CONTENTS

Page

The 25th Annual Fall Meeting 1

Future Meetings 1

IMPORTANT NOTICE - Proposed New Bylaw 2

NSF Bulletin 5

Association of American Medical Colleges 5

Proposal to Modify the Journals of the APS 6

Andrew C. Ivy 11

American Industrial Hygiene Association 14

Perkins Memorial Fund Committee 15

National Conference on Thrombosis and Hemostasis 18

Eighteenth Bowditch Lecture ... Rodolfo Llinás 19

Physiology in Medicine 47

Thyroid 48

Aspects of the Electrophysiology of Cortical Processes Related to the Development and Performance of Learned Motor Responses .... Charles D. Woody 49

30th Brazilian Cardiology Meeting 69

The John F. Perkins, Jr. Memorial Awards 70

Statistics on APS Membership 71

Computer Teaching Session Reprints 72

On Blood Pressure Control ... Gunter N. Franz 73

Endocrine Uroscopy: A Physiology Laboratory Exercise ... J. W. Bauman, Jr. and J. Bullock 87

News from Senior Physiologists 90

Some Cardiovascular Physiologists in the First Quarter of the Twentieth Century ... Louis N. Katz 97

THE 25th ANNUAL FALL MEETING

The 25th Annual Fall Meeting of the American Physiological Society will be held in Albany, N.Y. on August 12-16. It is to be sponsored jointly with the Division of Comparative Physiology and Biochemistry of the American Society of Zoologists.

The host institutions are the Albany Medical College and the State University of New York at Albany. The meeting will be held on the campus of the State University of New York at Albany.

The announcements for the meeting are scheduled to be mailed early in April by 3rd class mail. The deadline for receipt of abstracts will be June 1. Anyone not receiving an announcement by early May should contact:

The Local Organizing Committee
Dept. of Biological Sciences
State Univ. of New York at Albany
1400 Washington Avenue
Albany, N.Y. 12222

Phone: (518) - 457-5370

FUTURE MEETINGS

1974 Spring - Atlantic City, N.J. - April 7 - 12
Biochemists meeting in Minneapolis - June 2 - 7
1974 Fall* - State Univ. of New York at Albany - August 11 - 16
1975 Spring - Atlantic City, N.J. - April 13 - 18
1975 Fall - Sheraton-Palace Hotel, San Francisco - October 5 - 10
1976 Spring - Anaheim, California - April 11 - 16
1976 Fall - University of Pennsylvania, Philadelphia - August 16 - 19
1977 Spring - Atlantic City, N.J. - April 3 - 8
1977 Fall - Diplomat Hotel, Hollywood Beach, Florida - October 9 - 14

* The date for submission of abstracts for the 1974 Fall Meeting in Albany is June 1, 1974.

PROPOSED NEW BYLAW FOR ELECTION OF OFFICERS

ANNOUNCEMENT

At the Annual Business Meeting of the American Physiological Society in Atlantic City in April of 1973, the issue of revising procedures for election of officers was considered. The matter was placed on the agenda because a questionnaire circulated to all members revealed that 5 out of 6 of the respondents (665) would prefer to elect officers by mail ballot rather than by the present methods. At the Business Meeting, proponents of a change to a mail ballot argued that more members could then vote and that the agenda of the meeting would then be more open for discussion of substantive issues. Opponents of the change stated that the present election procedure assures that the members who are most interested in the governance of the Society (and thus attend the Business Meeting) have the largest role in selecting officers. After thorough discussion, the matter was referred to an ad hoc Committee charged with the responsibility to make recommendations to the Society on election procedures. This Committee (R. M. Berne, Chairman; R. Berliner,and J. Bassingthwaighte) reported to Council and to the membership attending the Business Meeting in Rochester in August 1973*. The Committee recommended that the Bylaw on election of officers be modified as specified below. This proposed Bylaw change will be considered formally at the Business Meeting which will take place in Atlantic City on Tuesday,April 9, 1974. Council urges all members to read the proposed changes, attend the meeting and vote on the issue.

---

* The major contribution to the report of the Committee was made by Dr. Elizabeth Tidball.

Present Bylaw

ARTICLE IV. Officers

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.

Proposed New Bylaw

ARTICLE IV. Officers

SECTION 4. Election of Officers. Nominations for President-Elect and for members of Council will be made by mail ballot before February 1 of each year. Each member may nominate no more than one candidate for each office. If a member wishes to nominate a certain person for President-Elect and for Council he must nominate that individual for each position. The ten candidates that receive the highest number of nominating votes will appear on the appropriate ballot for President-Elect or for Council.

Election of the President-Elect and members of Council will be made by mail ballot prior to April 1 of each year. Each voting member must indicate on the ballot his rank preference for all of the candidates on each ballot. The ballots will be counted according to the Election Plan. Two ballots, one for President-Elect and one for Council will be mailed together. The results of the elections will be announced at the Spring Meeting of the Society and the newly elected officers will take office on July 1 following their election.

OPERATION OF THE ELECTION PLAN

The procedure operates on a preferential system. Each person votes for all of the candidates. If the ballot does not comply with this regulation it will be discarded. (Voting for all candidates makes a person's choices count most.)

Place #1 next to first choice, 2 next to second choice, etc. until all candidates have been voted for.

Example:

Brown

Jones

King

Smith

Reed

Counting Ballots

For each candidate the number of ballots on which his name received a 1 is tabulated.

Example: Assume 100 ballots were cast and the first choices were distributed as follows:

Brown	4
Jones	20
King	26
Smith	38
Reed	12

No one received a majority. Take Brown's votes and add them to those of the candidate in the #2 position on Brown's ballots.

Jones	20+1 = 21
King	26+1 = 27
Smith	38+2 = 40
Reed	12+0 = 12

Still no majority. Now take Reed's ballots and distribute them to the people marked #2 on Reed's ballots. If Brown is #2 on any of Reed's ballots, allot them to the person marked #3 on Reed's ballots, since Brown is out of the race.

Jones	21+3
King	27+3
Smith	40+3

There were 3 votes for Brown in the number two position on Reed's ballots, hence these votes go to Smith who was number 3 on Reed's ballots.

Jones	21+3 = 24
King	27+3 = 30
Smith	40+3+3 = 46

Still no majority. So now take Jones' ballots and divide as before, giving them to King or Smith, whoever has the higher ranking on Jones' ballots.

King	30+9 = 39
Smith	46+15 = 61

Now Smith has a majority and is elected. If the above example is for Council and a replacement on Council is needed for the person elected President-Elect, then King is the choice for the unexpired term of the Council member elected to President-Elect. Counting of the election ballots will be performed by the Executive Secretary in the presence of two additional members of the Society, selected by Council.

The advantage of this method is that it approximates the way a person would be expected to vote on a second, third or whatever ballot if his or her first choice was not elected on the first ballot, or was out of the running after the first ballot. If everyone is encouraged to mark

their ballots fully, they essentially are given the privilege of making their subsequent choices count in the election and hence have participated in several rounds of balloting.

PLEASE READ THIS PROPOSAL OVER CAREFULLY AND BE PREPARED TO VOTE ON IT AT THE FIRST APS BUSINESS MEETING IN ATLANTIC CITY IN APRIL.

Robert M. Berne, M.D.
Past-President
Chairman, ad hoc Committee
on Election Reform

NSF BULLETIN

The National Science Foundation has begun publication of a new monthly NSF Bulletin designed to assist the public conducting business with the Foundation by providing news about programs and calling attention to the availability of other, more specific information sources. The NSF Bulletin to be issued monthly except July and August, is available through the Publications Resource Office, National Science Foundation, Washington, D. C. 20550.

ASSOCIATION OF AMERICAN MEDICAL COLLEGES

The Executive Council of the AAMC voted to make the Weekly Activities Report (WAR) available to interested Medical School Faculty at an annual individual subscription rate of $10.00. A sample copy is enclosed with this issue. Address all correspondence or subscription requests to:

Association of American Medical
Colleges
Membership and Subscriptions
1 Dupont Circle, N.W.
Washington, D. C. 20036

TO ALL MEMBERS OF THE SOCIETY

In the near future you will receive a questionnaire from the Publications Committee concerning the proposal on the adjacent page for modifying the American Journal of Physiology and the Journal of Applied Physiology. We hope that you will read and consider the proposal now so that the questionnaire can be answered promptly.

PROPOSAL TO MODIFY THE JOURNALS OF THE AMERICAN PHYSIOLOGICAL SOCIETY

The publications of the American Physiological Society comprise one of its most important functions. Responsibility for these publications rests in the Publications Committee, which is responsible to the Council of the Society.

The current Publications Committee has undertaken to examine the present state of our scientific journals to establish the extent to which they are fulfilling their goals for the membership of the Society, for the scientific community as a whole, and for financial stability.

In the course of these deliberations, there were suggestions for modifications that might enhance the prospects for fulfilling these objectives. One particular proposal that seems to merit further consideration involves the restructuring of the American Journal of Physiology and the Journal of Applied Physiology - merging the two journals and issuing several specialty journals and an abstracts journal that would provide an overview of their contents. The purpose of this presentation is to provide the membership of the Society with an outline of this proposal and to determine the sentiment of the Society with respect to implementing this kind of change, to seeking another approach, or to continuing current practice.

AMERICAN JOURNAL OF PHYSIOLOGY and JOURNAL OF APPLIED PHYSIOLOGY

The American Journal of Physiology is the oldest journal of the Society. Traditionally, it is broad in scope. Since its beginning in 1898, it has reported the progress of physiology, and its editorial policies have insured critical scientific appraisal of each report prior to publication. This generalized coverage has been retained in the face of increasing specialization and despite the formation of specialized off-shoots of the Society, often with their own publications. Prompted largely by interests stimulated during World War II, the Society developed a collateral journal, the Journal of Applied Physiology, to enlarge its scope.

The Journal of Applied Physiology began publication in July 1948. As its title indicates, this journal is intended to be more applied than is the American Journal of Physiology. It also includes most papers involving human experimentation and, in effect, serves as a "Respiration Journal" as well as an important one for papers on exercise and environment. The "Special Communications" section is a popular feature of the journal.

The American Journal of Physiology and the Journal of Applied Physiology are both monthly publications. Each is issued in two volumes annually. For the sake of editorial surveillance and critical review, both journals are subdivided into ten sections, each with its own Section Editor(s). The Section Editors and Editorial Board are the same for the two journals. The governing policies are the same. Since neither

journal has a chief editor, the Publications Committee sets policy and guidelines, relying heavily on the Section Editors and a skilled staff in Bethesda. Each section is run (almost independently) under the broad directives of the Publications Committee.

Sectionalization

One of the chief attractions of the American Journal of Physiology and the Journal of Applied Physiology is the broad coverage they provide. On the other hand, despite the subdivisions of the journals according to specialties, an increasing number of Socicty members look to specialty journals for information that relates to their particular interests. Sensing a need to maintain a broad overview of physiology while satisfying the specific needs of many members led the Committee to serious consideration of the possibility of modifying the two journals by combining them into a single journal but differing from the present journals in two aspects: 1) sectionalization into separate journals according to specialties and 2) a separate periodical of current abstracts of all papers that appear in the specialty journals.

Specialty Journals

Each section would appear monthly or bimonthly in one or more volumes a year. A section would be devoted to one or more related topics. Among some possible combinations that have been suggested for sections are:

1. Heart and Circulation
2. Respiration (could include exercise)
3. Transport (kidney, G.I., etc.)
4. Muscle
5. Environmental Physiology
6. Physiological Chemistry (Endocrinology, Metabolism, Hematology)
7. General Subjects

It should be noted that neurobiology, a current section in the journals, does not appear as one of the proposed sections. It is anticipated that this section would be incorporated in an expanded Journal of Neurophysiology. During the past year, in consultation with the Chief Editor whose term is nearing completion, the Publications Committee initiated measures not only to secure new leadership for the Journal of Neurophysiology but also to broaden its scope. Since negotiations are under way to modify the character of this journal, its future is being considered separately from that of the Journal of Applied Physiology and the American Journal of Physiology.

