CONTENTS

JOHN JAMES RICHARD MACLEOD
1876-1935

Dr. MacLeod was a Scotch-English physiologist who received his training at Williams of Aberdeen. He was a teacher and demonstrator of physiology at London Hospital and a lecturer in biochemistry at Cambridge. When G. N. Stewart transferred to the chair of physiology at the University of Chicago Dr. MacLeod was called to the professorship of physiology at Western Reserve University in 1903.

He was at once elected to membership in the American Physiological Society and quickly became an active scientific contributor and aggressive leader in the affairs of the Society. He served on Council from 1915 thru 1920, was President of the Society in 1921 and 1922 and served as Associate Editor of Physiological Reviews for several years. The first Porter Fellow, J. Hepburn, worked under MacLeod's direction on the reactions of the respiratory center to lack of oxygen at Toronto in 1920.

MacLeod's earliest contributions to the Society's programs were on biochemical themes, especially on renal function and on problems of sugar metabolism. He was a wonderfully clear speaker and writer. He had an easy and clear style in the exposition of scientific themes that made him a most successful teacher and lecturer. His publications are an indication of his wide range of interests, including work on the chemistry of carbamates and purine metabolism, physiology of the intracranial circulation, ventilation, surgical shock, etc. His textbook, Physiology in Modern Medicine, first published in 1918, was unique and maintained leadership in its emphasis on the important roles of chemistry in physiology for many succeeding editions.

At the 34th annual meeting of the American Physiological Society in New Haven in 1921 the paper by J. J. R. MacLeod introducing F. G. Banting and C. H. Best on the beneficial influence of certain pancreatic extracts on pancreatic diabetes was the initial announcement of the insulin researches that led to the isolation of insulin. E. A. Doisy, G. S. Eadie, S. R. Bliss, J. R. Murlin and A. S. Ringer also contributed papers dealing with pancreatic extracts. Insulin was isolated, purified, tested and first announced from the physiological laboratories of Toronto by a paper by F. G. Banting and C. H. Best, introduced by J. J. R. MacLeod at the joint meeting of the Federation in Toronto, December 1922. The Nobel Prize in Physiology was granted to MacLeod and Banting in 1923 for the discovery of insulin. The Prize was divided with C. H. Best and J. B. Collip.

MacLeod was called from Western Reserve to the University of Toronto in 1918. The crowning personal honor in his brilliant career was the call, in 1928, to the Regis Chair of Physiology in his Scottish Alma Mater, Aberdeen University. From 1930 to 1933 he was also Dean of the Faculty of Medicine of Aberdeen. He died March 16, 1935.

APS
MEETING CALENDAR

1966 Spring - Atlantic City, N.J., April 11-16

1966 Fall - Baylor Univ., Houston, Texas, Aug. 29-Sept. 2

1967 Spring - Chicago, Ill., April 16-21

1967 Fall - Howard Univ., Washington, D.C., Aug. 23-26

1968 Spring - Atlantic City, N.J., April 15-20

1968 International Physiological Congress - Washington, D.C., Aug. 25-30

1968 Fall - No Fall Meeting due to the Congress

1969 Spring - Atlantic City, N.J., April 13-18

1969 Fall - Oklahoma State Univ., Stillwater and Univ. of Oklahoma Med. Ctr., Oklahoma City, Okla.

G. I. GROUP LECTURE

Dr. Lowell E. Hokin, Professor of Physiological Chemistry at the University of Wisconsin will give the Sixteenth Annual Lecture before the Gastrointestinal Group of the American Physiological Society on Thursday, April 14, 1966, during the Spring Meeting of the Federation of American Societies for Experimental Biology, in Atlantic City. His topic will be, "Phospholipid Metabolism in the Membranes of Pancreatic Acinar Cells during Protein Secretion."

SPECIAL APS PROGRAMS AT THE SPRING MEETING April 11-16, 1966

SYMPOSIA

"The Central Regulation of Ventilation" - J. H. Comroe, Jr., Chairman

"Peripheral Vasodilator Mechanisms" - R. S. Alexander, Chairman

"Hormonal Regulation of Arterial Pressure and Salt Balance" - J. H. Laragh, Chairman

TEACHING SESSION

"Animal Care Programs in Physiology Education" - B. J. Cohen, Chairman

THIRTY-MINUTE INTRODUCTORY TALKS

"Diffusion of Respiratory Gases"- R. E. Forster

"Renal Metabolism of Ammonia" - R. F. Pitts

"Instantaneous Blood Flow" - D. E. Gregg

"Membrane Transport of Na and K Ions" - D. C. Tosteson

"Capillary Blood Flow and Transcapillary Exchange" - E. M. Renkin

"Receptor Mechanisms" - W. R. Loewenstein

SYMPOSIA SUGGESTIONS

Dr. A. P. Fishman, Cardiorespiratory Laboratories of Columbia University, College of Physicians and Surgeons, New York, who is the Chairman of the APS Program Committee, requests members to submit suggestions for symposia topics for the Spring Meeting of 1967. The program has been finalized for the 1966 meeting but the Program Committee would like to have suggestions throughout the year so as to allow plenty of time to arrange the program for 1967. Suggestions for 30-minute introductory talks also will be welcome. Other members of the Program Committee are: - S. B. Barker and W. L. Nastuk.

HOMEWORK FOR MEMBERS
(The President's Message)
John M. Brookhart

Included in this issue of The Physiologist you will find a complete listing of your Society's existing Bylaws. Printed on the left-hand page is a rather thorough revision which your Council is presenting for your consideration at the Society's Spring meeting. Since your opinion will be asked for at the time of the Business meeting, it seems appropriate to take this means to inform you about some of the background of these proposed changes.

The proposed Bylaws reflect primarily the operational changes imposed on the Society by virtue of its growth in size and growth of its activities. These growth-related changes have made it advantageous to alter the organization of its central offices in such a way as to improve the quality of the services carried out for the Society and to strengthen the exercise of fiscal responsibility by the officers of the Society. The need for these changes in organization has been accentuated by certain parallel changes which have occurred in the offices of the Federation of American Societies for Experimental Biology attendant upon the resignation of Dr. Milton O. Lee. And finally, the increasing degree to which the Society operations are influenced by Federal and State agencies, makes it mandatory that its Bylaws present a clear and accurate picture of certain modes of operation.

The operational changes reflected in the proposed new Bylaws have been in the planning phase for over two years. They result from the combined judgments of your Council, whose membership changes each year, supported by the advice and counsel of the Finance and Publications Committees, whose members also rotate. The actual revision of the Bylaws has been carried out by an ad hoc committee consisting of Drs. Nathan Shock, Wade Marshall, J. H. U. Brown and Ray Daggs who have also been at work for about two years. The Bylaws Committee has sought the continuing advice of legal counsel and a number of the new items reflect the legal needs of a non-profit organization, incorporated in Missouri but operating from central offices in Maryland. It was your Council's original intention to coordinate the organizational changes with Dr. Lee's retirement in December 1966. However, Dr. Lee's illness has made it necessary to reorganize the Central Office activities at a date one year earlier than originally planned. In this sense, the proposed Bylaws recognize current and existing operations rather than plans for the future.

Article I and II of the proposed Bylaws are totally new and are included for legal reasons. The seal is printed on the title page of The Physiologist.

Article III now contains all the necessary material pertaining to membership. Much of it has simply been transferred from the old Article VII entitled Standing Rules. You will see that Article III first defines the various categories of membership, then proceeds to the mechanisms for nomination, election, and expulsion. Sections 1, 2 and

3 contain nothing new. Section 4 incorporates a single new sentence which emphasizes the possibility of transition from Associate Member to a Regular Member. Section 5 is a totally new definition of Retired Members which recognizes an operating procedure of long standing. Section 7 now describes rather precisely the mechanism of nomination for membership which has been in use for approximately four years, and describes the relationship between the Membership Committee and Council in the nomination procedure. The definition, duties and composition of the Membership Committee are spelled out in a later Article. Sections 8 and 9, concerning election and voting, simply summarize concisely several scattered references to these procedures which were previously in Article VII, Standing Rules. No new practices or departures from previous operations are proposed in these two sections. Section 10 is a totally new section. The need for this section develops only on rare occasions. However, there have been times in the past when your Council felt this need most acutely. Thus, the need for Section 10 has been demonstrated; its wording has been carefully done with legal advice; your Council strongly recommends its acceptance and approval.

Article IV of the proposed Bylaws supplants Article II of the existing Bylaws and deals with Officers of the Society. To a great extent, this Article simply consists of a re-arrangement of previously existing, scattered statements into a logical and orderly sequence. Section 1 deals only with the composition and the duties of the Council. It contains nothing new except the definition of a quorum. The following sections define the offices and the election procedure without essential changes except for the terminal sentence of Section 5 which, again, recognizes current practice.

Article V of the proposed Bylaws also reflects primarily a re-organization of material from the existing Bylaws. It defines and outlines the duties of the four most important standing committees without whose help the Council could not discharge its responsibilities effectively. Section 1 defines the composition and duties of the Publications Committee. The third sentence, dealing with the Publications Manager, is a new statement. It identifies the mechanism whereby the Council exercises its responsibility over publications. The necessity for this statement stems from the fact that, for reasons of health, Dr. Lee is no longer able to carry on as the Society's Managing Editor. At the same time, it recognizes the need of the Society for a full-time Publications Manager to direct the increasing activities of the publication office and redactorial service. The Society's publication business has now become so large as to require a single, full-time manager to maintain a satisfactory level of productivity and efficiency. Your Council now feels that the Society's publication efforts are of sufficient magnitude and complexity to justify an operational pattern which is independent of the publication services offered by the Federation. The Publications Manager specified in this section will supervise these activities. The final two sentences of the section are also new, but simply recognize current practice.

Section 2 describes the Finance Committee in essentially the same

terms as are used in the existing Bylaws. The new content is in the next to the last sentence which empowers the Council to acquire the services of a full-time Business Manager. Your Council recommends the inclusion of this statement in the Bylaws in recognition of the need for a business office which is independent of the Federation. The size of the operation is now so great that efficiency cannot be attained through services purchased from the Federation. The establishment of this new operation will enable your officers to obtain more reasonable control of cost-accounting, circulation records, purchasing, and other activities than could be done previously. As a result of this change, many operations formerly carried out through Dr. Lee's office as Managing Editor by the Federation Business Office will now be carried out by the Society's own employees, under the supervision of its own Business Manager.

Section 3 does a more complete job of specifying the Membership Committee and its duties than is done by Article VII, Section 5 of the existing Bylaws. Section 4 officially recognizes the existence of a most important aspect of the Society's activities. An Education Committee has been in existence and has worked hard for many years. Your Council thinks it only proper to readjust the Bylaws to recognize reality.

Article VI, dealing with dues and retirement, involves no significant changes.

Article VII describes the financial organization of the Society as it now stands. This general structure has evolved over the years and represents no departure from current practices. The new sections, 1, 2, 4, 5 and 6, have been included as a result of legal advice in order to establish powers and limitations more clearly and to afford a better basis for the fiscal responsibilities of the Society's officers and employees.

Articles VIII, IX and X, dealing with Publications, Meetings and Affiliations, represent no change from current practice. They serve to clarify minor points, some of which have been carried in the Operational Guide for many years.

