levels in mothers averaged 0.94 ± 4.2 mg/ml (3 of 16 infants had no measurable immunoglobulin M level while 3 infants demonstrated levels measuring 0.16, 0.17, and 0.04 mg/ml). Transplacental passage of specific antibodies from mothers to neonatal infants in *Schistosoma mansoni* infection seemingly is due to serum immunoglobulin G.
- 3771 IDENTIFICATION OF INTESTINAL HELMINTH EGGS IN OLD WORLD PRIMATES. (E.) Schilling, P. (Natl. Naval Med. Ctr., Bethesda, Md.), M. T. Jessee and J. A. Stunkard. *Lab Anim Care* 20(1):83-87, 1970.
- 3772 MEXAFORM AND ENTOBEX THERAPY IN AMEBIC DYSENTERY. (E.) Tjaij, J. K. (Med. Sch. U. North Sumatra, Medan, Indonesia), N. Raid, T. Irawati, D. Siregar, K. I. Hiong and T. B. Eng. *Paediat Indonesta* 9(5):210-214, 1969.
- 3773 PAROMOMYCIN AS EFFECTIVE TREATMENT OF *TAE-NIA* INFECTIONS. (E.) Botero, D. (Sch. Med., U. Antioquia, Medellin, Colombia). *Amer J Trop Med Hyg* 19(2):234-237, 1970.
- 3774 *TOXOCARA CANIS* INFECTION IN BABOONS: I. ANTIBODY, WHITE-CELL, AND SERUM-PROTEIN RESPONSES FOLLOWING INFECTION. (E.) Aljeboori, T. I. (Sch. Hlth., Oklahoma U., Oklahoma City) and M. H. Ivey. *Amer J Trop Med Hyg* 19(2):249-254, 1970.
- 3775 AN APPLICATION OF THE KERMAK-McKENDRICK THEORY TO THE EPIDEMIOLOGY OF SCHISTOSOMIASIS. (E.) Goffman, W. (Dept. Preventive Med., Case Western Reserve U., Cleveland, Ohio) and K. S. Warren. *Amer J Trop Med Hyg* 19(2):278-283, 1970.
- 3776 SCHISTOSOMIASIS MANSONI IN THE CHIMPANZEE: THE NATURAL HISTORY OF CHRONIC INFECTIONS AFTER SINGLE AND MULTIPLE EXPOSURES. (E.) Sadun, E. H. (Walter Reed Army Inst. Res., Washington, D.C.), F. Von Lichtenberg, A. W. Cheever and D. G. Erickson. *Amer J Trop Med Hyg* 19(2):258-277, 1970.
- 3777 INTESTINAL PARASITES AND NUTRITIONAL STATUS: II. PARASITIC INFECTION IN CHILDREN IN SOUTH CAROLINA. (E.) Lease, E. J. (Sch. Pharm., U. South Carolina, Columbia), B. W. Dudley and M. F. Ziegler. *J S Carolina Med Ass* 66(2):42-45, 1970.
- 3778 PREVALENCE OF INTESTINAL PARASITES IN LUCKNOW. (E.) Vidyarthi, S. C. (King George's Med. Coll., Lucknow, India). *Indian J Med Sci* 23(12):654-660, 1969.
- 3779 POSSIBILITY OF REINFECTION BY OXYURIS IN A SAMPLE POPULATION OF CHILDREN. (It.) DiRocco, P. (Hosp. Celesia Di Gerrivarolo, Italy). *Ig Mod* 62(5-6):333-338, 1969.
- 3780 PARASITIC INVASIONS OF THE ALIMENTARY TRACT OF VIETNAMESE APPRENTICES AND THEIR ERADICATION. (E.) Gerwel, C. (Med. Acad., Poznan, Poland), E. Chwiot, R. Karlewicz and Z. Pawlowski. *Bull Inst Mar Med Gdansk* 20(3-4):217-220, 1969.
- 3781 FILTRATION OF *SCHISTOSOMA MANSONI* BY EXTRACORPOREAL BLOOD CIRCULATION. (Por.) Vieira, O. M. (Fac. Med. Fed., U. Rio De Janeiro, Brazil), M. A. Santos, H. Murad, J. Hugill and M. De Andrade. *Hospital* 76(5):1729-1738, 1969.
- 3782 TEN CASES OF MEDICAL CURE OF CIRCUMSCRIBED AMEBIC ABSCESS OF THE LIVER: STUDIED CLINICALLY AND BY LIVER SCANNING. (Fr.) Payet, M. (Clin. Med., Dakar, Senegal), M. Sankale, Y. Bresson, J. P. Anceles and G. Ballon. *Presse Med* 77(49):1805-1808, 1969.
- 3783 ANTIPARASITIC ACTION OF A NEW DRUG IN HOOKWORM DISEASE. (Sp.) Canal Feijoo, E. J. (Fac. Med., Nat. U. Tucuman, Argentina), E. Iglesias, M. Norymberg and R. Robinson. *Prensa Med Argent* 56(42-43):1858-1863, 1969.