Sections would be international in character as the two journals now are.

Each section would appear as a separate publication, which could be purchased separately.

Each section would be issued under the general title "American Journal of Physiology" or "American Journal of Physiology/Journal of Applied Physiology" with the section title.

Each journal would have its own editor-in-chief and editorial board.

The contents of all journals would be included in a general annual index.

The Publications Committee would coordinate the subdivisions.

Abstracts

In addition to the special-interest journals, there would be an abstracts journal. Such a publication would provide a summary of each paper appearing in the various journals for that particular month. In this way our membership and readership would be provided with an overview of current physiology that would also serve as a ready guide to the papers in the individual sections. A serious effort would be made to improve the quality and content of the abstracts and to standardize them. One possibility that has been discussed is to provide each member of the Society with a subscription to the Abstracts as part of the membership assessment.

Implications of the Proposed Plan

1. Fate of the Journal of Applied Physiology. If it should prove advantageous to use "American Journal of Physiology" as the master title, there would seem to be three likely alternatives for the Journal of Applied Physiology: 1) retain its name and identity for a section primarily devoted to respiration, exercise, and environment; 2) entitle the master journal "American Journal of Physiology/Journal of Applied Physiology" rather than "American Journal of Physiology"; 3) relinquish the title "Journal of Applied Physiology." Because of the high esteem in which this journal is held by a considerable number of Society members and nonmembers, the last alternative seems least desirable.

2. Scientific Quality of Each Section. By creating a separate distinguished editorial board responsible to an editor-in-chief for each section, it seems likely that the attraction of the journals for papers of the greatest scientific merit and significance would increase.

3. Financial Significance for the Society. This matter will be explored in detail by the Publications Committee if the concept of sectionalization plus current abstracts is attractive to the membership. In general it seems reasonable to anticipate that an expanded journal of excellence in physiology would continue to remain attractive to the subscribers, particularly to libraries and institutions.

4. Cost to Members. The current subscription rates for Society members are $30.00 for the American Journal of Physiology and $22.50 for the Journal of Applied Physiology. It seems reasonable to expect that the cost for each specialty journal would be not more than the mem-

bers' rate for AJP. Each member would have the option of subscribing to one or more sections. As mentioned above, it is anticipated that the abstracts journal could be provided to our members as part of the Society membership. As with other financial implications, this aspect will be explored in detail if the idea of sectionalization and current abstracts is enthusiastically received.

5. Implications for Information Retrieval. Careful consideration would be given to a key-word classification system that would serve our authors and readers most effectively.

Summary

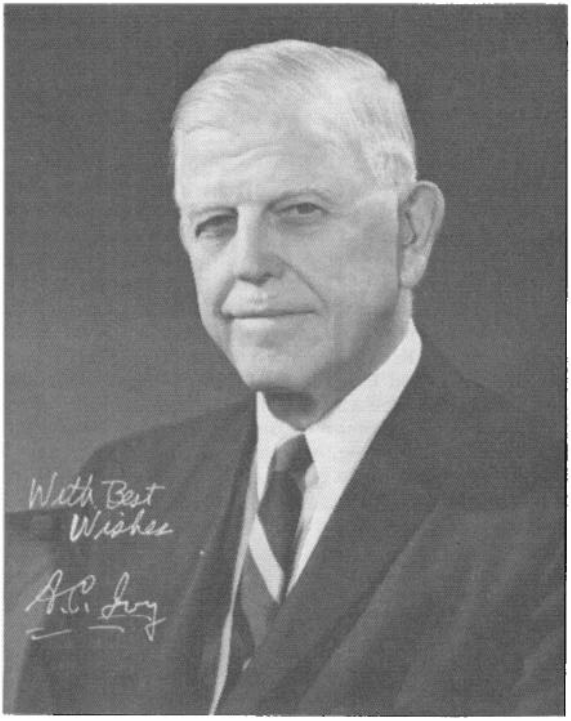
After exploring many alternatives for improving the quality of its publications, the Publications Committee has focused on two major journals, the American Journal of Physiology and the Journal of Applied Physiology. The Committee is currently considering two alternatives: continuation of the present organization of the two journals or a modification that would consolidate the two journals, issued as seven or more specialty journals. In the "new journal," which would carry the general title "American Journal of Physiology" (or a modification thereof to incorporate the Journal of Applied Physiology), a comprehensive overview of the contents would be provided by a serial publication of abstracts of all papers published in the various sections.

Publications Committee

Peter F. Curran, Chairman
Alfred P. Fishman
Paul Horowicz

ANDREW C. IVY

1893 -



A recent photograph of Dr. Ivy.

Dr. Andrew Conway Ivy was elected President of the Society at its fifty-first meeting in Toronto in 1939. He had served as Secretary for the previous five years.

He was born in Farmington, Missouri, on February 25, 1893. The family soon moved to Cape Girardeau, Missouri, where his father, Henry McPherson Ivy, was Professor of Chemistry at the State Normal School. Ivy's first research was done while a student at that school. The area was psychology and the topic of one study was "The Effect of Disciplined and Undisciplined Play on Post-recess Conduct in Fifth Grade Students." In 1913, at age 20, he received the Bachelor of Arts and Bachelor of Pedagogy degrees. He already had decided to study medicine but did not have enough money, so he took a position as principal and coach of athletics at a high school in Clarksdale, Mississippi. In two years he saved enough money to resume his education. In 1915 he entered the University of Chicago, a school he selected because his father and brother had attended it and because he thought that he could get a part-time job there.

At the University of Chicago he quickly fell into the orbit of Anton J. Carlson, a legendary figure who was popularly referred to by the appropriately legendary name of Ajax. Carlson directed Ivy's interest to gastrointestinal physiology which was to remain the focus of his career. The research studies for his master's degree (M.S., 1917) and doctorate (Ph.D., 1918) were in gastric physiology. While completing the work toward the M.D. degree (Rush Medical School, 1922) he was Instructor in Physiology at the University of Chicago (1917 to 1919) and Associate Professor of Physiology at Loyola University School of Medicine (1919 to 1923).

He returned to the University of Chicago as Associate Professor of Physiology for two years, 1923 to 1925, and then was called to the chair of Physiology and Pharmacology at Northwestern University as Nathan Smith Davis Professor where he remained until 1946. From 1946 to 1953 he was Vice President of the University of Illinois in charge of the Chicago professional colleges; this was the period of most rapid growth of this great medical center. In 1953, amid the much publicized controversy over his work on Krebiozen, he resigned the Vice Presidency and continued as Distinguished Professor of Physiology and Head of the Department of Clinical Science at the University of Illinois. From 1961 to 1966 he was Research Professor of Biochemistry at Roosevelt University. Since 1966 he has been working, seven days a week as usual, at the Ivy Cancer Research Foundation, a privately supported organization with offices and laboratories in the heart of Chicago's loop. Since 1962 his research has been devoted exclusively to the body's defense mechanisms against cancer.

The pattern of many irons in many fires began early and persisted. In college Ivy played second base in baseball, competed in cross country track, played quarterback and defensive end in football, performed gymnastics, was on the basketball team, played tennis, wrestled, and boxed. ("I could stand up to anyone in my weight, 135 pounds. I defeated 'all comers' in the sixth regiment of Missouri in 1909.") He played violin in the college orchestra and helicon bass in the college band. At the University of Chicago he was on the debating team and sang second tenor in the University choir and glee club. The income helped him study medicine. While interning at two hospitals he taught physiology at two medical schools and conducted a large research program. And so it went. Throughout his long career he has often held several major positions simultaneously. He thrives on work.

In 1919 Ivy married Emma Anna Kohman who also received her Ph.D. in physiology from the University of Chicago. She has stood beside him literally and figuratively, always helping when needed, always stalwart. Their five sons are all in medical activities, four as doctors, one with a pharmaceutical company.

Between 1919 and 1955 Ivy and his coworkers published more than 1500 papers, an average of more than 40 papers per year for more than 35 years. Science Citation Index shows that during the period from 1964 to 1971 Ivy's articles were cited more often than any other scientist in the world. His work covered almost every aspect of gastrointestinal

physiology. Some contributions have come to be regarded as classics. Examples include the introduction of subcutaneously transplanted organs to prove the existence of humoral mechanisms for gastric and pancreatic secretion, the discovery of the hormone cholecystokinin, the discovery of urogastrone, and the elucidation of the effects of total gastrectomy in animals. Few know that Ivy had deep and continuing interests in several areas outside of gastroenterology including physiology of the uterus in labor, experimental intersexuality, aviation medicine, artificial respiration, cardiac pain, preparation of fresh water from sea water, protection from flash burns, and treatment of typhoid carriers. He introduced the "Ivy bleeding time", a procedure still in use for diagnosing clotting abnormalities. His book on "Peptic Ulcer" with Doctors Grossman and Bachrach is an internationally recognized text book.

Unknown to many physiologists, Dr. Ivy has worked on the physiological aspects of cancer since 1917. As a result of observations on dogs with cancer of the thyroid, he developed the hypothesis that the body of multicellular animals contains an "anticancer substance" (or substances) which is involved in the prevention of cancer and body resistance to cancer, and that it should be possible to concentrate and isolate the substance. He believes the substance to be present in all cells and especially in reticuloendothelial cells. He calls this substance "carcalon." The existence in the liver of animals of an ether-soluble substance which inhibits the growth of breast tumor in C3H mice has been recently confirmed. (L. C. Strong: Cytobios: 5, 119-124, 1972).

Dr. Ivy considers the training of physiologists and gasteoenterologists as his greatest contribution. More than 300 of his academic offspring are teaching in medical schools throughout the world; many hold high academic positions. Dr. Ivy always regarded teaching as his first responsibility. ("It is the duty of those who know to teach.") As with all to which he addressed himself, he put everything he had into it. He has inspired many students.

Dr. Ivy has held many high positions, only a few of which are mentioned here. He was founder and Scientific Director (1942 to 1943) of the Naval Medical Research Institute, and Executive Director of the National Advisory Cancer Council from 1947 to 1951. He was President of the American Gastroenterological Association in 1940. He engineered the founding of that Association's Journal, Gastroenterology, and served a decade (1942 to 1952) as its first managing editor.

Dr. Ivy has received many honors. A sampling: five honorary Doctor of Science degrees, one honorary Doctor of Laws degree, the Distinguished Alumni Award of the University of Chicago, and The Certificate of Merit from the President of the United States.

A man of action, Andrew Ivy has given more than verbal support to humanitarian causes in which he believes. He was for many years the prime mover and, in many instances, the founder of organizations devoted to humane goals such as eradication of tuberculosis, prevention and treatment of alcoholism, elimination of discrimination in higher education, and protection of animal research against antivivisectionism.

He was principal consultant at the Nuremberg Tribunal on War Crimes and he formulated a code of conditions for use of human subjects in medical experiments that foreshadowed the Declaration of Helsinki.

He was Chairman of the Board of Publication Trustees of the Society from 1945 to 1948. In the latter capacity, he was responsible for "discovering" Dr. Milton O. Lee and persuading him in 1947 to take Dr. Donald Hooker's place as Managing Editor of the Journals of the Society.

Dr. Ivy's term as President was the last undisturbed prewar period. He presided at the meetings in New Orleans in 1940 and in Chicago in 1941.

Dr. Ivy is known to be a man of much determination and courage. Physiologists who worked with him closely have a warm friendship with him and know him as a man of high ideals and broad vision, with a wide knowledge of physiology and much wisdom and skill as an executive. In Chicago, he was particularly vigorous and effective in the defense of the use of animals for medical research. He attends meetings of the Society and has worked long and faithfully for the Society and its publications and for the advancement of physiology.

Taken from "History of the American Physiological Society - The Third Quarter Century 1937-1962" by Wallace O. Fenn and from "Presentation of the Julius Friedenwald Medal to Andrew Conway Ivy" by Morton I. Grossman (Gastroenterology 58: 747-749, 1970).