Article XI is entirely new and has been included for the sole purpose of assisting the Society in the maintenance of its exempt status relative to Federal and State tax laws. Articles XII and XIII require no special comment.

In summary, it is your Council's opinion that the proposed revision of the Bylaws presents a much clearer and more detailed description of the Society and its operations than can be obtained from the existing Bylaws. You should recognize that Council is not proposing any amendments to the Constitution adopted in 1953. It is only proposing alterations of the Bylaws which traditionally describe the means by which the Society attempts to live up to the name and purpose outlined in the constitution. In these days of increasingly important inter-relationships with governmental bodies, through tax laws and through granting agencies, it is important that the Bylaws describe clearly the manner in which the Society operates. It is to this end that the Council recommends adoption

of these proposed changes.

You will note that all of the limitations on powers of officers and uses of funds contained in the existing Bylaws have been carefully preserved in the proposed changes. Some powers, now existing in general terms, have been more explicitly stated. The general organization of the Bylaws has been vastly improved.

I am still not certain how I will present this proposal to the Business meeting next April. You will note that, according to the existing Bylaws, a three-fourths majorityof the members present is required for adoption of the proposed changes. I earnestly hope you will do your homework, come to the Business meeting and vote your opinion. If the proposed changes cannot be approved en bloc, it may be necessary to discuss and vote on each individual article.

PHYSIOLOGY AND PHARMACOLOGY FOR PHYSICIANS

As of January 1966 Physiology for Physicians became Physiology and Pharmacology for Physicians. The American Society for Pharmacology and Experimental Therapeutics has joined with the American Physiological Society in this joint venture. The new publication has the same format as Physiology for Physicians; is published monthly; has a joint physiologist - pharmacologist editorial board; runs 4 to 8 pages per issue; and is written primarily for the practicing physician. There will be six articles written by physiologists and six by pharmacologists, generally alternating from month to month each year. The regular subscription price, on a calendar year basis is $5.00.

If a university department wishes to have the publication available for medical students, bulk subscriptions (no less than 100 copies to one address), can be had at a 50% reduction in price, prepaid on a calendar year basis.

NEW BYLAWS

ARTICLE I. Principal Office

SECTION 1. The Society shall have its principal place of business at 9650 Rockville Pike, Bethesda, Maryland 20014. The Central Office shall house all activities delegated to the employees of the Society.

ARTICLE II. Corporate Seal

SECTION 1. The corporate seal of the Society shall be a circle surrounded by the words, THE AMERICAN PHYSIOLOGICAL SOCIETY. The seal shall also show the founding date and the date and place of incorporation.

SECTION 2. The Executive Secretary-Treasurer shall have custody of the seal. It shall be used on all official documents requiring it, and shall be placed on the documents by the Executive Secretary-Treasurer upon approval by Council.

ARTICLE III. Membership

SECTION 1. The Society shall consist of regular members, honorary members, associate members, retired members and sustaining associates.

SECTION 2. Regular Members. Any person who has conducted and published meritorious original research in physiology, who is presently engaged in physiological work, and who is a resident of North America shall be eligible for proposal for regular membership in the Society.

SECTION 3. Honorary Members. Distinguished scientists of any country who have contributed to the advance of physiology shall be eligible for proposal as honorary members of the Society.

SECTION 4. Associate Members. Advanced graduate students in physiology at a pre-doctoral level, teachers of physiology, and investigators who have not yet had the opportunity or time to satisfy the requirements for regular membership shall be eligible for proposal for associate membership in the Society provided they are residents of North America. Associate members may later be proposed for regular membership.

SECTION 5. Retired Members. A regular or associate member who has reached the age of 65 years and/or is retired from regular employment may, upon application to Council be granted retired member status.

SECTION 6. Sustaining Associates. Individuals and organizations who have an interest in the advancement of biological investigation may be invited by the President, with approval of Council, to become sustaining associates.

SECTION 7. Nominations for Membership. Two regular members of the Society must join in proposing a person for regular membership, honorary membership or associate membership, in writing and on forms provided by the Executive Secretary-Treasurer. The Membership Committee shall investigate their qualifications and recommend nominations to Council. Council shall nominate members for election

OLD BYLAWS

The material in ARTICLES I and II of the new Bylaws does not appear in the Old Bylaws.

The address - Rockville Pike, Bethesda is the new official designation of what was called Wisconsin Ave., Washington.

ARTICLE I. Membership

SECTION 1. The Society shall consist of members, honorary members, associate members and sustaining associates.

SECTION 2. Members. Any person who has conducted and published meritorious original research in physiology and/or biophysics and who is a resident of North America shall be eligible for membership in the Society.

SECTION 3. Honorary Members. Distinguished scientists of any country who have contributed to the advance of physiology shall be eligible for proposal as honorary members of the Society.

SECTION 4. Associate Members. Advanced graduate students in physiology at a predoctoral level, teachers of physiology, and investigators who have not yet had the opportunity or time to satisfy the requirements for full membership shall be eligible for associate membership in the Society provided they are residents of North America.

No Retired Member section in old Bylaws.

SECTION 5. Sustaining Associates. Individuals and organizations who have an interest in the advancement of biological or biophysical investigation may be invited by the President, with the approval of Council, to become sustaining associates.

at the Spring and Fall meetings of the Society. A list of nominees shall be sent to each regular member at least one month before the Spring and Fall meetings.
SECTION 8. Election of Members. Election of regular members, honorary members and associate members shall be by secret ballot at Spring and Fall business meetings of the Society. A two-thirds majority vote of the members present and voting shall be necessary for election.
SECTION 9. Voting. Only regular members shall be voting members. Honorary, retired and associate members shall have the privilege of attending business meetings of the Society but shall have no vote.
SECTION 10. Expulsion Procedures. Any member of the Society whose conduct is found by a majority vote of the Council to be, or to have been, detrimental to the best interests or reputation of the Society or at variance with the purposes and provisions of the Bylaws shall be expelled from membership. No member shall be expelled until he has been afforded an opportunity for hearing before the Council or a special committee duly designated by the Council.

ARTICLE IV. Officers

SECTION 1. Council. The management of the Society shall be vested in a Council consisting of the President, the President-Elect, the immediate Past-President, and four other regular members. The terms of the President and of President-Elect shall be one year. The terms of the four additional Councilors shall be four years each and they shall not be eligible for immediate reelection except those who have served for two years or less in filling interim vacancies.
A quorum for conducting official business of the Society shall be five of the seven elected members of Council.
The Chairman of the Publications Committee; the Chairman of the Finance Committee; and the Executive Secretary-Treasurer are ex-officio members of the Council without vote.
The Council may fill any interim vacancies in its membership. Council shall appoint members to all committees.
SECTION 2. President. A person shall serve only one term as President, except that if the President-Elect becomes President after September 30 he shall continue as President for the year beginning the next July 1. The President shall

(Election and privileges of members is stated under)

ARTICLE VII. Standing Rules.

1. Election to Membership. Two members of the Society must join in proposing a person for membership, in writing and with a statement of his qualifications. The Council may, from the persons so proposed, nominate candidates for election to membership. Nominations shall be presented at Spring and Fall meetings; a two-thirds majority vote of the members present and voting at the next following Fall or Spring meeting shall be necessary for election. If a Spring or Fall meeting of the Society is not held, the procedures of nomination and/or election of new members may be effected by mail. The names of the candidates nominated by Council for membership and statements of their qualifications signed by their sponsors shall be available for inspection by members during the Society meetings at which their election is considered.

2. Election to Honorary Membership. The proposal of an honorary member shall be made by two members of the Society to the Council in writing. The Council may, from the candidates so proposed, make nominations to the Society at a Spring meeting. A two-thirds majority vote of the members present shall be necessary for election. Honorary members shall have the privilege of attending business sessions of the Society but shall have no vote. They shall pay no membership fees.

3. Election to Associate Membership. Associate members shall be proposed, nominated and elected in the same manner as full members. Associate members shall have the privilege of attending business sessions of the Society but shall have no vote. Associate members may be nominated for full membership.

ARTICLE II. Officers

SECTION 1. The management of the Society shall be vested in a Council consisting of the President, the President-Elect, the Past-President for the previous year, and four other members. The terms of the President and of the President-Elect shall be one year. The terms of the four additional Councilors shall be four years each and they shall not be eligible for immediate reelection except those who have served for two years or less in filling interim vacancies. A person may serve only one term as President, except that if the President-Elect becomes President after September 30 he shall continue as President for the year beginning the next July 1.

SECTION 5. The Council may fill any interim vacancies in its membership or vacancies on any Board or Committee of the Society, unless otherwise provided.

chair all sessions of the Council and business meetings of the Society and shall be an ex-officio member of all committees without vote.

SECTION 3. President-Elect. The President-Elect shall serve as Vice-President of the Society and as official secretary of the Council. Should he have to function as President prematurely, the Council shall select from among its own members an official secretary.

SECTION 4. Election of Officers. Nominations and election of a President-Elect and Councilor(s) shall be by secret ballot at the Spring business meeting of the Society. They shall assume office on July 1 following their election.

SECTION 5. Executive Secretary-Treasurer. The Council shall be empowered to appoint and compensate an Executive Secretary-Treasurer who shall assist it in carrying on the functions of the Society including the receipt and disbursement of funds under the direction of the Council. He shall be responsible for management of the Central Office of the Society under general supervision of the Council.

ARTICLE V. Standing Committees

SECTION 1. Publications Committee. A Publications Committee composed of three regular members of the Society appointed by Council shall be responsible for the management of all of the publications of the Society. The term of each member of the Publications Committee shall be three years; a member may not serve more than two consecutive terms. The Council shall designate the Chairman of the Committee who shall be an ex-officio member of the Council, without vote. Council is empowered to appoint and compensate a Publications Manager who shall assist in carrying out the functions of the Publications Committee under the supervision of the Executive Secretary-Treasurer. The President, Executive Secretary-Treasurer and the Publications Manager shall be ex-officio members of the Publications Committee without vote. The Committee shall have the power to appoint editorial boards for the Society's publications. The Committee shall present an annual report on publications and policies to the Council for approval and present an annual budget coordinated through the Executive Secretary-Treasurer, to the Finance Committee for its approval and recommendation to Council.

SECTION 2. Finance Committee. A Finance Committee, composed of three regular members of the Society appointed by Council, shall receive the total coordinated budget proposals annually from the Executive Secretary-Treasurer and shall determine the annual budgets, reserve funds and investments of the Society, subject to approval by the Council. The term of each member of the Finance Committee shall be three years; a member may not serve more than two consecutive terms. The Council shall designate the Chairman of the Committee who shall be an ex-officio member of the Council, without vote. Council is empowered to appoint and compensate a Business Manager who shall assist in carrying out the functions of the

SECTION 3. The President-Elect shall serve as Vice-President and Secretary. Should he have to function as President prematurely, the Council shall select from among its own members a Secretary.

SECTION 2. Nomination and election of a President-Elect and Councilor(s) shall be by ballot at the Spring meeting of the Society. They shall assume Office on July 1 following their election.

SECTION 4. The Council shall be empowered to appoint and compensate an Executive Secretary-Treasurer who shall assist in carrying on the functions of the Society, including the receipt and disbursement of funds under the direction of the Council.