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- 3784 BIOLOGIC-CHEMICAL MODE OF ACTION OF THE TAPEWORM DRUG N-(2'-CHLORO-4'-NITRO-PHENYL)-5-CHLORO-SALICYLAMIDE: I. INFLUENCE ON ENZYME SYSTEMS. (Ger.) Putter, J. (Bayer AG Drug Co., Wuppertal-Elberfeld, Germany). *Arzneimittelforschung* 20(2):203-205, 1970.
- 3785 A CASE OF EXTRAINTestinal AMEBIASIS IN AN OLDER INFANT. (Sp.) Lopez Poumian, G. (Hosp. Infant., Mexico) and M. Salas. *Bol Med Hosp Infant Mexico* 26(6):811-817, 1969.
- 3786 RECURRENT MALABSORPTION SYNDROME WITH ACHYLIA, JEJUNAL MICROBIAL AND PARASITIC INFESTATION. (Fr.) Tolot, F. (no affil), A. Carel, J. P. Lenglet and M. Abry. *J Med Lyon* (1176):1675-1681, 1969.

- 3787 FURTHER OBSERVATIONS ON THE LIVER FLUKE (*FASCIOLA HEPATICA* L.) HOMOGENATE CAPILLARY PERMEABILITY ACTIVITY. (E.) Baglioni, T. (Fac. Vet. Med., U. Milan, Italy), A. Locatelli and C. Paoletti. *Path Europ* 4(4):384-386, 1969.
- 3788 A STUDY OF TWO IMMUNOLOGICAL TESTS IN THE DIAGNOSIS AND PROGNOSIS OF HYDATID DISEASE. (E.) Bradstreet, C. M. P. (Standards Lab. Serological Reagents, London, England). *J Med Microbiol* 2(4):419-433, 1969.

• D:Livbil:Cirrh (3659)

DESCRIPTION OF INDEXES

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The SUBJECT INDEX is based on a hierarchial system of classification in which *major index terms* are modified by one or more *key word descriptors*. The *key word descriptors* are listed in decreasing order of importance and describe the content of the abstract or citation. In addition, in this indexing system, some *key word descriptors* will also be used as *major index terms*, thus providing in-depth indexing of each document. An abstract or citation number, in brackets, will be found after the *key word descriptors*. Abstracts will be identified by an asterisk outside of the brackets.

An illustrative example of this indexing system follows:

INTESTINE, LARGE

Colon, Carcinoma, Radiological Detection, Rectum (0188)*

COLON

Cancer, Polyps, Radiological Detection (0188)*

RECTUM

Cancer, Polyps, Precancerous (0188)*

CANCER

Large Intestine, Detection, Radiology (0188)*

DIAGNOSIS

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Numbers followed by an asterisk refer to abstracts in the text. Other numbers refer to citations.

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The CHAIRMAN. This concludes the hearing on the National Digestive Diseases and Nutrition Act. I wish to thank all who participated. (Whereupon, at 1:10 p.m., the hearing was adjourned.)



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