AMERICAN INDUSTRIAL HYGIENE ASSOCIATION

The American Industrial Hygiene Association will hold its annual conference on May 12-17, 1974 in Miami, Florida, at the Hotel Fontainbleau. During the conference, the AIHA Ergonomics Committee will sponsor three paper sessions. These papers may be of interest to members of the American Physiological Society. A copy of the complete AIHA program may be obtained from Mr. William E. McCormick, Managing Director, American Industrial Hygiene Association, 66 S. Miller Road, Akron, Ohio 44313.

PERKINS MEMORIAL FUND COMMITTEE

Report of First Six Years of Operation and Discussion of Future Program

The John F. Perkins, Jr. Memorial Fund was established in 1967 to promote cultural and scientific benefits associated with international aspects of Physiology. The initial gift from the Perkins family has been supplemented annually by relatives and friends of Dr. Perkins with a view to providing sufficient capital endowment to permit operation of the Memorial from investment income. The funds are given to, and administered by the American Physiological Society. Responsibility for planning programs supported by the Fund is vested in the Perkins Memorial Fund Committee, which consists of two Past-Presidents of the American Physiological Society, two of its current councilors and one member of the Perkins family. The Executive Secretary of the Society is a member of the Committee, ex officio. Drs. Pappenheimer and Rahn agreed to guide the Committee during the first six years of operation and Mrs. John Perkins has been of constant help on behalf of the Perkins family. Members of Council who have rotated through the Committee were or are, Drs. Forster, Brobeck, Knobil, B. Schmidt-Nielsen and Selkurt.

The initial program adopted by the Committee provides supplementary aid to families of foreign scientists who are to work in the United States. John Perkins had noted that fellowships, research grants or sabbatical salaries were often inadequate to permit young physiologists from abroad to bring their families with them to the United States. The program initiated by the Memorial Committee was therefore designed to enable young scientists to bring their families and thus make full use of the cultural, as well as the scientific benefits associated with international exchanges. The program is unique in that it pre-supposes that the visiting scientist and his host have already made arrangements for scientific collaboration, and have sufficient funds to cover the needs of the visiting scientist himself. Application to the Perkins Fund is then made jointly by host and visitor to provide the extra amount needed to bring the family of the visitor and to encourage their participation in cultural and social activities.

From 1968-1974, the Fund has assisted the families of 13 physiologists from 9 different countries. Almost from the beginning, it became clear that relatively small sums were sufficient to make it possible for the applicant to bring his family, and in several cases the applicants would have decided not to come at all without their families. The average award has been about $3,000 and the total expenditures of about $40,000, spread over 6 years have already made possible a year of family-life in this country for more than 50 foreign guests, including the children. A brief description of each award is given in Table I.

TABLE I

FELLOWSHIP AWARDS 1968-1974

Recipient	Number of Children	Home University (Country)	Host (University)	Year of Tenure
Dr. & Mrs. A. Chinet	1	Switzerland	Farhi (Buffalo)	68-69
Dr. & Mrs. R. Holland	4	Australia	Forster (Penn.)	69-70
Dr. & Mrs. K. Norum	3	Norway	Glomset (Washington)	69-71
Dr. & Mrs. S. Nosaka	2	Japan	Wang (Columbia)	69-70
Dr. & Mrs. D. Denison	3	England	West (California)	70-71
Dr. & Mrs. Y. Ohta	3	Japan	Farhi (Buffalo)	70-71
Dr. & Mrs. J. Wieth	2	Denmark	Tosteson (Duke)	70-71
Dr. & Mrs. J. Kay	2	England	Grover (Colorado)	71-72 Sept.
Dr. & Mrs. D. Robertshaw	0	Nairobi	Taylor (Harvard)	1972
Dr. & Mrs. K. Pleschka	3	W. Germany	Wang (Columbia)	72-73
Dr. & Mrs. M. Zade-Oppen	2	Sweden	Tosteson (Duke)	72-73 April
Dr. & Mrs. A. Malan	2	France	Rahn (Buffalo)	72-73
Dr. & Mrs. R. Cross	3	Australia	Barger (Harvard)	73-74 Sept.

Evaluation of Initial Program (1968-1974)

An informal written report has been requested of each recipient. These reports, written in narrative style, describe both the professional and social activities of the recipient, together with comments on long term effects, such as continuing correspondence with friends made in this country, and reactions of children on returning home. Our initial intention was to ask for this report two years after the family had returned home; the reason for this delay was to allow time for the scientific work to reach full fruition, and for the initial glow of excitement of travel to be replaced by some feeling for the long term benefits.

So far, we have received 8 such reports, of which two were written spontaneously before receiving our request. These reports, together with informal photographs, which accompany them, are filed at the APS Headquarters; some of them will undoubtedly be of special interest to physiologists of the future. All responses, written or verbal, have been highly favorable - both from recipients and hosts. Most of the 13 recipients have published one or more technical articles based on work accomplished during the visit, and some have reported that their research and subsequent professional orientation have been profoundly influenced as a result of their visit. A recent recipient has suggested forming an association of past-Perkins Fellows to meet every three years at the International Congress of Physiology. At least one Perkins Fellow has made arrangements for a young United States scientist, whom he met here, to spend a year abroad. There seems little reason to doubt that all of the Fellows, thus far, have established warm relationships with people in this country, and that these will be of an enduring nature.

Continuation of Initial Program

Since no doubts have been expressed about the value of the present program, there seems no reason to alter it in any essential way. If the Fund continues to make possible visits by two scientists and their families each year, it seems obvious that in the course of time, the program will have a very significant impact on the world of international physiology and perhaps, via the children, in other fields as well.

Nevertheless, the Committee is considering ways to improve the present mode of operation of the Program. Three suggestions have been made and approved by members of the Committee.

1) Extension of awards to U.S. Physiologists who are planning to work abroad for a year. The need for this type of support has developed during the past few years, owing partly to reduction of Federal Funding in this country and partly to devaluation of U.S. currency. Supplementary support in the range of $3,000-$5,000 may be a decisive factor in making possible a highly productive year abroad for a U.S. physiologist and his family. The Committee will therefore consider applications made jointly by U.S. physiologists and their foreign hosts.

2) Announcing the Perkins Awards. Except for initial announcements in 1968 in "The Physiologist" and in "Respiration Physiology", the availability of the Awards has not been widely disseminated. This was intentional because the program was experimental; most of the awards were associated with hosts who knew John Perkins personally, and who were known by members of the Committee to be sympathetic with aims of the Memorial. With six years of experience behind us, it now seems appropriate to emphasize the availability of the Fellowships to a broader group, both here and abroad. This can be done partly through publication of the present report in "The Physiologist" and partly through IUPS and Secretaries of foreign physiological societies.

3) Establishment of a Memorial Lectureship at the Triennial Meetings of IUPS. For this purpose the Perkins Committee would be authorized to withdraw a sum of the order of $1,000 every 3 years to support an IUPS lecturer. Selection of the Lecturer (from any nation) would be entrusted to Council of IUPS. Dr. Rahn will discuss this possibility at the next meeting of IUPS Council in Stockholm.

Mrs. J. F. Perkins
Dr. H. Rahn
Dr. B. Schmidt-Nielsen
Dr. E. Selkurt
Dr. O. Reynolds
Dr. J. R. Pappenheimer, Chairman

NATIONAL CONFERENCE ON THROMBOSIS AND HEMOSTASIS

A National Conference on Thrombosis and Hemostasis will be held in Dallas, Texas, November 20-22, 1974 sponsored by the Council on Thrombosis of the American Heart Association.

The meeting will provide a national interdisciplinary forum for the discussion of new scientific and medical advances relating to the problems of thrombosis and hemostasis.

Symposia are planned on the Relationship Between Thrombosis and Atherosclerosis; Initiation Mechanisms of Coagulation; Thrombosis Regulating Mechanisms; Prosthetic Devices, Surfaces and Thrombogenesis; and Thrombotic Disease: Diagnosis and Therapy.

Workshops involving specific problems in blood platelets, coagulation, and immunology are included in the program. Abstracts will be solicited for free communications. All interested are invited to attend. No registration fee is required for members of the Council on Thrombosis or for those registered for the Scientific Sessions of the American Heart Association. All others will pay a registration fee of $50. For further information and for abstract forms write to Section on Scientific Programs, American Heart Association, 44 East 23rd Street, New York, New York 10010.

EIGHTEENTH BOWDITCH LECTURE

Motor Aspects of Cerebellar Control

RODOLFO LLINÁS
Division of Neurobiology
Dept. of Physiology & Biophysics
University of Iowa, Iowa City

A tacit assumption in the design of most single cell neurophysiological research is the tenet that the electrical activity displayed by single elements must ultimately explain all behavioral responses of animals. While this assumption has been accepted a priori as a central working hypothesis by neurobiologists, not until recently has sufficient information regarding the properties of nerve circuits been available to allow its verification. One area where this assumption can now be seriously tested is the cerebellar cortex.

Among all regions in the central nervous system (CNS), the cerebellar cortex is probably the best known from anatomical, physiological, and developmental points of view. The majority of the cellular elements comprising this cortex are well characterized morphologically at light and ultrastructural levels, as well as electrophysiologically at intra- and extracellular levels (26, 53). The question now at hand is whether we can correlate, in some way, the activity of these elements with the more holistic properties of the nervous system: specifically, can we correlate the electrical activity of the neuronal circuits in the cerebellum with the regulation of movement? - allegedly one of the functions of the cerebellum (cf. 67).

The cerebellum is regarded today as a set of central nuclei comprising vestibular and reticular relays as well as the cerebellar nucleus proper, superimposed on which there is a two-dimensional sheath of organized cellular elements - the cerebellar cortex. The interplay between the cerebellar cortex and its central nuclei is believed universally to constitute the crux of cerebellar function. Thus, while all excitation mediated through the cerebellum must of necessity be relayed through the cerebellar or vestibular nuclei, it is also correct that these cerebellar nuclei must at all times be under the influence of the cerebellar cortex - one of the most sophisticated neuronal circuits in the CNS.

Given that the cerebellar nuclei and cortex probably receive matching sets of information (68, 69), it may be assumed that these nuclei function as a set of sequencing and distribution relays, capable of channeling afferent activity towards the forebrain, the brain stem or the spinal cord. On the other hand, related afferent information reaches the cerebellar cortex directly and is integrated with inputs from other areas of the CNS before being poured back, as an inhibitory barrage (45, 46), onto its nuclei. In the final analysis, the cerebellum may be viewed more as an in-line corrective filter, rather than as a site for the initiation of motor commands.

General Morphological Organization of the Cerebellar Circuits

Morphologically the cerebellar input has been divided into two categories: 1) input to the central nuclei, and 2) input to the cerebellar cortex. The central nuclei receive collaterals from cerebellar cortical afferents arising from the forebrain, the brain stem and the spinal cord (5, 68, 69) and project, via the superior and inferior cerebellar peduncles, to different regions of the brain stem and thalamus (5, 25, 47, 80).

The cortex itself can be described as a sheath of neurons having, in humans, dimensions 120 cm in length and 17 cm in width (16), folded in an accordion-like manner to form the so-called cerebellar folia. This sheath of cells - one of the few neuronal structures which are continuous through the midline of the brain - is comprised of three main layers; the most superficial, the molecular layer, has a thickness of approximately 400 μ from the surface of the pial-glial membrane to the Purkinje cell layer. The Purkinje cell layer is one cell deep. The third strata is the granule cell layer of 200-300μ depth. Next to the granular layer lies the cerebellar white matter, which represents the efferent and afferent paths of the cerebellar cortex.