ARTICLE V. Publications

SECTION 2. A Publications Committee composed of three members of the Society appointed by the Council shall be responsible for the management of all of the publications of the Society; the Managing Editor, Executive Secretary and President of the Society shall be members ex-officio, without vote. The Committee shall have the power to appoint a Managing Editor and editorial boards for the Society's publications. The term of each member of the Publications Committee shall be three years; a member may not serve more than two consecutive terms. The Council shall designate the Chairman of the Committee who shall be an ex-officio member of the Council, without vote. The Committee shall present an annual report on publications and policies to the Council for approval and an annual budget to the Finance Committee for its approval.

ARTICLE VI. Committees and Representatives

SECTION 2. A Finance Committee, composed of three members of the Society appointed by Council, shall receive budget proposals annually from the Committees, the Council and the Executive Secretary of the Society and shall determine the annual budget, reserve funds and investments of the Society, subject to approval by the Council.

The term of each member of the Finance Committee shall be three years; a member may not serve more than two consecutive terms. The Managing Editor, the President, and the Executive Secretary shall be ex-officio members, without vote. The Council shall designate the Chairman

Finance Committee under the supervision of the Executive Secretary-Treasurer. The President-Elect, Executive Secretary-Treasurer and the Business Manager shall be ex-officio members of the Finance Committee, without vote.

SECTION 3. Membership Committee. A Membership Committee, composed of six or more regular members of the Society appointed by the Council, shall receive and review processed applications for membership and make recommendations for nomination to the Council. The term of each member of the Membership Committee shall be three years; a member shall not be eligible for immediate reappointment. The Chairman of the Committee shall be designated by the Council.

SECTION 4. Education Committee. An Education Committee, composed of five or more regular members of the Society and representatives of such other societies as may be designated by the Council, appointed by the Council, shall conduct such educational, teaching and recruitment programs as may be required or deemed advisable. The term of each member of the Education Committee shall be three years. The Chairman of the Committee shall be designated by the Council. The Executive Secretary-Treasurer may act as Executive Director of the educational programs with approval of the Council. The Committee shall present an annual report to the Council and an annual budget through the Executive Secretary-Treasurer to the Finance Committee for its approval.

(The Program Advisory Committee and other committees are covered in the Operational Guide).

SECTION 5. The Council may appoint such special and other standing committees as it deems necessary or that are voted by the Society. The Council may name regular members of the Society as representatives to other organizations whenever it deems such action desirable.

ARTICLE VI. Dues

SECTION 1. Annual Dues. The annual dues for regular members and associate members shall be determined by the Council and shall be paid in advance of July 1. Honorary members and retired members shall pay no membership dues.

SECTION 2. Non-payment of Dues. A regular or associate member whose dues are two years in arrears shall cease to be a member of the Society, unless after payment of his dues in arrears and application to the Council, he shall be reinstated at the next meeting by vote of the Council. It shall be the duty of the President-Elect to notify the delinquent of his right to request reinstatement.

SECTION 3. Retirement. A regular or associate member who has been granted retired membership status is relieved

of the Committee who shall be an ex-officio member of the Council, without vote.

ARTICLE VII. Standing Rules

5. There shall be a Committee on Membership appointed by and advisory to the Council.

(Education Committee does not appear in the Old Bylaws)

6. There shall be a Program Advisory Committee appointed by Council.

ARTICLE VI. Committees and Representatives

SECTION 1. The Council may appoint such special and standing committees as it deems necessary or that are voted by the Society. The Council may name members of the Society as representatives to other organizations whenever it deems such action desirable.

ARTICLE III. Dues

SECTION 1. The annual assessment on members and on associate members shall be determined by the Council and shall be due in advance of July 1.

SECTION 2. A member whose dues are two years in arrears shall cease to be a member of the Society, unless after payment of his dues in arrears and application to the Council, he shall be reinstated at the next Spring meeting by special vote of the Council. It shall be the duty of the Secretary to notify the delinquent of his right to request reinstatement.

SECTION 3. A member who has retired from employment because of illness or age may, upon application to the Council,

from the payment of dues but retains the other privileges of his former membership status, except voting privileges.

ARTICLE VII. Financial

SECTION 1. Society Operating Fund. The Society Operating Fund shall consist of all funds, other than Publication Operating Funds and Publication Contingency and Reserve Funds, restricted or unrestricted, uninvested or invested, short or long-term. The Executive Secretary-Treasurer shall be the responsible agent to the Council with signatory powers. Signatory powers may be delegated to the Business Manager by the Executive Secretary-Treasurer.

SECTION 2. Publications Operating Fund. The Publications Operating Fund shall consist of all funds that involve receipts, expenses, short-term investments relating to the annual receipts, disbursements and continuing operation of the Society's publications. The Executive Secretary-Treasurer shall be the responsible agent to the Council with signatory powers. Signatory powers may be delegated to the Publications Manager and/or the Business Manager by the Executive Secretary-Treasurer.

SECTION 3. Publications Contingency and Reserve Fund. The Publications Contingency and Reserve Fund shall consist of the long-term capital investments of publication earnings. The Executive Secretary-Treasurer, with advice from the Finance Committee, shall have discretionary and signatory powers, except for withdrawals. Authority for any withdrawal from this fund, shall require the following five signatures: (1) the Chairman of the Publications Committee (alternate, the senior member of the Committee); (2) the President of the Society (alternate, the President-Elect); (3) the Executive Secretary-Treasurer (alternate, the Publications Manager); (4 and 5) any two members of Council. The Finance Committee shall not recommend to Council the expenditure of any of this capital fund for non-publication purposes without the consent of the Publications Committee. The Finance Committee shall be responsible for the separate investment of the reserve fund for publications; any capital gains from such investment shall accrue to the fund (capital losses will, however, reduce its value). The disposition of any dividends, interest or income, other than capital gains, from this invested fund may be used for emergency support of any of the activities of the Society, including publications, as determined annually by the Council but the primary goal shall be to increase the investment capital.

SECTION 4. Fiscal Year. The official fiscal year shall be from January 1 through December 31.

SECTION 5. Audit. All statements of net assets and related statements of income, expenditures and fund capital shall be audited annually by an independent auditing firm.

SECTION 6. Bonding. All persons having signatory powers for the funds of the Society shall be bonded.

be relieved from the payment of the annual member assessment.

(Does not appear in the Old Bylaws)

(Does not appear in the Old Bylaws)

ARTICLE VI. Committees and Representatives

SECTION 2..... The capital fund of the present Board of Publication Trustees (defined as the investments and unencumbered funds of that Board as of April 1, 1961) shall be a reserve fund for publications and may be used by the Publications Committee to finance new or established publications without authorization of the Finance Committee (though subject to approval by Council). The Finance Committee shall not approve the expenditure of any of this capital for non-publication purposes without the consent of the Publications Committee. The Finance Committee shall be responsible for the separate investment of the reserve fund for publications; any capital gains from such investments shall accrue to the fund (capital losses will, however, reduce the value of it). Annual income from the investment of the fund may be used for any of the activities of the Society including publications. ...

(Does not appear in the Old Bylaws)

(Does not appear in the Old Bylaws)

(Does not appear in the Old Bylaws)

ARTICLE VIII. Publications

SECTION 1. The official organs of the Society shall be the American Journal of Physiology, the Journal of Applied Physiology, Physiological Reviews, the Journal of Neurophysiology, The Physiologist, and such other publications as the Society may own. All publications shall be under the jurisdiction and management of the Publications Committee unless otherwise designated by the Council. The names of the journals and publications may be changed by the Council on recommendation from the Publications Committee and any publication may be dropped by Council on recommendation from the Publications Committee.

ARTICLE IX. Meetings

SECTION 1. Spring Meeting. A meeting of the Society for transacting business, electing officers and members, presenting communications, and related activities, shall ordinarily be held in the Spring of each year.

SECTION 2. Fall Meeting. A Fall meeting of the Society shall be held at a time and place determined by the Council for presenting communications, electing members, and for transacting business except for the election of officers and adoption of amendments to the Bylaws. Under exceptional circumstances Council may cancel such a meeting.

SECTION 3. Special Meetings. Special meetings of the Society or of the Council may be held at such times and places as the Council may determine.

(Section 4 of Old Bylaws covered in above)

SECTION 4. Quorum. At all business meetings of the Society fifty regular members shall constitute a quorum.

SECTION 5. Parliamentary Authority. The rules contained in Roberts Rules of Order shall govern the conduct of the business meetings of the Society in all cases to which they are applicable and in which they are not inconsistent with the Bylaws or special rules of order of the Society.

ARTICLE X. Society Affiliations

SECTION 1. The Society shall maintain membership in such organizations as determined by Council.

ARTICLE XI. Regulations

SECTION 1. General Prohibitions. Notwithstanding any provision of the Constitution or Bylaws which might be susceptible to contrary interpretation:

a. The Society is organized and operated exclusively for scientific and educational purposes.
b. No part of the net earnings of the Society shall or

ARTICLE V. Publications

SECTION 1. The official organs of the Society shall be the American Journal of Physiology, the Journal of Applied Physiology, Physiological Reviews and such other publications as the Society may own.

ARTICLE IV. Meetings

SECTION 1. A meeting of the Society for transacting business, electing officers and members, presenting communications, and related activities, shall be held in the Spring of each year, with other member Societies of the Federation of American Societies for Experimental Biology, except that under exceptional circumstances the Council may cancel such a meeting.

SECTION 2. A Fall meeting of the Society shall be held at a time and place determined by the Council for presenting communications and for transacting business except the election of officers.

SECTION 3. Special meetings of the Society or of the Council may be held at such times and places as the Council may determine.

SECTION 4. Regional meetings of the Society, for the purpose of presenting scientific communications may be authorized by the Council.

ARTICLE VIII. General

SECTION 2. Quorum. At all business meetings of the Society, fifty members shall constitute a quorum.

SECTION 3. Parliamentary Authority. The rules contained in Roberts Rules of Order shall govern the conduct of the business meetings of the Society in all cases to which they are applicable and in which they are not inconsistent with the Bylaws or special rules of order of the Society.

(Does not appear in the Old Bylaws)

(Does not appear in the Old Bylaws)
(Necessary to meet legal requirements for a non-profit organization)

may under any circumstances inure to the benefit of any member or individuals.

c. No substantial part of the activities of the Society shall consist of carrying on propaganda, or otherwise attempting to influence local, state or national legislation. (All activities of the Society shall be determined by Council). The Society shall not participate in, or intervene in (including the publishing or distributing of statements) any campaign on behalf of any candidate for public office.

d. The Society shall not be organized or operated for profit.

SECTION 2. Distribution on Dissolution. Upon lawful dissolution of the Society and after payment of all just debts and obligations of the Society, Council shall distribute all remaining assets of the Society to one or more organizations selected by the Council which have been approved by the United States Internal Revenue Service as organizations formed and dedicated to exempt purposes.

ARTICLE XII. General

SECTION 1. Records. All official records, archives and historical material shall be held in the Central Office in the custody of the Executive Secretary-Treasurer.

SECTION 2. Procedures and Customs. The Society shall maintain a current Operational Guide detailing the procedures and current customs of the Society operations as well as the duties and responsibilities of officers, committees, and major employees. The Operational Guide shall be maintained current by the Executive Secretary-Treasurer as determined by the Council.

(The section on presentation of papers covered in the Old Bylaws is covered in the Operational Guide mentioned above, since the rules may change frequently. Current rules for presenting papers will be distributed to members each year).

ARTICLE XIII. Amendments

Section 1. Presentation. Proposed amendments to these Bylaws must be endorsed by the Council and presented in writing at a business meeting of the Society.

SECTION 2. Adoption. These Bylaws may be amended at any Spring business meeting of the Society by a two-thirds majority vote of the regular members present and voting.

(Does not appear in the Old Bylaws)
(Necessary to meet legal requirements
for a non-profit organization)

(Does not appear in the Old Bylaws)

(Does not appear in the Old Bylaws)

ARTICLE VII. Standing Rules

4. Presentation of Papers. At a Spring meeting of the Society, held in conjunction with the Federation meetings, a member or honorary member may present orally or by title, be co-author of, or introduce not more than one scientific paper, except upon invitation of the Council. An associate member or a non-member may present orally one scientific paper only if sponsored by a full member of the Society. At the Fall meeting a member, honorary member, or associate member may present orally not more than one paper, except upon invitation of Council. Upon invitation by the Council, a member may contribute papers to specially designated sessions of the Society without forfeit of his privilege of presenting a regular scientific communication.

ARTICLE VIII. General

SECTION 1. Amendments. These Bylaws, except Article VII, may be amended at any Spring meeting of the Society by a three-fourths majority vote of the members present. The Standing Rules of ARTICLE VII may be amended by a majority vote of the members present at either a Spring or Fall meeting of the Society.

GROWTH AND CHANGES AT BEAUMONT

The Federation has grown and changed in the last few years. All six adhering societies to the Federation now have their central offices located at Beaumont. (Beaumont is the official name of the Federation campus). The official address has been changed from Wisconsin Ave., Washington, D. C. to 9650 Rockville Pike, Bethesda, Md. 20014.

The six societies and their executives are:

American Physiological Society - Ray G. Daggs - Exec. Sec'y-Treas.
American Society of Biological Chemists - Robert A. Harte - Exec. Officer
American Society for Pharmacology and Experimental Therapeutics - Ellsworth B. Cook - Exec. Officer
American Society for Experimental Pathology - Ralph E. Knutti - Exec. Officer
American Institute of Nutrition - James Waddell - Exec. Sec'y.
American Association of Immunologists - Sheldon Dray - Sec'y-Treas.

All but Dr. Dray are in residence but he maintains an office at Beaumont. Biochemistry, Pathology and Nutrition have their offices in the original Beaumont building while Physiology, Pharmacology and Immunology are located in the new building, now officially named the Milton O. Lee Building. The Federation Executive Offices are in the original Beaumont building and the Federation Business Offices are in the Lee building.

There has been a reorganization of the Federation with designated officers and appointed officials (See the 1965 Federation Directory, pages 8 thru 12, for details). The present officers are:

President - Karl H. Beyer, Jr. (Pharmacology)
Vice President - K. M. Brinkhous (Pathology)
Secretary - J. F. A. McManus
Treasurer - J. D. Hardy (Physiology)

The appointed full-time officials are:

Executive Director - J. F. A. McManus
Comptroller - J. R. Rice

APS REORGANIZATION

The Society has grown in size and activities to the extent where it was felt by Council that it could operate its own activities. The reorganization was tentatively planned for January 1967 when Dr. M. O. Lee would normally retire. Due to ill health Dr. Lee retired from active duty with the APS and the Federation a year or so early. This action necessitated some more immediate action on the part of APS and the Federation. Both the APS and the Federation made several changes in their organizational structure. Dr. J. F. A. McManus replaced Dr. Lee as Executive Director of the Federation.

In the past the Federation provided the redactory services for the APS journals as well as most of the business office services. Beginning January 1, 1966 the APS began operating its own business office and publication services. Since the Federation has also increased in size and activities (all six adhering societies now have offices at Beaumont) this independent action on the part of APS does not jeopardize the operations of the Federation. The Federation is continuing to supply the APS with certain services, such as payroll; mail service; addressographing; offset printing; etc. on a job cost basis.

Management of APS Central Office: Dr. R. G. Daggs as Executive Secretary-Treasurer of APS is head of the Central Office and is responsible to Council. He acts as executive for all committees of the Society and is the APS Council's representative on the Federation Program Committee and the Beaumont House Committee. Along with the Chairmen of the Publications Committee and Finance Committee he sits on Council without vote.

Publications: Miss Sara F. Leslie, who had been Dr. Lee's Executive Editor for both APS and Federation publications, is now full time Publications Manager and Executive Editor for APS. She supervises a staff of copy editors and others concerned with the American Journal of Physiology; Journal of Applied Physiology; Journal of Neurophysiology; Physiological Reviews; the Hand Book series; and Special Publications.

Dr. Daggs remains Editor of The Physiologist; Associate Editor of Physiological Reviews; and along with Dr. E. B. Cook of the Pharmacology Society supervises the publication of Physiology and Pharmacology for Physicians. This new publication is handled by the APS Business Office as a separate restricted account.

Business Office: Mr. Walter A. Sonnenberg, who had been Dean of Administration at New College, Sarasota, Florida and before that Assistant Comptroller at Massachusetts Institute of Technology, came with APS as full time Business Manager in September 1965. Mr. Sonnenberg is a certified public accountant and his past experiences make him well qualified for the position of Business Manager. The various operations of the business office such as fiscal records; audits; billing; bookkeeping; grants; circulation and subscription records; etc. come under his immediate supervision.

New Quarters: The Society rents from the Federation the entire third floor of the new building and wing at Beaumont. This permits all of the APS activities to be centralized . All employees of APS work for APS only. Members of the Society, when in Washington, are invited to stop by and visit with us in the new quarters.

ASSESSMENT FOR THE 1968 INTERNATIONAL CONGRESS OF PHYSIOLOGY

At the 94th Business Meeting of the American Physiological Society, April 11, 1965, members present voted to assess themselves $10 each year for three years to provide unrestricted funds for the International Congress of Physiology to be held in Washington, D. C. in the fall of 1968. It was felt that if the members themselves showed enough interest by personal contributions it would be easier to approach industry and various agencies for the additional funds needed to hold the Congress.

This is to report the results of the collection up to January 1, 1966, a time when practically all members had paid their dues for the period from July 1965 to July 1966.

84% of the members who had paid their dues for this period also paid the assessment.

$21,835 have been collected so far. This includes $925 from 48 regular members who have paid the assessment for more than one year; and $45 collected as contributions from associate members.

If members continue to respond to the assessment at this rate for the next two dues-years, the ultimate fund should amount to something a little over $65,000.

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TENTH BOWDITCH LECTURE

The Pituitary Growth Hormone: An Adventure in Physiology*

ERNST KNOBIL

It is with deep humility and much trepidation that I approach this lecturn to deliver the tenth Bowditch Lecture, the first to be devoted to an endocrinological subject. This broad and fertile area of physiology abounds with talented spokesmen and many more able than I could have been found with the greatest ease.

At the time of Professor Bowditch's death in the early spring of 1911, endocrine physiology was but in its tenderest infancy as an object of legitimate scientific enquiry. Bayliss and Starling had published their brilliant investigations of secretin as a regulator of pancreatic function just nine years before, christening with the name "hormone" their own extracts as well as those obtained by Oliver and Shäfer from the adrenal medulla a few years earlier. Aschner in Germany and Harvey Cushing in this country were only then beginning to array their first inklings of the functions of the adenohypophysis into a partially meaningful order, a task, I hasten to add, yet to be completed. It is tempting to suppose that endocrinology, now a vigorous and intractable adolescent, might have matured earlier had Bowditch obtained the place he sought in Brown-Séquard's laboratory when he went to Paris in 1868 (4). Nevertheless, Dr. Bowditch's interests were far from foreign to the subject of this lecture for in 1877 he published a monograph entitled "The Growth of Children" in which he detailed his studies of the influence of sex as well as of ethnic, social, economic and other environmental factors on the growth rate of Boston school children (2).

The story of the pituitary growth hormone, in the experimental sense, begins with the discovery by Aschner (1) and by Cushing (5) around the time of Bowditch's death, which I have already alluded to, that hypophysectomy of puppies leads to a retardation or cessation of their growth. Aschner's experiments were the more convincing because his operations were complete and his animals survived for prolonged periods. In Cushing's hands, complete hypophysectomy resulted in death within a few days after the operation and his chronic studies were limited to animals possessing pituitary remnants. While both workers concluded that the pituitary gland was necessary for normal growth, Cushing believed that the gland was also necessary for life whereas Aschner espoused the contrary view which is now generally held. Since that time, nearly every known vertebrate form, including man, has been divested of its hypophyseal apparatus with a resultant arrest, or at best a retardation of growth.

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*Supported in part by grants A-3754 and AM-05655 from the National Institutes of Health, USPHS.

Early attempts at replacement therapy were confined largely to the feeding of dessicated pituitary tissue and, as can be imagined, the results, all claims to the contrary, were less than spectacular. It was not until 1922 that Herbert Evans (6) announced his dramatic discovery that the injection of alkaline extracts of bovine pituitary glands to normal rats caused then to reach supranormal dimensions, an observation which he quickly confirmed in the dog with the resultant famous photograph of the two dachshunds so familiar to perusers of physiology textbooks. The concept that the anterior lobe of the pituitary secretes a specific hormone which governs bodily growth, however, remained a tenuous one until the mid-1940's when Evans' group in California (18) and Wilhelmi and co-workers, then at Yale (26), succeeded in isolating a crystalline, seemingly homogeneous protein from adrenohypophysial tissue which, when injected in small quantities into normal or hypophysectomized rats, produced striking increases in size without any other notable effects ascribable to the known hormones of the pituitary.

The effects of purified preparations of growth hormone when given to hypophysectomized rats are, to me at least, nothing short of astounding (Fig. 1).

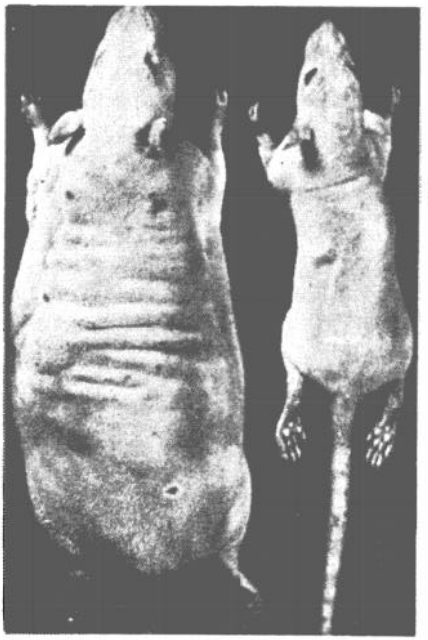

Fig. 1. The effects of bovine growth hormone treatment in the hypophysectomized rat. The animal on the right is the untreated, hypophysectomized control. From H. Selye in Hypophyseal Growth Hormone, Nature and Actions, p. 190, R. W. Smith et al., eds., Blakiston, New York, 1955.

In briefest summary, the hormone increases the size of the skeleton, the muscle and connective tissue mass and induces a general splanchnomegaly. The central nervous system and its derivatives, such as the eyes, are notably exempt from the growth stimulating actions of the hormone as are the endocrine glands which derive specific hormonal stimuli from the adenohypophysis and the accessory organs of reproduction whose growth is regulated by the gonadal hormones. In addition, as you all know, growth hormone inhibits the peripheral utilization of glucose, promotes fat mobilization and inhibits fat synthesis (13).