Among the truly outstanding morphological characteristics of this cortex is the stereotyped form and synaptic organization of its neuronal elements, throughout its extent (80). The granule cell layer receives one of the two main afferents to the cerebellar cortex - the mossy fiber system (35, 38, 41, 43, 57, 80) (Fig. 1). This granule cell layer projects into the molecular layer and bifurcates in a T-fashion to generate the so-called parallel fiber (PF) system (80). These PFs run parallel to each other and contact all of the elements in the cerebellar cortex: Purkinje cells, interneurons of the molecular layer: the basket and stellate cells, and interneurons of the granule cell layer: the Golgi cells (Fig. 2), throughout the phylogenetic scale (22, 36, 38, 39, 42, 43, 48, 71, 80, 91).

The Purkinje cells are themselves rather unique. They are probably the largest neurons in the CNS; in the cat they receive as many as 60, 000 to 80, 000 synaptic inputs from PFs (75, 89). They are also unique in their dendritic arborization, being close to isoplanar in an orthogonal sense with respect to the direction of the PFs. The other neuronal elements in the molecular layer are the basket and stellate cells (80); their axons run at right angles to the PFs and establish contact with the soma and dendrites of Purkinje cells (19, 21, 35, 40, 42, 43, 71, 80, 91) and have an inhibitory action on this neuron (3, 29, 31, 58, 59, 73). PFs also contact Golgi cells which produce inhibition of the mossy fiber and granule cell synapse in a manner resembling the feedback inhibitory system (30, 58) as well as a feedforward inhibitory system via mossy fiber collaterals (20, 28, 41, 57, 71) directly on Golgi cell dendrites.

The second input to the cerebellar cortex is represented by the climbing fiber system (Fig. 1). This extremely straightforward afferent system establishes a one-to-one monosynaptic contact with the Purkinje cell (i.e. one climbing fiber per Purkinje cell) (80). This junction is rather remarkable, inasmuch as a single climbing fiber may generate as many as 300 synapses on a given Purkinje cell dendritic tree (56). The synapses

are generated via spinous junctions (42, 48, 51, 71, 91). The climbing fiber systems also sends collaterals to Golgi and basket cells (15, 19, 28).

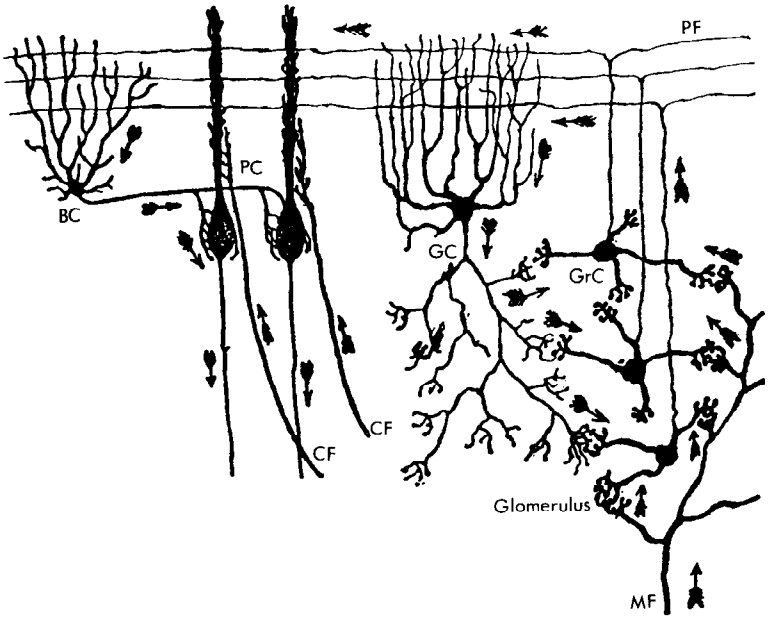


Fig.1. Drawing of cerebellar neuronal circuits. The mossy fiber (MF) enters in contact with granule cell (GrC) dendrites via the glomerulus. Granule cell generates an ascending axon which divides to form parallel fibers (PF) which contact Golgi (GC), basket (BC), stellate and Purkinje cells (PC). Second afferent system, shown to the left, is a monosynaptic contact between an ascending climbing fiber (CF) and the dendrites of a Purkinje cell. The direction of "nervous conduction" is as indicated by the original arrows. (Modified from Ramón y Cajal, 80).

Functional Significance of the Climbing and Mossy Fiber Systems

Rather than attempting to review the many hypotheses available today regarding the functional significance of these two afferents (cf. 54, 67), I would prefer to describe two sets of experiments which may give some insight into the functional properties which characterize these two systems.

a) Climbing fiber system

Both anatomically and physiologically, it is known that the climbing fiber (CF) system arises to a great extent from the inferior olivary (IO) nucleus as a form of termination of the IO cerebellar pathway (27, 72, 94). Besides generating the CF afferent system, the olivo-cerebellar

projections send axon collaterals to the cerebellar (4, 68, 69) and Deiters' nuclei (2).

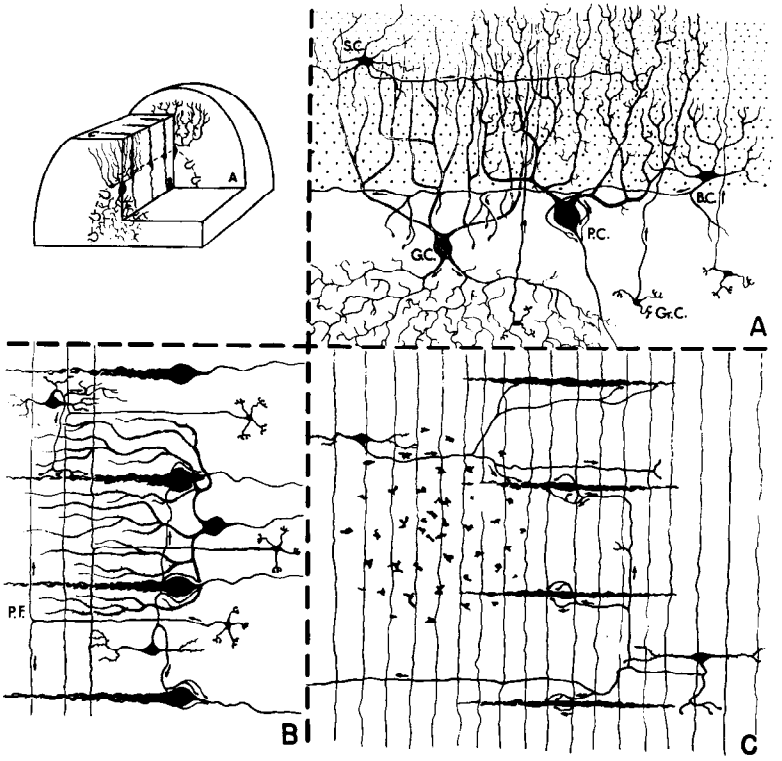


Fig.2. Detail of the geometrical organization of the neuronal elements of the cerebellar cortex. The drawing demonstrates different sections through a cerebellar folium. A: transverse plane; B: saggital plane; C: tangential plane. The cellular elements are displayed in drawings A, B and C respectively, as though the cerebellar cortex were to be transparent. The orthogonal organization of the parallel fibers, with respect to the isoplanar characteristics of the dendrites of Purkinje cells and basket and stellate cells, are self-explanatory. Note that the axons of the basket and stellate cells run at right angles with respect to parallel fibers and the dendritic tree of Golgi cells is close to cylindrical rather than isoplanar. BC, basket cell; GC, Golgi cell; GrC, granule cell; PC, Purkinje cell; PF, parallel fiber; SC, stellate cell.

i) Harmaline activation of the climbing fiber system. Though little is known regarding the functional properties of the CF afferents, the recent discovery that harmaline may uncover a rhythmic firing in the IO system in a more or less specific manner is indeed rather significant (50, 61, 70). The fact that harmaline acts through the CF system has recently been demonstrated directly by intracellular recording from

Purkinje cells (61). Following harmaline injection, intracellular recordings from Purkinje cells demonstrate prolonged, rhythmic action potentials in every way similar to those evoked by the electrical activation of the CF afferents (27). An example of such potentials is seen in Figure 3. As will be seen subsequently, these large all-or-none spikes are generated at a rather constant rhythm of 8-10/second.

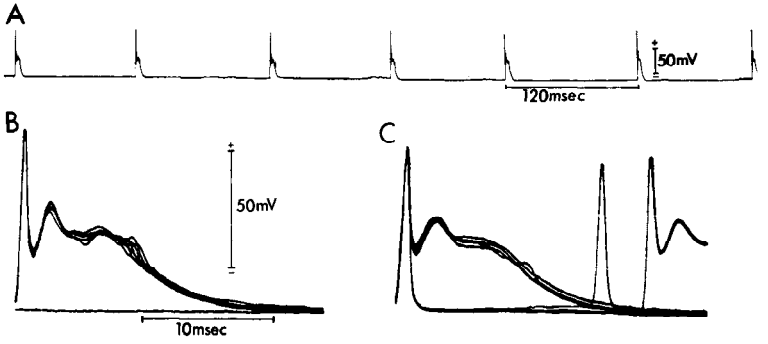


Fig.3. Climbing fiber activation of Purkinje cells following harmaline administration. A: Repetitive activation of Purkinje cells via climbing fiber system, shown at slow sweep speed. B: Same records as in A, but shown at higher gain and sweep speed. The action potential triggered the oscilloscope sweep. In C, several single spikes occurred which allow a direct comparison between mossy fiber generated spike and the typical climbing fiber activation. Amplitude and voltage calibration as indicated. (Modified from 61).

From a purely electrophysiological point of view, harmaline has helped to clarify several details of the organization of the olivo-cerebellar system, both at the cortical and the nuclear cerebellar levels. Cortically, these findings strongly support the assertion that the CF system originates from the IO (27, 72, 94). They further demonstrate that, as originally stated (27), the burst response in the Purkinje cell can be brought about by a single action potential in a CF. Also, the all-or-none character of the CF activation of the Purkinje cell and the chemical nature of the synaptic transmission are now testable using a non-electrical means of rather specific IO stimulation (Fig. 4).

The finding that the bursting activity in Purkinje cells may be recorded for a protracted time, both intra- and extracellularly, has allowed a comparison between duration of intracellular excitatory postsynaptic potential (EPSP) and the spike burst seen extracellularly (Fig. 5). Another point which was readily testable relates to the CF activation of basket cells; however, no clear inhibitory postsynaptic potentials (IPSPs) were observed in Purkinje cells following the CF EPSP. To what extent this is due to lack of anesthesia needs to be determined (14).

As far as the origin of the tremor is concerned, several experiments suggest that the IO is responsible for the genesis of this rhythm. Thus, an inferior peduncle lesion restricted to the olivo-cerebellar pathway

prevents the harmaline tremor as well as the rhythmic activation of Purkinje and cerebellar nuclear cells (61). Similarly, the reticular and vestibular systems and the motoneurons at spinal cord level are also unaffected by harmaline following this lesion. The IO, on the other hand, may continue to show a 10/second rhythmic firing even when this center is isolated from the spinal cord and the rostral brain stem (61). Since the rhythmic activity of the IO remains grossly unmodified following transection of the neuraxis at C-1 cervical level and at pontine level, it has been postulated that harmaline acts directly on the IO cells themselves (61; see below).