Clearly, however, the increase in the size of the growth hormone treated animal, as the briefest glance at the photograph will reveal, can be attributed only to an accretion of tissue mass, and that the hormone, in some manner, has stimulated net protein synthesis. This conclusion can be reached without the benefit of biochemical experiments, sophisticated or otherwise. The question then becomes, how does growth hormone stimulate protein synthesis, a complex chain of events central to any consideration of growth. We were sufficiently temerarious some years ago to ask this question and I should like to devote a portion of this hour to the recounting of the consequences.

In vivo techniques for the study of the regulation of protein metabolism such as carcass analyses, nitrogen balance and amino acid tolerance studies had been utilized to the limit of their usefulness and, while confirming the supposition that growth hormone stimulates protein synthesis, their complexity precluded the shedding of significant light on the site of action of the hormone. We, therefore, sought a simpler system more amenable to the investigation of the question at hand. The isolated rat diaphragm, incubated in vitro, met our requirements for a suitable model after several other less propitious ones had in turn been abandoned (Fig. 2).

It may be seen that diaphragm muscle removed from normal animals incorporated nearly twice as much C^{14}-labeled leucine into protein during a 1 hour incubation period than tissue removed from hypophysectomized rats and that treatment of the hypophysectomized diaphragm donor with growth hormone for several days restored the in vitro amino acid incorporating activity to normal (17). The next step was to determine whether growth hormone, added directly to the tissue in vitro, would have a similar effect. To our delight, this was indeed the case (Table 1).

This marked the first time that an in vitro effect of growth hormone on any aspect of amino acid metabolism had been demonstrated although Manchester and Young in Cambridge made the same observation independently at essentially the same time (20). If a stimulation of amino acid incorporation could in some manner be equated with a stimulation in protein synthesis, a point which was later to become of paramount concern to us, the results of this simple experiment would immediately imply that the action of growth hormone on its target tissues was a direct one rather than, as had been suggested by Best and others (c.f. 13), an effect of the hormone on the beta cells of the pancreas, there stimulating an increased production of insulin which in turn was thought to be the true growth hormone. They also cast serious doubt on the rather

popular view advanced by Greenbaum that the primary site of action of growth hormone is adipose tissue where, by virtue of its well documented lipolytic effect, it would make increased quantities of fatty acids available for oxidation thus providing increased supplies of energy-rich substrates which in turn would "drive" the protein synthetic mechanism of the cell (8).

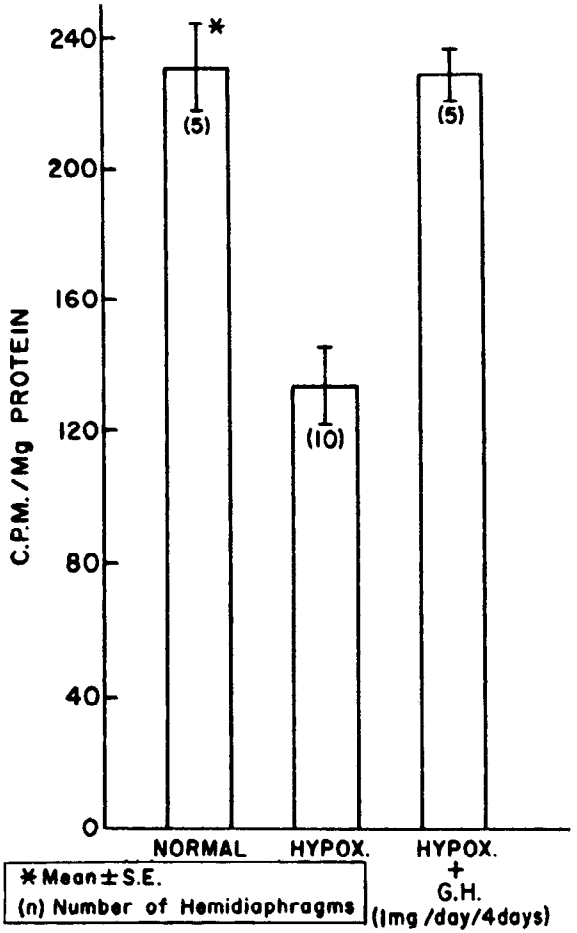

Fig. 2. The influences of hypophysectomy and in vivo growth hormone treatment on the incorporation of leucine-2-C^{14} into the protein of diaphragms of fed rats incubated in vitro for 60 minutes. From (17).

TABLE 1

Effect of in vitro Addition of Simian and Bovine Growth Hormones on the Incorporation of Glycine-2-C^{14} into Diaphragm Protein of Hypophysectomized Rats*

Growth Hormone μg/ml		No. of diaph. pairs	C. P. M./mg Protein Control	G. H.	Diff.	P
Simian	10	7	83± 7	132± 9	48± 7	<0.01
	50	11	53± 4	79±5	25± 5	<0.01
Bovine	10	10	71± 4	80±9	9± 9	>0.3
	50	7	65±10	85±10	20±5	<0.01

*Similar results were originally reported using leucine as the tracer amino acid (Kostyo, J. L. and E. Knobil, Endocrinology 65:525, 1959).

The first step in the chain of events which leads to the synthesis of protein from amino acids is the entry of amino acids into the cell. Stimulated by the suggestion of Christensen that cellular growth may be regulated by the rate of amino acid entry into the cell and by the studies of his group (23) which showed an effect of growth hormone injection into rats on the in vivo disposition of the non-metabolizeable amino acid alpha-aminoisobutyric acid (AIB) we investigated the relationship between growth hormone and cellular AIB-C^{14} accumulation in the isolated diaphragm preparation (Fig. 3).

The results of our first experiments, reported in 1959 (16), clearly show that hypophysectomy markedly diminishes and the addition of growth hormone to muscle tissue from hypophysectomized rats immediately restored to normal the capacity of the cell to accumulate the amino acid against a rather steep concentration gradient. That this action of growth hormone on the transport of AIB is independent of protein synthesis and, therefore, not secondary to an acceleration of this process was demonstrated by repeating the above experiment in the presence of puromycin at a concentration which virtually abolishes protein synthesis in this system (Fig. 4).

Under these circulstances, the action of growth hormone on AIB accumulation is still fully evident. Now armed with the tantalizing working hypothesis that growth hormone stimulates protein synthesis by increasing the supply of amino acids to the cells, we set out to determine whether the observations made on the behavior of the non-metabolizeable AIB could be extended to naturally occurring amino acids. (Fig. 5).

We were most encouraged to find that growth hormone stimulated the penetration of a number of neutral amino acids into the intracellular compartment and that these same amino acids competitively inhibited

the transport of AIB giving credence to the interpretation that a common transport system was involved and that the activity of this system was, at least in part, growth hormone dependent. Unhappily, however, this effect of growth hormone could not be demonstrated for all neutral amino acids using our rather crude measure of membrane transport (Fig. 6).

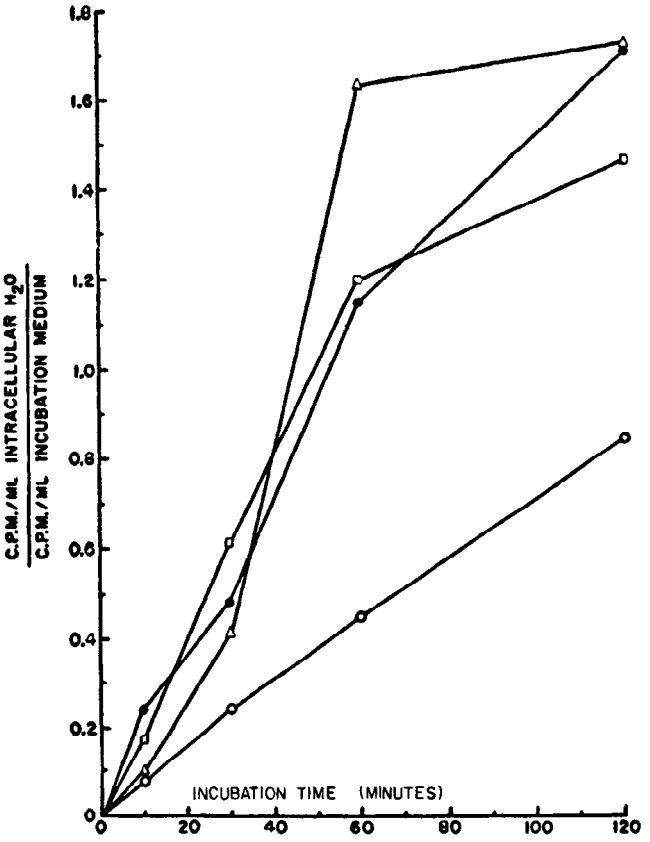

Fig. 3. Intracellular penetration of AIB-1-C^{14} into "intact" rat diaphragm preparations from normal ●, hypophysectomized 0, hypophysectomized + simian growth hormone added to the incubation medium (25 µg/ml)Δ and hypophysectomized animals + bovine growth hormone added to the medium (25 µg/ml) □. From (16).

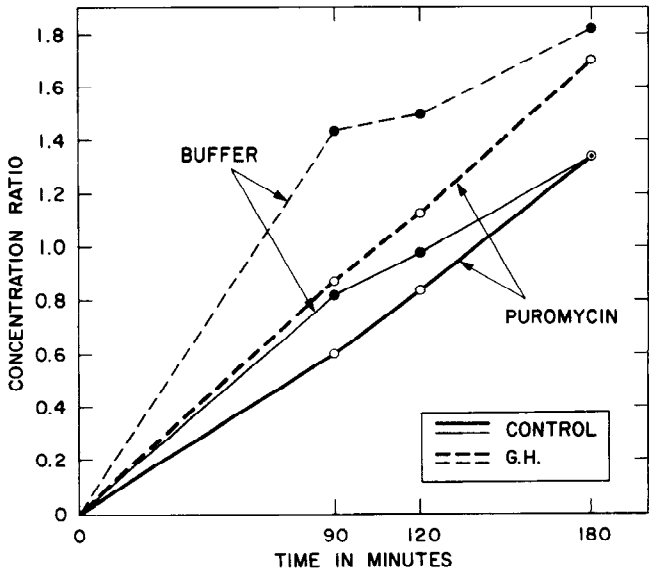

Fig. 4. The influence of growth hormone (50 μg/ml of incubation medium) on the penetration of AIB-1-C^{14} into diaphragm muscle cells of hypophysectomized rats when protein synthesis was essentially blocked by the addition of puromycin (500 μg/ml) to the incubation system. The final accumulation of AIB in response to growth hormone is the same in the presence and absence of the inhibitor. Each point represents the mean of 6 observations.

Yet these malevolent amino acids competitively inhibited the growth hormone dependent transport of AIB and other neutral amino acids. In view of the smallness and multiplicity of the pools of these amino acids we reasoned that our inability to detect an increase in their distribution ratio between extracellular fluid and total cell water did not necessarily invalidate our hypothesis but we were rather shaken when we contemplated the results obtained with the dicarboxylic amino acids (Fig. 7).

Not only did growth hormone not increase their penetration into muscle cells but it did not stimulate their incorporation into protein in marked contrast to every other naturally occurring amino acid studied. This distressing result was obtained again and again, no matter how the conditions of the incubation system and all of its components were varied. These observations could be interpreted in two ways: either growth hormone stimulated the synthesis of a protein which does not contain the dicarboxylic acids, a rather unlikely possibility, or that the increase

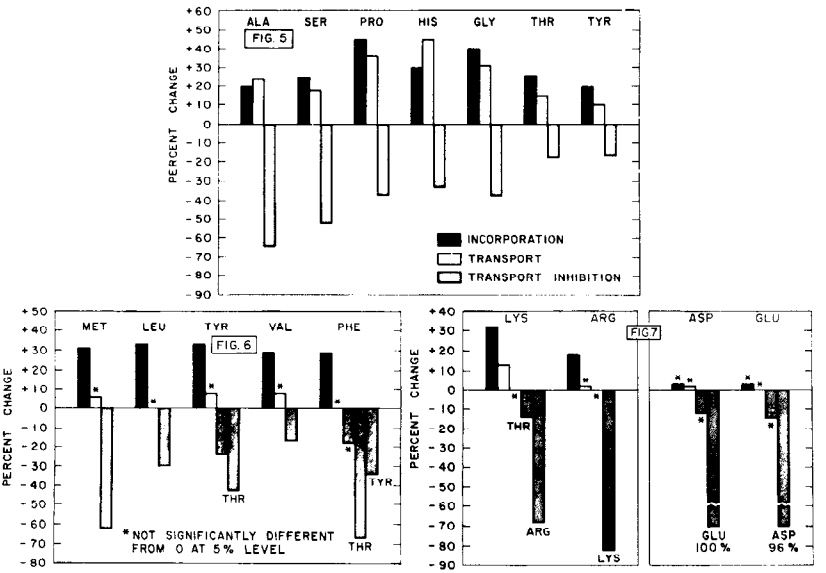

Fig. 5. The influence of growth hormone (50 μg/ml) on the incorporation into protein (solid bars), the accumulation in the intracellular compartment (open bars) and the inhibition of AIB accumulation (hatched bars) of some amino acids when added to diaphragm muscle from hypophysectomized rats as measured isotopically at the end of 90 minutes of incubation. Each bar represents the mean of at least 6 paired observations (control hemidiaphragm compared with growth hormone treated diaphragm from the same rat). All changes are statistically significant at the 5% level.

Fig. 6. See Fig. 5. The inhibition of threonine and tyrosine accumulation in addition to that of AIB was also studied in some of these experiments.

Fig. 7. See Figs. 5 and 6. None of these amino acids inhibited the influence of growth hormone on AIB accumulation although they did interfere with the intracellular penetration of the indicated naturally occurring amino acids.

in specific activity of protein observed with all the other amino acids did not represent an increase in protein synthesis but rather an enrichment in the specific activity of the various amino acid pools as a result of increased transport. Strength was given to the second alternative by the fact that diaphragms removed from growth hormone treated rats incubated in the presence of glutamic acid, under the same conditions employed in the previous experiments, incorporated considerably more of the amino acid into protein than their controls. This implied

that when sufficient time is allowed for protein synthesis to be truly stimulated, the dicarboxylic acids are incorporated at an increased rate just as expected. We felt, therefore, that our working hypothesis was still tenable but reluctantly concluded that the in vitro diaphragm preparation revealed but a prelude to the stimulatory action of growth hormone on protein synthesis. The possibility, however, that amino acid transport was not the sole site of action of growth hormone had to be considered for the simple reason that no causative relationship between an increase in amino acid supply and a stimulation of protein synthesis had been established, nor for that matter that the supply of amino acids was limiting in the cells of hypophysectomized animals. Our attempts to resolve these fundamental questions, while yielding keenly interesting results, were far from illuminating. I shall describe but one of these.

If growth hormone stimulates protein synthesis by accelerating the supply of amino acids to the interior of the cell, it should be possible to mimic the action of the hormone by loading the cell with amino acids by some other means. This was accomplished quite simply by increasing the concentration of a complete amino acid mixture in the incubation medium. One amino acid of the mixture, threonine, was labeled and its entry into the cell water as well as its incorporation into protein studied in diaphragms from hypophysectomized and from normal rats (Fig. 8).

The control experiments consisted of adding the labeled threonine alone (open circles). It can be seen that, as the concentration of threonine in the incubation medium is increased, the specific activity of the endogenous threonine pool is increased with a resultant increase in the specific activity of the protein, just as expected. When, however, the complete amino acid mixture was added to the system in concentration increments proportional to those of threonine, an unequivocal stimulation of threonine incorporation into protein could be observed, despite the fact that the entry of threonine into the cell was competitively inhibited by the other neutral amino acids in the mixture. At first glance the results of this experiment might be interpreted as triumphant support of our working hypothesis. Yet, the diaphragms from normal rats were more sensitive to amino acid loading than those from hypophysectomized animals, while the reverse is true for their response to growth hormone. Further experiments revealed, to our chagrin, that if leucine was substituted for threonine as the tracer amino acid in the mixture, its incorporation into protein was not increased, suggesting that it may be limiting in this system. This led to the discovery that leucine alone could markedly stimulate the incorporation of threonine into protein and that the bulk of the effect of the complete amino acid mixture could be accounted for by its leucine content. Valine had a similar but much smaller effect but the other amino acids tested were inactive. Sidney Roberts and his colleagues (9) have, independently, made observations reminiscent of our own using liver slices incubated in vitro. While we are convinced that we are dealing with an important phenomenon, we have been unable to incorporate it as yet into a compelling scheme for the mechanism of action of growth hormone.

While we were struggling with the foregoing, Jack Kostyo, my collaborator in the early phases of this work, reported that growth hormone added to rat diaphragms incubated in a sodium free medium, a procedure which abolishes amino acid transport, was nevertheless able to stimulate amino acid incorporation into protein (15). He concluded that growth hormone had an effect on amino acid incorporation into protein quite independent of its action on amino acid transport. We were forced, albeit reluctantly, to the same conclusion by the results obtained from experiments quite different in design (Table 2).

We found, just as Manchester and Krahl had in the case of insulin (19), that growth hormone stimulates the incorporation of a variety of non-amino acid substrates into protein. As far as we have been able

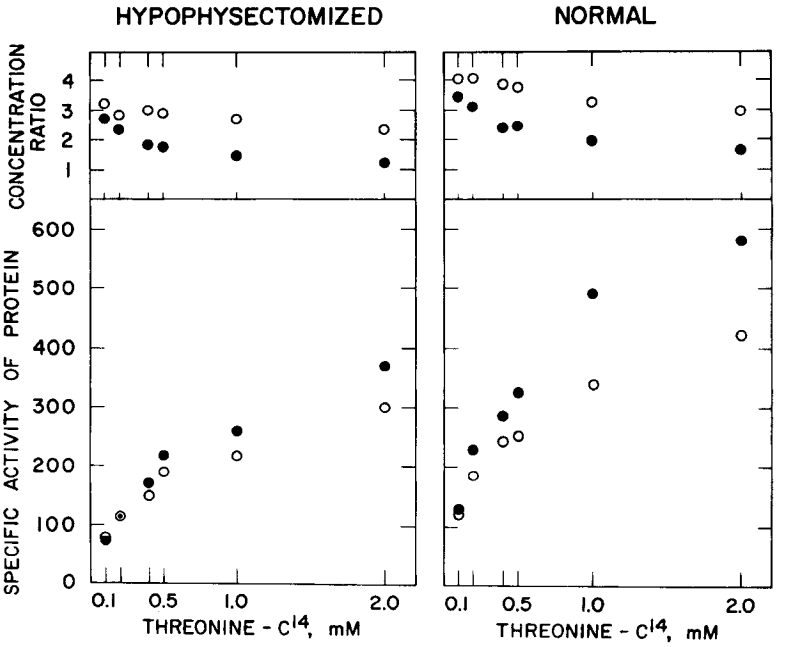

Fig. 8. The effect of a complete amino acid mixture, solid circles, on the intracellular accumulation (upper panels) and incorporation into protein (lower panels) of threonine-C^{14} added to isolated hemidiaphragms of normal and hypophysectomized rats. The concentration increments of the complete amino acid mixture in the incubation medium were the same as those used in the control experiments (open circles) where threonine-C^{14} was added alone. The period of incubation was 90 minutes. Each point represents the mean of 4-6 observations. The presence of the amino acid mixture stimulated the incorporation of the labelled amino acid while inhibiting its entry into the muscle cells.

TABLE 2

Incorporation of ^{14}C labeled Substrates into the Protein of "intact" Hemidiaphragms from Hypophysectomized Rats

Substrate	Control	Growth Hormone*	P
	CPM/mg protein		
1-^{14}C pyruvate (0.9 mM)	131 ± 9.5(6)**	171 ± 4.0(6)	<0.01
2-^{14}C pyruvate (0.9 mM)	267 ± 15.3(6)	333 ± 24.1(6)	<0.05
^{14}C formate (2.0 mM)	13 ± 0.6(33)	16 ± 0.5(24)	<0.001
2-^{14}C succinate (2.2 mM)	63 ± 14.9(16)	82 ± 2.9(18)	<0.01
$H^{14}CO_3$ (24.8 mM)	83 ± 2.7(18)	96 ± 4.4(18)	<0.01
1-^{14}C acetate (2.0 mM)	272 ± 7.4(11)	312 ± 10.9(11)	<0.02

* 50 μg/ml
** mean ± S.E., number of observations in parentheses.

to determine, none of these compounds penetrates the intracellular compartment at an increased rate in the presence of growth hormone. It appears, therefore, that in addition to its action on membrane transport of amino acids, growth hormone can act beyond this step to stimulate protein synthesis. These sites of action seem to be independent since each can be demonstrated in the absence of the other. To what extent, if at all, they are normally related remains to be determined.

The recent revolution in biology has had a profound impact on endocrinological thought with particular reference to the mechanism of hormone action. The striking observations of Karlson and his colleagues (11) that the insect hormone ecdysone produces changes in chromosomal morphology associated with the production of nuclear RNA has captivated students of mammalian hormone action who in the past few years have performed a large number of experiments designed to show that the actions of a variety of hormones can be interpreted in terms of their control of messenger RNA synthesis at the genetic level. This messenger RNA, in turn, directs the synthesis of specific proteins of physiological or structural import according to the now classic scheme of Jacob and Monod. In the case of growth hormone a rather impressive array of evidence has been presented which leads to the

conclusion that treatment of rats with the hormone results in an increase in hepatic messenger and other RNA production some 12 hours later (14). We wished to see whether the very early effects of growth hormone, as we have studied them in vitro and presumably at closer range to the initial sites of its action, were also associated with changes in RNA metabolism (Fig. 9).

We found first of all that exposure of the tissue to growth hormone for two hours did not significantly increase the incorporation of adenine into RNA. Pre-incubation of the diaphragms with actinomycin D for 30 to 120 minutes virtually abolished RNA synthesis. Under these circumstances, growth hormone had a tendency to depress RNA synthesis even further. We then tested the action of growth hormone on glycine accumulation in the presence of actinomycin D under these same conditions, conditions under which RNA synthesis is profoundly inhibited (Fig. 10).