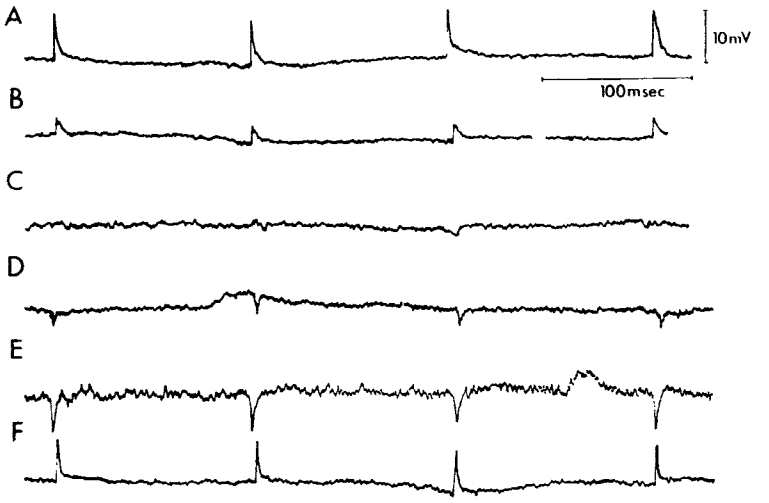


Fig.4. Reversal of climbing fiber EPSP intracellularly recorded from a Purkinje cell. A: "Spontaneous" EPSPs occurring after harmaline injection. B to E: D.C. current injection through the recording electrode generates a depolarization which produces a decrease in the amplitude of the EPSP (B), a disappearance (C) and finally a reversal of the EPSP (E to E). In F the depolarizing direction of EPSP returns after removing intracellular current injection.The current levels from B to E are 10, 20, 30 and 40 nA respectively. (Modified from 61).

In short, three important points arise from the harmaline findings regarding the generation of movement. First, harmaline tremor (1, 70, 86, 97) is accompanied by rhythmic, neuronal activity which involves IO, cerebellar, vestibular, reticular and motoneuronal pools which are capable of carrying a rather phasic motor command (17, 50, 61, 70). Secondly, the IO which initiates this rhythm can generate the tremor only through the activation of the cerebellar nuclei (61). Thirdly, simultaneous recordings from multiple Purkinje cells indicate that the CF afferents generate action potentials in a highly synchronous manner following administration of harmaline. In conclusion, the findingd have been taken to mean that the harmaline tremor may be related to the properties of synchronous firing of IO cells (61). In fact, in a recent

series of morphological and physiological studies in the IO, it has been discovered that IO neurons are electrotonically coupled, indicating that synchronous firing may be a normal tendency for IO neurons (55, 92).

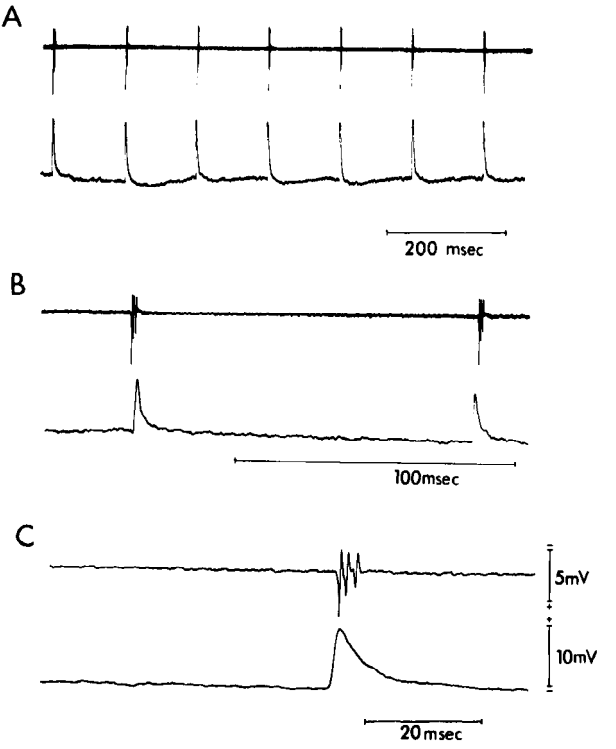
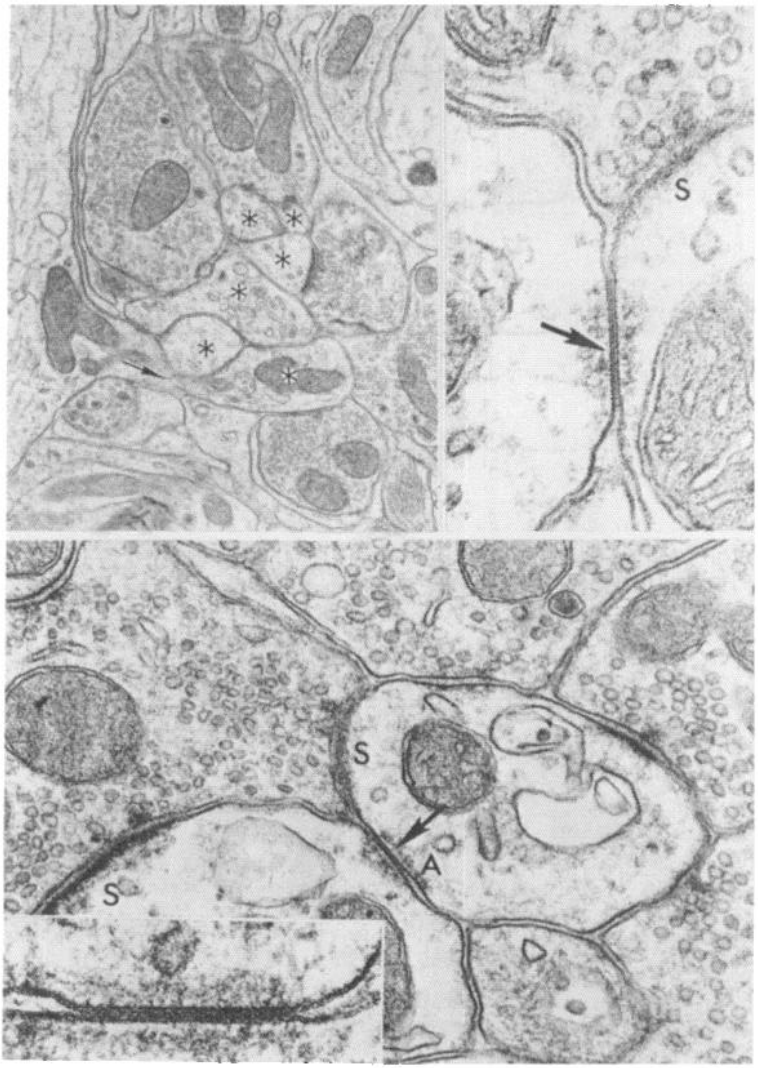


Fig.5. Extra- and intracellular records from a Purkinje cell after harmaline injection. Upper traces in A to C are the extracellular spike bursts which characterize the CF activation of Purkinje cells. The lower traces are intracellular recordings from the same cell demonstrating the all-or-none EPSP produced by the CF activation. The strict rhythmic nature of the CF activation can be observed in A and B. The records in C at higher sweep speed give further details of the intra- and extracellular character of the Purkinje cell response. (Modified from 61).

ii) Morphological and physiological basis for electrical interactions between IO neurons. Following the harmaline experiments, it became apparent that the harmaline action was probably taking effect very near or directly at the IO nucleus. Moreover, harmaline probably acts on all CNS cells; its action is apparently that of blocking sodium pumping (18). If the resting potential of IO neurons is partly maintained by an electrogenic sodium pump and the neurons are electrotonically coupled, the blockage of an electrogenic polarizing mechanism could be sufficient to generate synchronous rhythmic firing in these cells.


S
S
A
S

Interactions observed between IO neurons in previous experiments (27) have indicated that stimulation of cerebellar white matter may generate the so-called "climbing fiber reflex" (i.e. an excitation of cells following antidromic invasion of the IO). Since the synaptic potentials generated by this CF reflex showed an almost perfect synchrony from one stimulus to the next, it was suspected that interaction between olivary neurons had to have a rather high safety factor (27). A likely explanation for this property is to assume that the cells may be electrotonically coupled via gap junctions (11, 12). A recent anatomical study (92) has, in fact, demonstrated that IO cells contact each other by means of the closed membrane appositions (33) known as gap junctions (81, 82). These junctions occur at a specialized region - the glomerulus - formed by the coalition of small dendritic protrusions which approach each other from different IO cells and which are covered by a large number of synaptic terminals (Fig. 6). At high magnification the closed membrane apposition may be seen to display the typical septalaminar structure characteristic of gap junctions which are considered today to be the anatomical basis for electrotonic coupling (12, 76).

The ultrastructure of the IO glomerulus is clearly of interest inasmuch as it may be central in the functioning of the IO and thus in the functional properties of the CF system. The uniqueness of this glomerulus lies in the fact that the electrotonic interactions between IO cells occur through these core dendritic digits. This rather unusual form of coupling suggests, as will be discussed later, an important functional strategy for the electrical interactions. The actual functional properties of this coupling are shown in Figure 7. Here, antidromic invasion of the IO cells following white matter stimulation in the contralateral side of the cerebellum evoked antidromic invasion of the olivary cells. Besides the typical prolonged antidromic action potential (24), this form of stimulation, when subthreshold for antidromic invasion, generates a short latency membrane depolarization at about the same latency as the antidromic spike. In addition to its short latency, this depolarization is characterized by its graded nature (Fig. 8). Extracellularly, white matter stimulation generates an antidromic positive-negative "closed" field potential (64) in agreement with the spatial distribution of the neuronal dendrites in this nucleus (79) and also serves to demonstrate that the short latency depolarization is generated across the neuronal membrane rather than being part

---

Fig.6. Electron micrograph of inferior olivary glomerulus. Upper left corner: Intermediate magnification of inferior olivary glomerulus showing the site of dendritic attachment of side branch forming part of the core of the glomerulus (arrow). The different core branches are marked with asterisks. Surrounding this central core there is a set of synaptic boutons establishing synaptic contact with central core elements. The glomerulus is enveloped by a glial sheath. x 22,000 Upper right corner: Gap junction between two core elements in a glomerulus and a presynaptic bouton establishing a synaptic specialization with one of them (S). x 78,000 Lower right picture: another case of the gap junction between two core elements surrounded by synaptic boutons. x 44,000 Lower left corner: higher magnification of a gap junction illustrating the seven-layered structure of a gap junction. x 140,000 (Sotelo, Llinás and Baker; unpublished observations).

of the extracellular response. Given the short latency of this potential with respect to the arrival of the antidromic volley, as well as its graded nature and its lack of responsiveness to membrane potential changes, it has been concluded that the IO cells are electrotonically coupled (55).

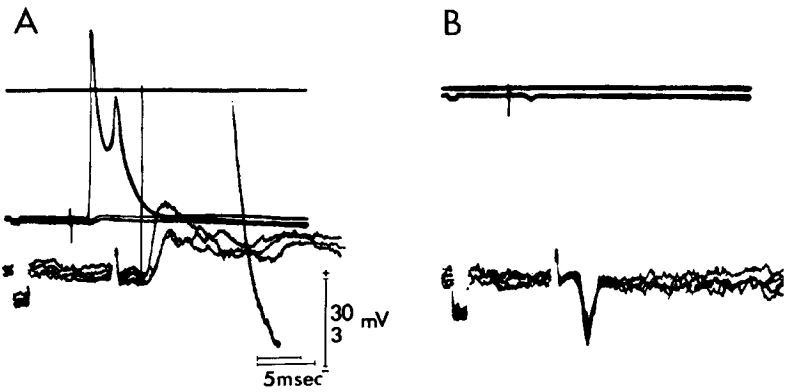


Fig.7. Intracellular recording from inferior olivary neuron. In A: Action potential in inferior olivary neuron following antidromic invasion from cerebellar white matter. Upper trace: reference line. Middle trace: low gain, D.C. recording. Lower trace: capacity coupled recording at higher gain. Following white matter stimulation, a short latency depolarization is seen when the activation is subthreshold for antidromic spike initiation. Note the prolonged nature of the action potential which characterizes inferior olivary spikes. In B an extracellular field potential was recorded immediately outside the cell to illustrate the size of the antidromic field potential seen extracellularly. Middle trace shows the D.C. shift as the electrode leaves the cell. Upper time calibration refers to D.C. recording. (Llinás, Baker and Sotelo; unpublished observations).

The presence of this coupling interaction between IO cells thus implies that the CF system may work, at least under certain conditions, as a highly synchronous input (10). Moreover, since the CF system is, from the viewpoint of connectivity, very strictly organized even from early ontogeny, its neuronal circuits must be considered rather rigid in their manner of operation. Given that each IO cell generates a certain number of CF terminals (each of which has under its command a given Purkinje cell) as well as collaterals to cells in the cerebellar nuclei, for every action potential in the IO cell a prespecified set of cerebellar neurons should be activated. The presence of coupling in the IO would further characterize the afferent system as a close-to-hardwired deterministic input where particular sets of cerebellar nuclei-Purkinje cell units - not unlike the motor units in skeletal musculature - may be recruited together.

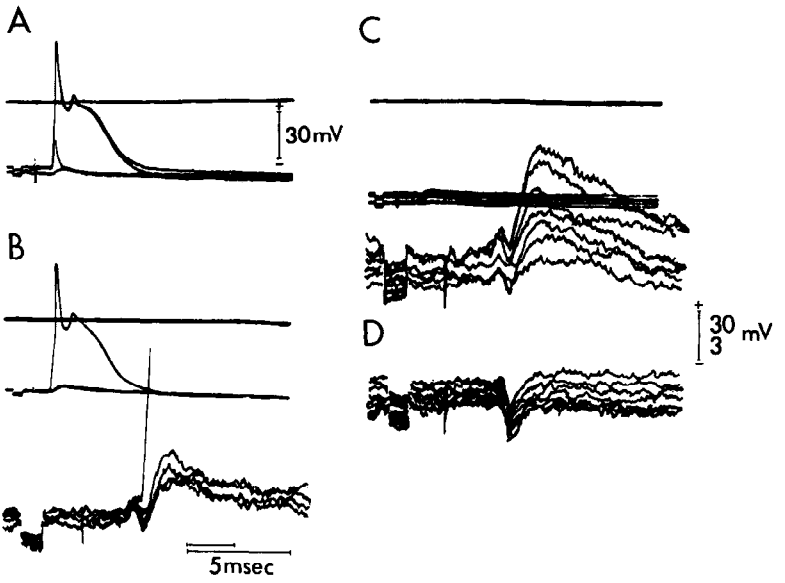


Fig.8. Graded nature of the short latency depolarization in inferior olivary neurons. The recording paradigm is the same as utilized in Fig. 7. A: Antidromic activation of IO neuron showing full antidromic spike as well as an IS-SD break. Note, as in previous figure, the rather prolonged nature of the antidromic spike. In B, as in A, a threshold activation demonstrates a short latency depolarization occurring almost simultaneously with antidromic invasion. This is especially clear in the high gain lower trace. In C, a hyperpolarization of the cell prevents antidromic invasion. (Note D.C. shift in C.) Under these conditions, an increase of the amplitude of the antidromic stimulus produces a graded short latency depolarization across the neuronal membrane. D: Extracellular field potential recorded in the immediate vicinity of the penetrated cell. Upper time calibration refers to D.C. recording. The lower time calibration in B refers to high gain records (B,C and D). (Llinás, Baker and Sotelo, unpublished observations).

The actual synchrony and timing for the activation of these units would thus be determined not only by the input to the IO cells but also by the degree of coupling between these neurons. In this respect, the strategic location of synapses onto the glomerulus strongly suggests that, as reported by Spira and Bennett (93) in Navanax, a certain amount of modulation of electrical coupling may result (Fig.9). Thus, while an input may activate directly a number of IO cells, a second input, or an elaboration of the first, may modulate the electrotonic interactions between the IO cells (55). The advantage of having variable electrotonic coupling is easily understood; it allows the generation of a large number of functional patterns by a rather stereotyped set of neuronal networks.

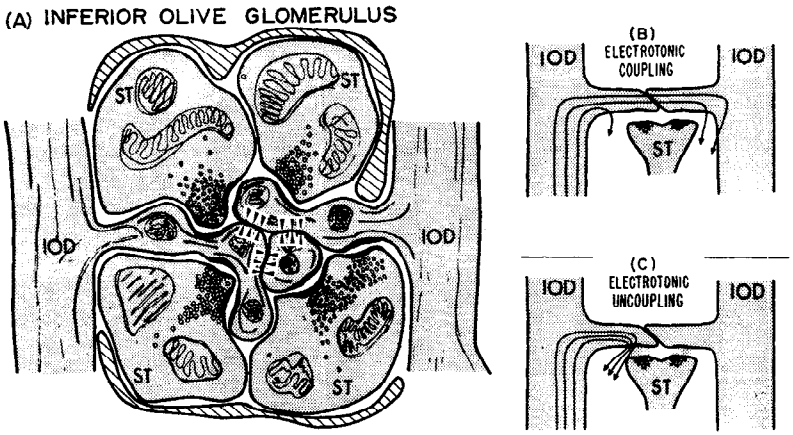


Fig.9. Diagram of the inferior olivary glomerulus. (A) General organization of the IO glomerulus. In the central core, dendritic branches are seen coupled by means of gap junctions (arrowheads). The central core is surrounded by synaptic terminals (SD) which establish contact with the core elements. (B) Illustrates the path of coupling current between two IO neurons. (C) Indicates hypothetical function for the synaptic junction at the glomerulus. When the synapses are activated, the conductance change produced by the synaptic transmitter action on the postsynaptic membrane produces a shunt at the glomerular level which reduces the coupling coefficient between the cells, since the current tends to be lost across the shunt.

In summary, regarding the motor properties of the olivo-cerebellar system, both the harmaline study and the research on the electrical properties of the IO suggest that the IO generates the activation of a particular set of neurons in the cerebellar cortex and nucleus, which in turn would have under their command, via vestibular and reticular pathways, a particular set of motoneurons at the cranial and spinal cord levels (Fig. 10). Since groups of cells in the IO may generate CF afferents which distribute in long sagittal zones (74), the IO clusters may be regarded as organized in particular motor sequences involving large parts of the body and utilizing Purkinje cells in a rather fixed manner.

Although little has been done regarding the truly physiological meaning of the CFs as far as common behavioral tasks are concerned, recent experiments (87) utilizing the visual CF projection to the vestibulo-cerebellum (66) suggest that this CF system is involved in the slow optokinetic responses which characterize eye movement in the rabbit. This hypothesis is based on results demonstrating that the CF system transmits direction-specific information with a maximal sensitivity at image velocities of about 0.5°/sec (Fig. 11). In this particular case, Simpson and Alley (88) proposed that the CF system serves as a movement detector used to establish retinal image position.

In the final analysis, however, several questions continually arise which must be solved before we can say that we understand the functional role of the CF system in a truly holistic sense. Probably among the most disappointing results arising from cerebellar electrophysiology has been

the almost total lack of correlation between CF activity and measurable behavioral acts. In most experiments done to date, the results have indicated a sensory involvement (32, 60, 78) of the CF system as well as a correlation with motor responses (95, 96). However, no concrete results have been obtained which relate the CF input with a measurable behavioral event in the unanesthetized vertebrate. This is true for both motor as well as perceptual functional correlates.

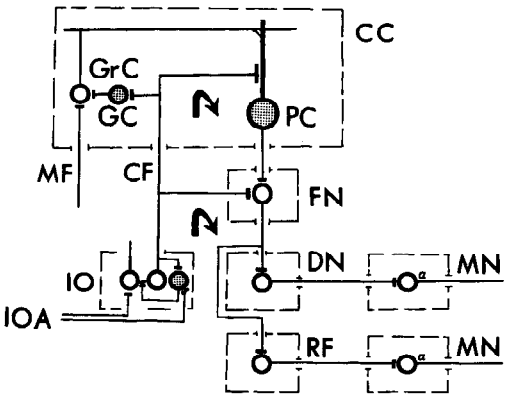


Fig.10. Inferior olivary pathway activated by harmaline. IO, inferior olive. Two IO cells are shown coupled. IO has collaterals which terminate in inhibitory interneurons (dotted screen) that produce recurrent inhibition and probably intervene in the cerebellar glomerulus. IO afferents (IOAs) terminate in IO cell proper as well as in the inhibitory interneurons. IO cells project to the cerebellum via the IO pathway, send collaterals to the fastigial nucleus (FN) and then terminate in the cerebellar cortex as climbing fibers in contact with Purkinje cells (PC). Through the Scheibel collaterals, they also contact Golgi cells (GC). Climbing fiber activation of the Purkinje cell produces at the fastigial nucleus an inhibition which follows the early excitation generated by the IO collaterals. Fastigial nucleus axons terminate on the Deiters' nucleus (DN) and reticular formation (RF) and, through them, on alpha motoneurons (MN) in the spinal cord. There are two levels of integration which occur following activation of a single IO cell: The recruitment of FN neurons by means of collaterals (lower arrow) and the inhibitory control of FN neurons by the cerebellar cortex through Purkinje cell axons (upper arrow). The FN generates movement through the spinal projection of vestibular and reticular pathways.

b) Mossy fiber system

As opposed to the CF afferents, the mossy fiber (MF) afferents are apparently organized in a functionally flexible manner where, rather than the stereotyped connectivity found in the one-to-one CF Purkinje cell synapse, a given fiber relays information to many thousands of glomeruli; furthermore, man may have as many as 200,000 PF inputs per Purkinje cell (34). A computer reconstruction (44) of a Golgi-stained alligator Purkinje cell can be seen in three different planes (Fig. 12). * The isoplanar character of the Purkinje cell ensures that

*This technique, which was developed in this laboratory, employs a PDP-15 (DEC) computer and graphics system and a Quantimet 720 (IMANCO) image analyzing computer system, Programs were developed by Mr. Michio Chujo. The approach is in some ways similar to that utilized by Wann et al. (98).

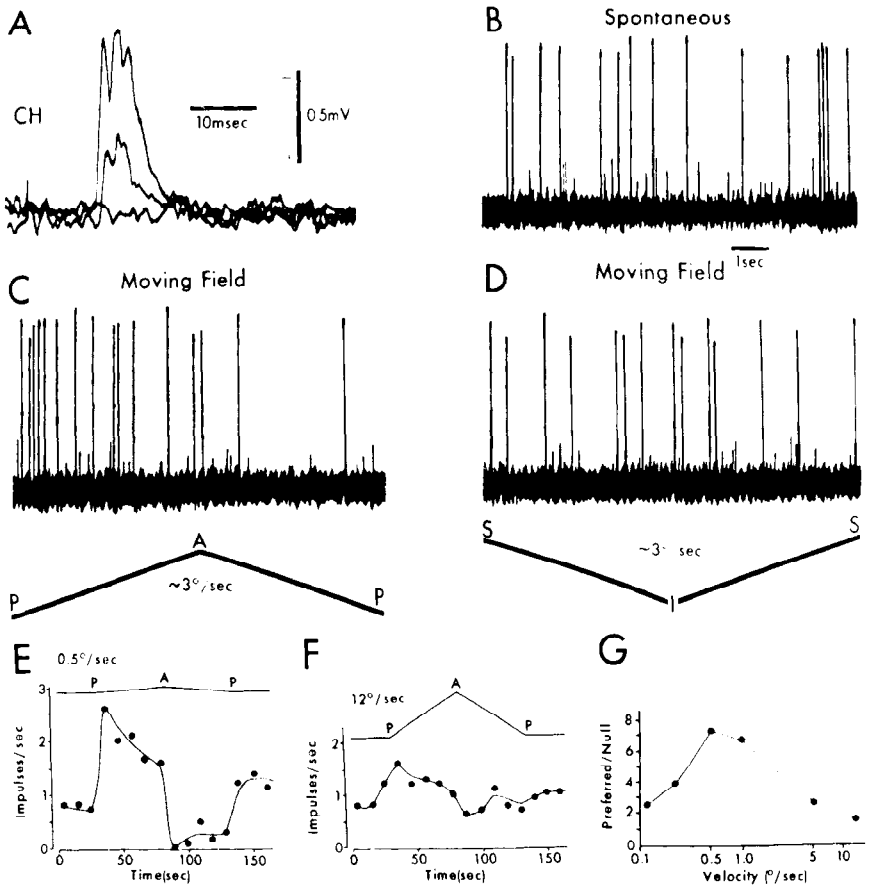


Fig.11. Climbing fiber activation of Purkinje cells in the rabbit, via moving visual targets. A: Characteristic extracellular climbing fiber activation of Purkinje cells following chiasmic stimulation. B: Spontaneous activity demonstrated by climbing fiber responses in the absence of moving stimulus. C: Increase in the number of climbing fiber responses produced by movement of the visual target, a large (100°) random pattern, from posterior to anterior in the visual field (approx. 3°/sec). Movement in the opposite direction (from anterior to posterior) produced a reduction of the climbing fiber response. In D, movement of the same visual target from superior to inferior (from S to I) or from inferior to superior (from I to S) produced no change in the climbing fiber response. In E and F: plot of frequency of climbing fiber response versus time when a visual target was moved at different velocities by means of motorized projector. In E, movements from posterior to anterior with a velocity of 0.5°/sec produced a marked increase in frequency of action potentials while movement from anterior to posterior produced a marked decrease of the response. In F, for the same unit as E, a velocity of 12°/sec generated a clear but smaller response. G: Plot of the ratio of frequency of climbing fiber responses produced by movement of the visual target, (posterior to anterior)/(anterior to posterior) for various target velocities. Note that the ratio (and thus the sensitivity of the climbing fiber response) was maximum at a velocity of 0.5°/sec and decreased with higher and lower velocities. (Simpson and Alley; unpublished observations).