The effect of growth hormone on glycine transport was indistinguishable from that in the control diaphragms to which no actinomycin D had been added. This was not too surprising in view of our earlier experiment where blockade of protein synthesis with puromycin similarly did not depress the action of the hormone on amino acid transport.

The stimulation of glycine incorporation into protein was also unaffected by the blockade of RNA synthesis (Fig. 11).

Since glycine incorporation into the proteins of control tissues progressively fell as the duration of exposure to actinomycin D was extended, the relative effect of growth hormone was actually the greatest when the inhibition of RNA synthesis was most profound. It could be argued, since in this experiment the action of growth hormone on glycine transport was unimpaired, that the increased incorporation of glycine into protein simply represents an increase in the specific activity of the glycine pool and that protein synthesis was in fact depressed. That this interpretation is probably not correct is suggested by preliminary experiments identical in design to the ones just described in which the influence of growth hormone on pyruvate incorporation was studied. In this instance, as I have already mentioned, the entry of the substrate into the cell is not accelerated by growth hormone, yet the effect of growth hormone on pyruvate incorporation into protein was fully evident and undiminished in the presence of actinomycin D.

These observations warrant the conclusion that the early actions of growth hormone on amino acid transport and protein synthesis are not the consequence of increased DNA dependent RNA synthesis and it is, therefore, difficult to visualize a direct genetic site of action of the hormone. It would appear rather, that growth hormone initially stimulates amino acid transport as well as the production of some unknown proteins perhaps associated with the cell membrane, and that these alterations in turn bring the nuclear directed protein synthetic machinery into full activity. It would be trite to add that much remains to be learned before the molecular mechanism of action of growth hormone on protein synthesis is fully understood, to say nothing of its effect on lipid and carbohydrate

metabolism which I have but mentioned. But, surprisingly, despite the vast complexity of the problem, significant progress is being made in a number of laboratories and I am optimistic that the solution to this and cognate questions of basic physiologic import will be found in the reasonable future.

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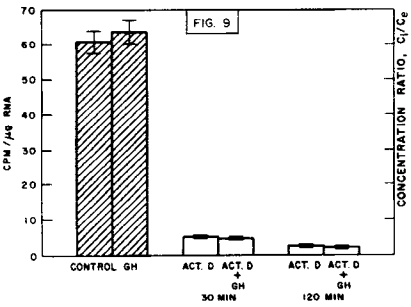

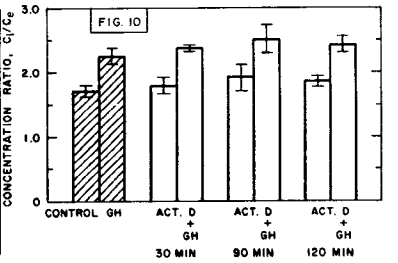

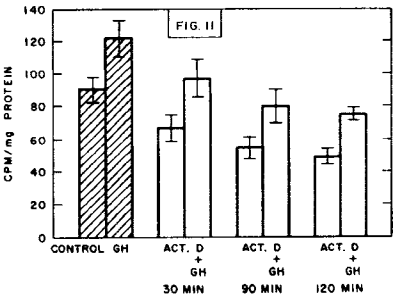

Fig. 9. Effect of growth hormone (50 µg/ml) on the incorporation of adenine-8-C^{14} into total RNA of hypophysectomized rat diaphragm muscle in the presence and absence of actinomycin D (20 µg/ml). The duration of pre-incubation with actinomycin D alone is indicated. Incubation was then continued for an additional 120 minutes. Six paired observations per group. Vertical lines represent the standard errors of the means.

Fig. 10. Effect of actinomycin D on the action of growth hormone on the accumulation of glycine-2-C^{14} by cells of hypophysectomized rat diaphragm muscle. Conditions of experiment and number of observations are the same as those in Fig. 9. Fig. 11. Effect of actinomycin D on the action of growth hormone on glycine-2-C^{14} incorporation into protein of the same diaphragms depicted in Fig. 10.

The best part of any adventure is usually the anticipation of it. I should like to part with tradition and end this lecture with a brief discussion of a very new and currently immerging aspect of growth hormone physiology: the regulation of its secretion by the adenohypophysis.

Since the discovery of growth hormone one of the questions uppermost in the minds of its students was the manner of its secretion in relation to changes in the growth rate of animals and man. Why do animals stop growing when they reach adult size? Is it because of a reduction in growth hormone secretion when adulthood is reached, or is it because tissues stop responding to continued growth hormone secretion? Since growth hormone has such profound pharmacological effects on protein, carbohydrate and fat metabolism, does its rate of secretion change in response to alterations in the nutritional environment? Are the metabolic shifts associated with fasting, such as fat mobilization, shifts which resemble the responses to growth hormone administration, mediated by an increase in endogenous growth hormone secretion?

None of these questions could be answered without the availability of a sensitive and specific assay for growth hormone in biological fluids. The standard tibia test for the assay of growth hormone so useful for the quantitation of pituitary extracts or of purified preparations of the hormone is not sufficiently sensitive for this purpose.

New doors were flung open on this previously inaccessible area of investigation by the recent introduction of extremely sensitive immunological methods for the assay of polypeptide hormones (27). Read (24) was the first to attempt this approach to the measurement of growth hormone in human plasma using the hemagglutination inhibition technique. Armed with the intelligence that growth hormone possesses a high degree of species specificity (12), he used rabbit antisera to a purified human growth hormone preparation which did not cross react with any of the other pituitary hormones and attempted to measure the concentration of endogenous growth hormone in human plasma. The method while extremely promising was not entirely successful, however, because of the presence of non-specific hemagglutination inhibitors in plasma. This problem was overcome by the application of the so-called radioimmunochemical method developed by Berson and his colleagues for the assay of insulin in plasma (28) to the measurement of growth hormone. With but minor adaptations of this technique, Berson and his group (7) and Hunter and Greenwood in London (10) succeeded in measuring, with confidence, concentrations of circulating growth hormone as low as 0.1 mμgm per ml of plasma. This powerful tool, which has the elegance of conceptual simplicity but is subject to the vagueries of all micro-methods, involves the interaction for several days between radioactive iodine labeled growth hormone with an antibody to the hormone. Adding known amounts of unlabeled growth hormone to this system displaces the iodinated form from the antibody and a standard curve is constructed by measuring the ratio of radioactive iodine that is antibody bound to that which is unbound. The degree to which a few microliters of plasma decrease the binding of the labeled hormone in the system can then be equated with a known amount of purified hormone. In a normal human population the average growth hormone concentration has been found to

be around 3 mμgm/ml of plasma. Using this technique a careful study by Berson and his collaborators (7) has failed to reveal a statistically significant difference between the plasma growth hormone concentration of growing children and that of adults. The newborn infant, however, which presumably does not need its pituitary for growth during the first months of life, has concentrations equalling those of acromegalics. This matter must remain in abeyance until further studies are carefully evaluated. For the moment, however, it appears that there are no major changes in the concentrations of circulating growth hormone with alterations in the growth rate of man. Unexpectedly, however, Berson's group as well as others have reported striking acute increases in plasma growth hormone concentrations in adult man in response to a variety of stimuli, the most consistent of which is insulin hypoglycemia. Exercise also produces a rapid rise in plasma growth hormone and prolonged fasting, according to some, results in a modest elevation (7). I shall return to the physiological significance of these changes in a moment.

The foregoing developments were paralleled by investigations of a quite different sort designed to determine whether the brain, which by virtue of its various releasing factors regulates the secretion of all the other adenohypophyseal hormones, also plays a role in the regulation of growth hormone secretion. Although there was no compelling reason to suppose that this was the case, a suggestive but not entirely convincing body of evidence supported the view that growth hormone secretion was not completely independent of central nervous control. Few people really paid much attention to this problem until Meites and his co-workers recently reported that the addition of hypothalamic extracts, but not those of cortical extracts, to rat pituitary glands in organ culture enhanced the synthesis and release of growth hormone as measured by the tibia test (21). This finding was rapidly confirmed and several laboratories were also able to demonstrate that the intracarotid injections of hypothalamic extracts but not of other materials associated with neural tissue resulted in a rapid depletion of pituitary growth hormone content (22, 25).

A new set of initials was therefore duly added to the endocrinological lexicon: G. R. F. (growth hormone releasing factor).

By this time, our own laboratory, after much effort, had succeeded in applying the radioimmunologic assay for growth hormone devised by Berson to the rhesus monkey utilizing highly purified simian growth hormone, prepared by Dr. W. D. Peckham, as our antigen (Fig. 12).

We began by studying the effects of prolonged fasting and other chronic phenomena including age on plasma growth hormone concentration in this species. In most instances the values we obtained varied rather wildly from day to day and we were unable, at this stage in our experience, to evaluate our results with confidence. We were, however, successful in confirming that the injection of insulin regularly produced an unequivocal increase in plasma growth hormone concentration in blood obtained by venepuncture 30 minutes later.

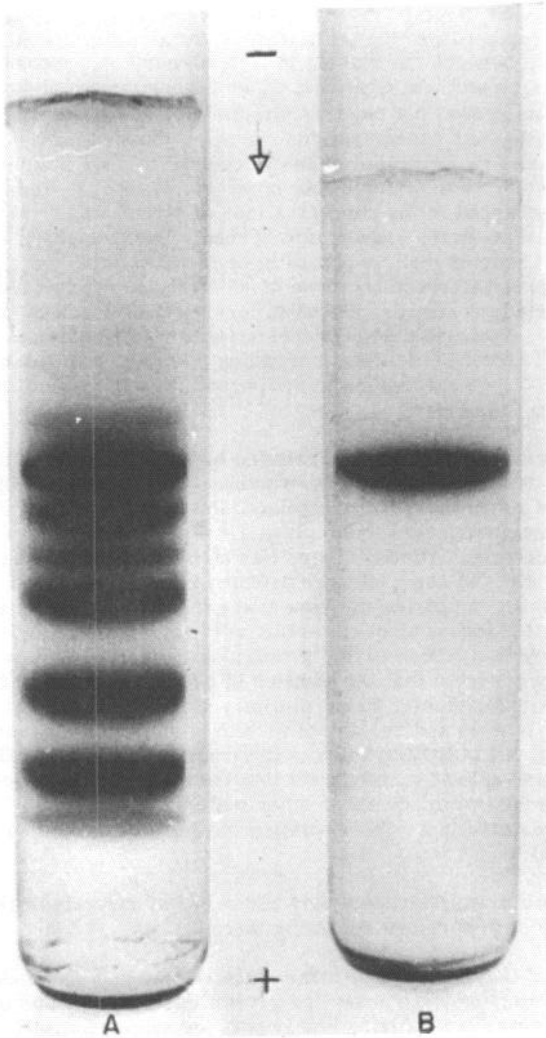

Fig. 12. Disc electrophoresis on polyacrilamide gel of simian growth hormone preparations. The direction of migration is downward. The tube on the left represents a relatively crude preparation which upon further purification by chromatography on DEAE-sephadex and density gradient electrophoresis produced the "single band" material depicted on the right.

We then turned to the study of moment to moment changes in plasma growth hormone concentration in normal, unanesthetized monkeys, with indwelling venous catheters, restrained in primate chairs. We obtained an acid extract of porcine hypothalamus with potent GRF activity as assayed in the rat pituitary growth hormone depletion test from Dr. Andrew Schally and administered the equivalent of 2 porcine hypothalami

intravenously. Figure 13 illustrates the results of our first experiment.

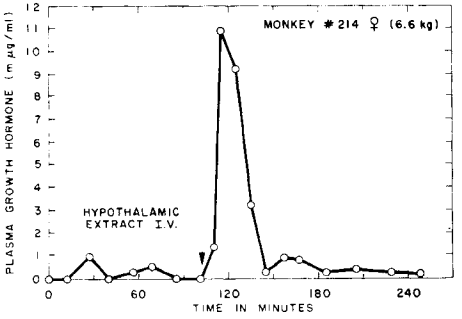

Fig. 13. The effect of a porcine hypothalamic extract (equivalent to 2 hypothalami) on the plasma growth hormone concentration in a rhesus monkey.

During the control period which began an hour after the placement of the catheter, the growth hormone concentrations varied between 0 and 1 mμgm per ml of plasma. We were struck by the rapidity of the response to the extract and the prompt return of the growth hormone concentration to control values. We have repeated this experiment a number of times and the results have been invariably the same at least qualitatively (Fig. 14). The injection of more than equivalent doses of a cerebral cortical extract, also supplied by Dr. Schally, had no such effect (Fig. 15). It soon became apparent, however, that the growth hormone concentrations were often quite elevated at the beginning of the sampling period, as in this instance, and gradually fell as the experiment progressed. A more extreme example of this is shown in Fig. 16. This animal was agitated and apprehensive for the first two hours of the experiment as she was toward the very end when the plasma growth hormone concentration began to rise.

When our monkeys appeared calm and contented the control values hovered around 1 mμgm/ml throughout the control periods. These and a number of other experiments forced us to the conclusion that growth hormone, like ACTH and some other pituitary hormones, is released in response to "stress." This served to explain the erratic results of our chronic experiments in which the animals were caught in their cages, restrained by two strong men and subjected to femoral punctures and in which juvenile monkeys were forcibly separated from their mothers. In this connection it may be of interest that when mothers and their babies were sampled simultaneously, their plasma growth hormone concentrations were essentially the same. When the mother had very elevated values, so had her baby and conversely, when the mother had low levels of growth hormone, the same was true for her offspring.

Another consideration in these early experiments was the vasopressin content of the hypothalamic extract. This was assayed by Dr. Schally and found to be .05 units/mg of extract or 0.5 units per extract injection

in most of our experiments. We found indeed that our animals blanched markedly after these injections and remained noticeably pale for an hour or so afterwards. We therefore tested the effects of pitressin and synthetic lysine-vasopressin and found, regrettably, that they too caused a prompt increase in plasma growth hormone concentration (Figs. 17 and 18).

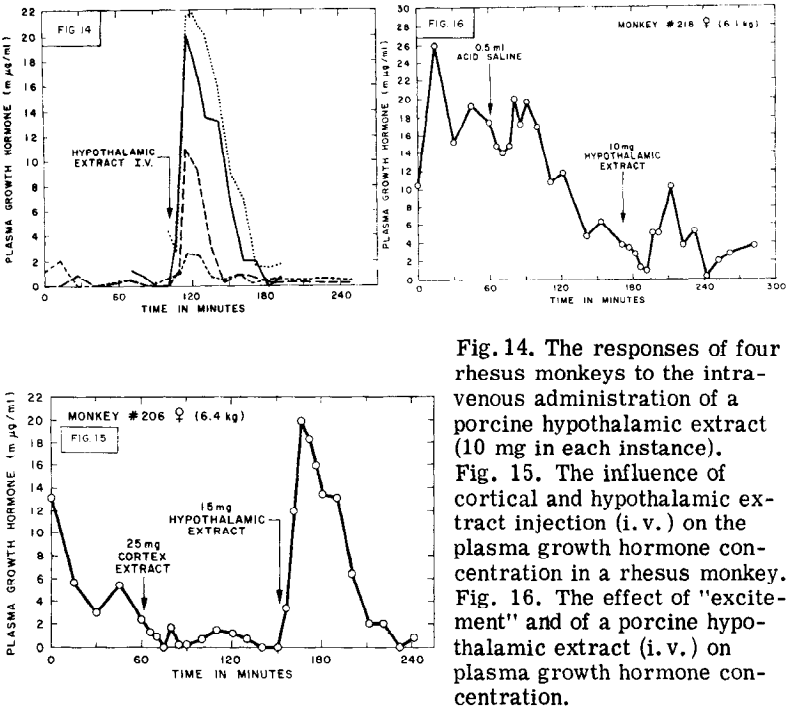

Fig. 14. The responses of four rhesus monkeys to the intravenous administration of a porcine hypothalamic extract (10 mg in each instance).
Fig. 15. The influence of cortical and hypothalamic extract injection (i.v.) on the plasma growth hormone concentration in a rhesus monkey.
Fig. 16. The effect of "excitement" and of a porcine hypothalamic extract (i.v.) on plasma growth hormone concentration.

Epinephrine had a similar effect. This is as far as we have gone to date. It has been reported by Schally and others that vasopressin has no effect on the release of growth hormone by rat pituitary cultures in vitro nor when it is injected intracarotidly into rats and the pituitary content of growth hormone measured shortly afterwards (25). I have no reason to doubt their results but we must await the availability of more highly purified extracts, studied in smaller doses than we have used heretofore, before the activity of a specific GRF can be confirmed in our system. It appears that, in our experiments, the large doses of pitressin, vasopressin and of epinephrine which we injected acted as noxious stimuli and as such caused the release of growth hormone. Whatever the physiological significance of this response to stress may be, it brings into question the specificity of the response to insulin hypoglycemia, a highly potent stress. Perhaps the small increase found in prolonged fasting may also be the result of discomfort and anxiety. In my view, therefore, it is not yet established that the small

fall in blood sugar concentration observed during prolonged fasting elicits an increase in growth hormone secretion by the pituitary which in turn can be held accountable for the profound metabolic changes observed. It is difficult to predict where these preliminary findings will lead us, but a new adventure is in the making and we are embarking on it with anticipatory elation.

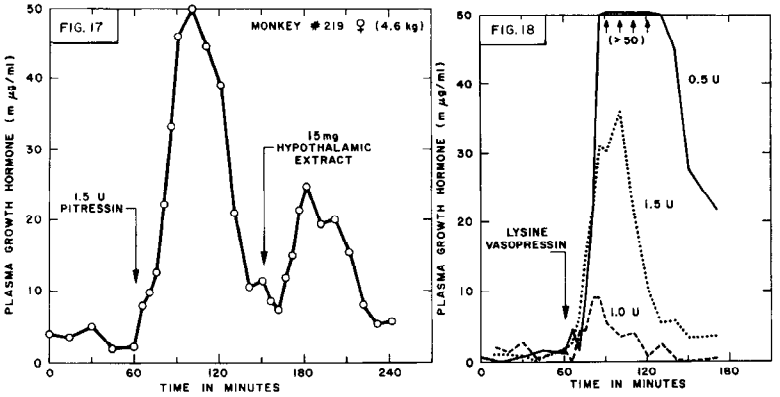

Fig. 17. The effect of the intravenous administration of pitressin and of a porcine hypothalamic extract on plasma growth hormone concentration.
Fig. 18. The effect of synthetic lysine vasopressin injection (i.v.) on plasma growth hormone concentration. The 4 small arrows indicate that the values at these times exceeded 50 mμg/ml. Note absence of a dose-response relationship.

I shall close by quoting from a memoir of Dr. Bowditch written by his youngest son, Manfred (3). In it he refers to an occasion when his father joined a contest in which members of his favorite club painted their self-portraits. He goes on to say "My father's product, in oils supplied by an artist friend, was notable both for its proof of his lack of skill with the brush, and for the evidence of his red-and-green color blindness. One of the most atrocious attempts at portraiture ever to be placed on canvas, it was awarded honorable mention by the Art Committee as 'chaste, tender and self-restrained'." I fondly hope that you will be able to accord me the same kindness.

Acknowledgements

My collaborators in the foregoing studies, in addition to Drs. J. L. Kostyo and J. Hotchkiss, were Dr. W. D. Peckham, Dr. B. Katorski, Dr. P. L. Lebovitz and Dr. V. Meyer. Their contributions far exceeded my own.

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NEWS ITEMS FROM SENIOR PHYSIOLOGISTS
(Continued from the November 1965 Physiologist)

John C. Scott is continuing as Research Professor of Physiology at Hahnemann.

Wilder Penfield is "in the home stretch with the biography of Alan Gregg - started four years ago."

Carlos Reed and his wife have moved to Westminster Terrace, 717 Neil Avenue, Columbus, Ohio, a new retirement center. He and Mrs. Reed are gathering material for a monograph on Gerontology to be written from the insider's point of view.

Walter Fleishmann is continuing as a consultant in research and hematology at the VA Hospital Mountain Home, Johnson City, Tenn.

Eugene L. Opie continues in experimental work in the Rockefeller Institute and University where he has had a laboratory ever since he retired as Professor of Pathology in Cornell University Medical College. (Editorial note: We believe Dr. Opie, who is 92 years old, is the oldest laboratory worker in the APS membership. Any news of other nonagenarians at work?)

Since 1958 George E. Wakerlin, formerly Professor of Physiology and Head of the Department, University of Illinois College of Medicine, has served as Medical Director of the American Heart Association with senior staff responsibility for the medical and community programs of the Association. In 1962, he received the Distinguished Service Award of the Medical Alumni Association of the University of Chicago, "In recognition of contributions of distinction to the advancement of the medical sciences."

After her retirement as Professor of Physiology at Woman's Medical College, Roberta Hafkesbring went to Seoul, Korea, where she taught for ten months as Professor of Physiology at Ewha Woman's University Medical School. This was a challenging and rewarding experience. She hopes to return in March 1966 for the spring session.

Victor Guillemin is writing a book on modern developments in physics, quantum mechanics and high energy particle phenomena for high school students, nonscience college students and the general public.

S. A. Asdell, Professor of Animal Physiology, Cornell University, Ithaca, retired in July. He is continuing research in reproduction, lactation, growth and in factors related to aging.

After retirement scheduled for June 1966 Joe Hinsey will remain for three years as Consultant at the Cornell Medical Center. He plans to continue with medical education and will also carry on his work with the China Medical Board of New York.

E. A. Spiegel recently received an honorary M.D. degree from the

University of Zurich.

Elaine Ralli, New York University College of Medicine has been studying the effects of pyridoxine given by injection in diabetics and has observed significant improvement when it was used in patients with diabetic ulcers and in some cases it improved the retinopathy.

Lester R. Dragstedt keeps actively at work in both research and teaching as Research Professor of Surgery at the University of Florida in Gainesville. His article on "An American by Choice; a story about Dr. A. J. Carlson" (Perspectives in Biology and Medicine 7: 145-158, 1964) will be appreciated by admirers of that legendary physiologist.

SECOND INTERNATIONAL BIOPHYSICS CONGRESS
Vienna, Austria, September 5-9, 1966

General sessions of invited papers will be devoted to energy transfer and conversion; to molecular aspects of differentiation; and to emerging developments in biophysics. Symposia will include ones on Molecular Biophysics; Cell and Membrane Biophysics; Communication and Control Processes; and Radiation Biophysics.

Deadline for abstracts of papers to be presented is May 15, 1966.

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