the cell should see as many PFs as possible within the spread of its dendritic tree (maximum convergence). The fact that each particular PF establishes one or probably two synaptic contacts with each Purkinje cell ensures that the cell receives information from as many PFs as possible (maximum divergence). This maximum convergence with maximum divergence is probably the most characteristic pattern of the PF-Purkinje cell organization and is apparently typical of the Purkinje cell throughout evolution (57). There is, therefore, a totally different arrangement of this input as compared to the CF system. This particular type of consideration has been taken to suggest that MF and CF systems utilize the Purkinje cell on a time-sharing basis (52). As in the case of the CF system, there are many experiments which now suggest at least sketchy explanations of the significance of this afferent system in the overall function of the cerebellar cortex.

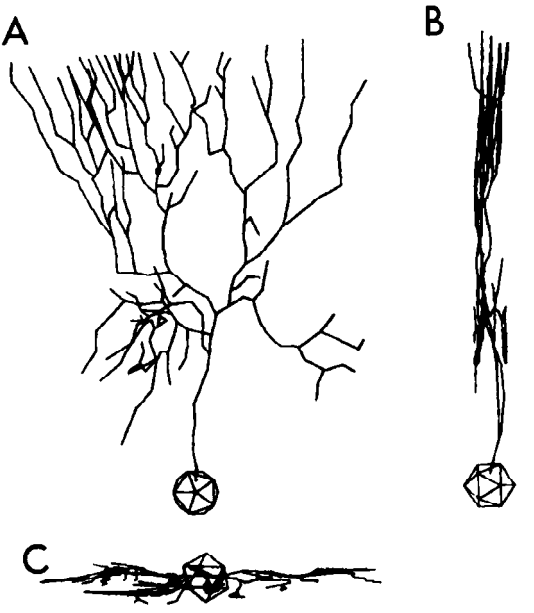


Fig.12. Computer reconstruction of a Purkinje cell. A: Cell reconstructed from a Golgi-stained, alligator Purkinje cell. B: Same cell rotated 90° along its vertical axis. C: View of the same Purkinje cell from the top following rotation in the horizontal axis. Picture illustrates the degree of isoplanarity which characterizes Purkinje cells.

In a recent set of experiments in Rhesus monkeys, a relation has been sought between Purkinje cell activation and eye movement (62). The experiments were performed in unanesthetized monkeys on a large turntable which allowed the generation of eye movements either by constant velocity horizontal rotation (optokinetic nystagmus) or in the dark by means of horizontal angular acceleration in an harmonic sinusoidal fashion (Fig. 13). Spontaneous "voluntary" eye movements were also studied. Eye movements were recorded with metal electrodes placed in the outer canthi and on the upper and lower orbital surfaces in line with the center of the transocular dipole. Purkinje cells were recorded from the cerebellar cortex with a new technique (101) which allows direct observation of the cerebellar cortex under the dissecting microscope and, thus, a precise location of the microelectrode on the cerebellar surface.

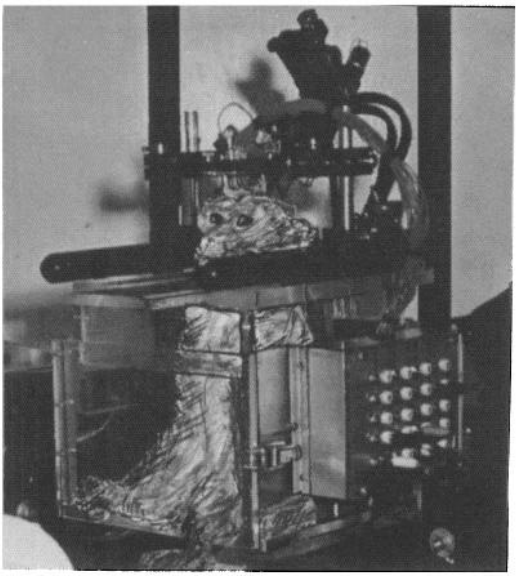


Fig.13. Photograph of experimental setup for Purkinje cell recording in awake Rhesus monkey. The animal's head was firmly fixed to a metal frame via a metal pedestal attached to the cranium with acrylic cement. The microelectrode was introduced by means of a micromanipulator mounted on a metal arch. Electro-oculograms were taken from the leads in the center of the pedestal. (Llinás and Wolfe; unpublished observations).

Actual recordings of Purkinje cells and eye movements can be seen in Figure 14. The upper traces illustrate Purkinje cell activity, and the lower traces the electro-oculogram (EOG). The type of data illustrated in these figures was recorded on tape and then fed into a computer such that vertical as well as horizontal eye movements could be studied. For the most part, this particular study covered horizontal eye movements. Simultaneous with these records, videotape records

were taken which allowed demonstration of eye movements and Purkinje cell activity. The study consisted of more than 50 Purkinje cells where optokinetic, vestibular and voluntarily induced eye movements were analyzed for different saccade amplitudes. In agreement with the cortical sites which generate eye movements (85), the Purkinje cells which display this behavior were almost exclusively restricted to vermal lobule VIa, although some have been seen in lobules VIb and VII. As previously observed by Wolfe (100), field potentials can be observed in the cerebellum preceding eye movements. At single cell level, it was found that these potentials correspond to Purkinje cell activation via MF afferents, in keeping with more recent observations in the cat (77).

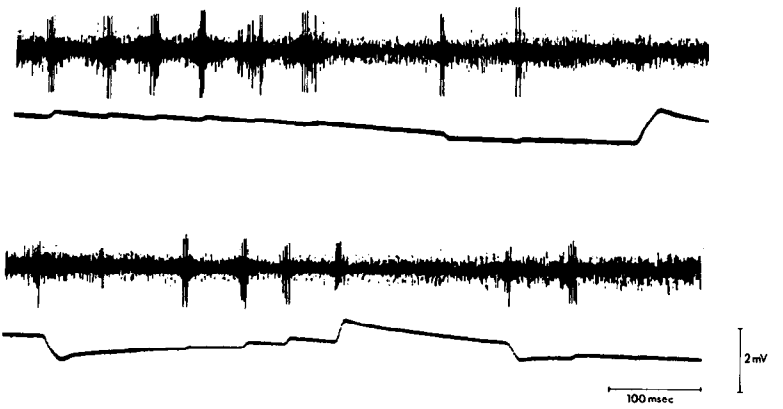


Fig.14. Recordings from Purkinje cells in the vermal lobule VI in the monkey during generation of horizontal eye movements. Purkinje cell activity is recorded in upper trace; electro-oculograms (EOGs) in the lower trace. Note that the Purkinje cells respond to eye movements in a transient manner. (Llinás and Wolfe; unpublished observations).

Two main findings can be derived from this work (62, 63). 1)Purkinje cell activity precedes eye movement by as much as 25 msec. 2) An appreciable number of Purkinje cells respond with a number of spikes which relate inversely to the amplitude of the saccadic movement.

The first finding is based on results such as those shown in Figure 15. The activity of the Purkinje cell begins to increase from its background level at approximately 25 msec prior to the initiation of the saccade. The actual delay between the generation of the rapid eye movement and the activation of motoneurons was found to be approximately 7 msec in accordance with similar findings in the cat (83). The peak Purkinje cell activity expressed as the number of events occurring at a set time with respect to the initiation of eye movement indicates that the peak activity occurs approximately at the onset or prior to the onset of the eye movement itself. Purkinje cell activity can be similar for ipsi- and contralateral directions (Fig. 16) although many units showing unidirectionality were also found.

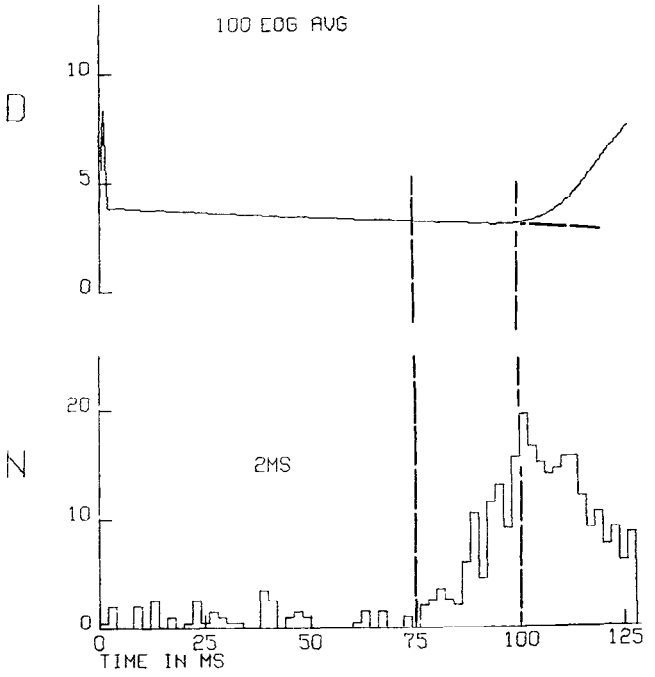
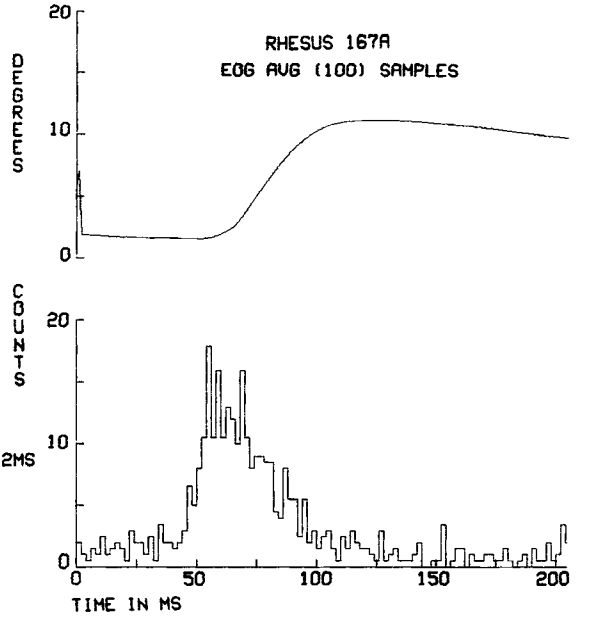
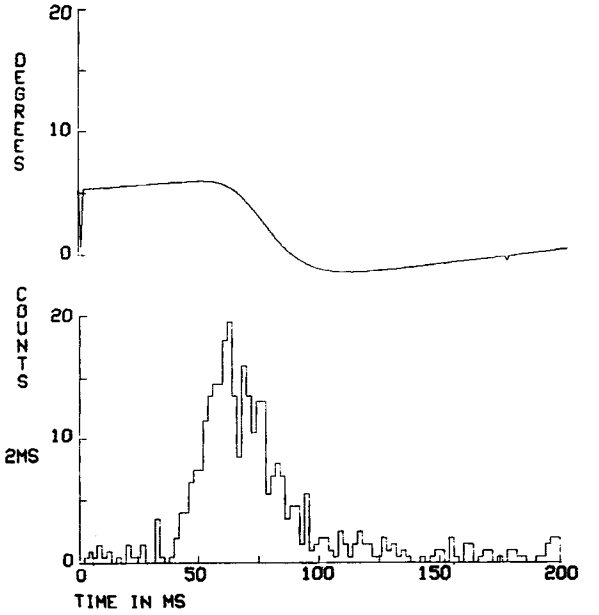


Fig.15. Histogram of the time relationship between Purkinje cell firing and the initiation of eye movement. One hundred EOGs of the same size were averaged, from taped material, in the upper record. The onset of the eye movements is marked by the second vertical line. The histogram gives a Purkinje cell spike count accompanying the same one hundred eye movements (N) against time (msec). The computation is initiated one hundred milliseconds prior to the commencement of the saccade. The first vertical line denotes onset of the increase in Purkinje cell activity over the background level. (Llinás and Wolfe; unpublished observations).

Fig.16. Purkinje cells responding to ipsi- and contralateral eye movements. Measurements were taken as in Figure 15. One hundred EOGs of approximately the same size were averaged in the upper record. Purkinje cell activity was recorded as number of counts of 2-msec bins in a period of 200 msec at 75 msec preceding and 125 msec following onset of EOG. This particular unit responded for ipsi- (upper results) as well as for contralateral eye movements (lower results). One hundred saccades measured. (Llinas and Wolfe; unpublished observations).


RHESUS 167A
EOG AVG (100) SAMPLES
DEGREES
20
10
0
COUNTS
2MS
20
10
0
0
50
100
150
200
TIME IN MS


DEGREES
20
10
0
COUNTS
2MS
20
10
0
0
50
100
150
200
TIME IN MS

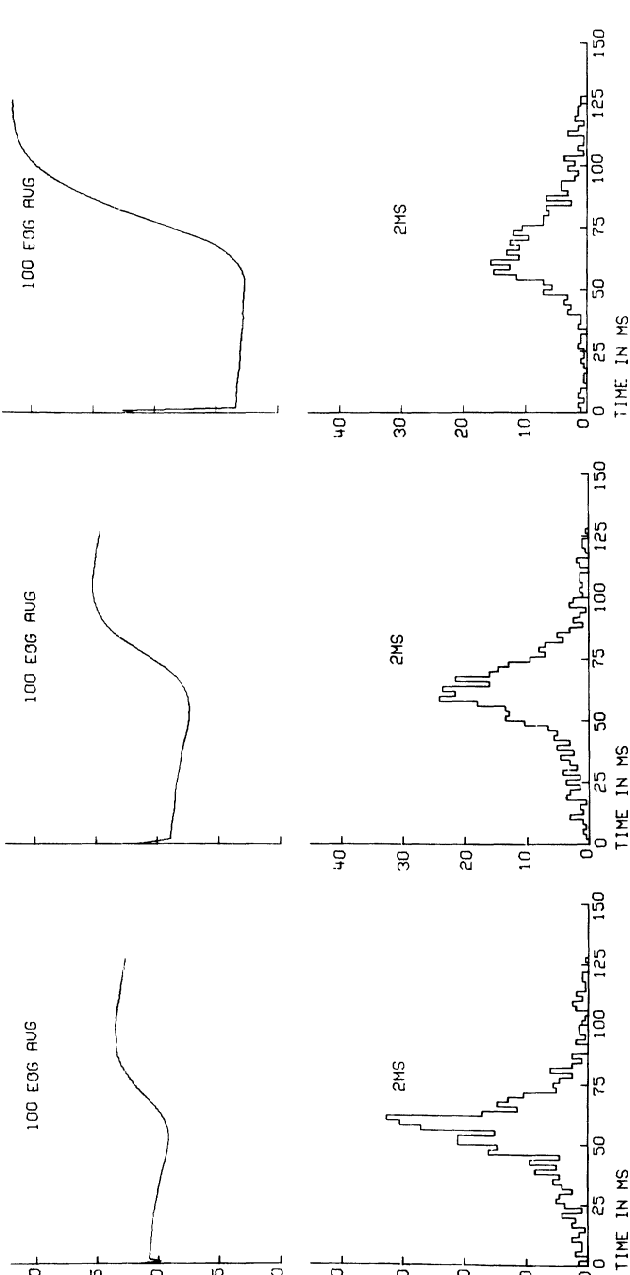


Fig.17. Inverse relationship between the amplitude of the EOG and the number of spikes generated in a Purkinje cell. The measurements were taken as in Fig.15. Note that as the amplitude of the EOG rises from 4-8 to 20, the total amplitude of the histogram is reduced, demonstrating an inverse relationship between the amplitude of the saccade and the number of action potentials which precede the saccade. (Llinás and Wolfe; unpublished observations).

The second finding relates to the inverse relation between Purkinje cell activity and saccadic amplitude. Thus, in the presence of small saccades, the total number of Purkinje cell spikes counted for 100 saccades is much larger than for the number of Purkinje cell spikes which precede the generation of large saccadic eye movements (Fig. 17). This type of information suggests that small eye movements are probably more precisely controlled than larger saccades; that is, the inverse relationship of amplitude of eye movement versus Purkinje cell activity may be related to the precise coordination of eye movements, especially around the area of foveal vision where eye movements are probably quite precise.

This particular type of experimental result illustrates a second form of cerebellar regulation which utilizes Purkinje cells in a less deterministic manner than seen before for the olivo-cerebellar system. Here, the eye movements are probably initiated by a saccadic generating system (84) and are then modified by the cerebellum for the generation of the proper saccadic amplitude. In this vein, clinical observations by Kornhuber (49) have suggested that, following cerebellar lesion in humans, there is a serious impairment of saccades. This may also be the case in monkeys (7) as well as in rabbits (23). Although it has been suggested that total cerebellar ablation may not modify saccadic movements (99), reversible impairment of cortical function must be performed before chronic complete cerebellar ablation studies can be properly understood. In any event, the types of experiments described above suggest that the saccadic generating system is intimately related to cerebellar vermis, especially to Lobus simplex, which is also known to receive auditory and visual inputs (90) as well as inputs from the neck and extra-ocular muscles (9, 13, 37).

The exact role which Purkinje cells play in the regulation of eye movements is as yet difficult to determine. It is tempting to suggest, however, that the Purkinje cells may tend to limit the number of action potentials produced by the oculomotor neurons and thus to serve as a brake to saccades which otherwise would be unduly large. At the same time, it is not possible to totally exclude the possibility that Purkinje cells may be related to the suppression of activity in the oculomotor system prior to saccadic generation. This has been observed intracellularly in oculomotor neurons by Baker and Berthoz (8) during nystagmus. However, careful analysis of saccades demonstrates that the Purkinje cell firing is not related to the preceding slow phase as the activity accompanies saccades even when starting from a fixed eye position. In any event, the point of interest here is that a great deal of the information fed into the cerebellum concerns activity which precedes the generation of movement rather than activity which serves as a feedback corrective signal. In our particular case, the activity of the MF system clearly precedes eye movement and thus cerebellar correction must be introduced into the motor pattern prior to actual generation of movement.

This type of example tends to suggest, especially as far as the MF system is concerned, that the cerebellar cortex may constitute a two-dimensional representation of the functional states and positions of the somatic musculature, joints and limbs at any given instant, as well as

the internal functional state (6, 65). This overall activity may then be utilized for the generation of new movements inasmuch as the system will automatically take dynamic as well as static parameters into consideration when applying the adequate correction to a descending motor command. From this point of view, therefore, the information received from the periphery serves more to upgrade the state of readiness of the cerebellar cortex into a continuously modified mirror of the motor functional state, rather than serving as a true feedback where the incoming information may be utilized for motor error correction.

Referring back now to the initial statement concerning the correlation of the activity of single cells to behavior, the conclusion is evident. There are cerebellar functional states, such as those accompanying the harmaline tremor and eye movements, where the problem may be approached quite rigorously in the immediate future. Among the frustrating problems that remain basically unsolved is that of a strict relationship between given CF activations and movement.

The question that must be asked at this time, however, is whether we are stating the problem appropriately. The very nature of the electrophysiological methodology today assumes that in order to establish a causal relationship between unitary responses and a behavioral event, a high correlation must be found between particular single unit events and the behavioral responses. This may be an oversimplification of the problem for at least two general types of reasons. 1) The behavioral events, although apparently similar at a gross level, may not be so at a more detailed level. 2) A multitude of equipotential neuronal circuits may be activated in parallel in the performance of a given behavioral act such that a precise correlation may be neither necessary or even likely. The latter may be the more pertinent regarding our problems with the CF system. While many of us have observed situations where a CF activation may, in a set of motor responses, be correlated with a particular set of movements, this correlation has been present, for the most part, only for a certain number of trials (i.e. no strict correlation could be established). This is to be expected, given the lack of convergence of the CF Purkinje cell system, especially when compared with the mossy fiber input - the system having probably the largest convergence in the whole of the CNS. However, it is my opinion that if one had the means to record a statistically significant number of Purkinje cells simultaneously, the question of CF function could be solved very rapidly. The fact is, we may not be skilled in battling with neuronal systems having a one-to-one organization basis simply because there are not many of them; rather, the more common "many-to-many" neuronal interactions are our everyday fare!

Acknowledgements

I would like to thank my colleagues - Drs. K. E. Alley, R. Baker, J. I. Simpson, C. Sotelo, and J. W. Wolfe - for allowing me to utilize collaborative unpublished material. The research was supported by USPHS Grant No. NS-09916 from the National Institute for Neurological Diseases and Stroke. The oculomotor study in awake Rhesus monkeys was carried out at the USAF School of Aerospace Medicine at Brooks AFB in San Antonio, Texas.

REFERENCES

1. Ahmed, A., and R. W. Taylor. The analysis of drug-induced tremor in mice. Brit. J. Pharmacol. 14: 350-354, 1959.
2. Allen, G. I., N. H. Sabah, and K. Toyama. Synaptic actions of peripheral nerve impulses upon Deiters neurones via the climbing fibre afferents. J. Physiol. (London) 226: 311-333, 1972.
3. Anderson, P., J. C. Eccles, and P. E. Voorhoeve. Postsynaptic inhibition of cerebellar Purkinje cells. J. Neurophysiol. 27: 1138-1153, 1964.
4. Angaut, P., and C. Sotelo. The fine structure of the cerebellar central nuclei in the cat. II. Synaptic organization. Exp. Brain Res. 16: 431-454, 1973.
5. Ariëns-Kappers, C. U., G. C. Huber, and E. C. Crosby. The Comparative Anatomy of the Nervous System of Vertebrates, Including Man. Vol. 3. New York: Hafner, 1960.
6. Arshavsky, Y. I., M. B. Berkinblit, O. I. Fukson, I. M. Gelfand, and G. N. Orlovsky. Origin of modulation in neurones of the ventral spino-cerebellar tract during locomotion. Brain Res. 43: 276-279, 1972.
7. Aschoff, J. C., and B. Cohen. Changes in saccadic eye movements produced by cerebellar cortical lesions. Exptl. Neurol. 32: 123-133, 1971.
8. Baker, R., and A. Berthoz. Spontaneous nystagmus recorded in trochlear motoneurons following labyrinthine lesion. Brain Res. 32: 239-245, 1971.
9. Baker, R., W. Precht, and R. Llinás. Mossy and climbing fiber projections of extraocular muscle afferents to the cerebellum. Brain Res. 38: 440-445, 1972.
10. Bell, C. C., and R. J. Grimm. Discharge properties of cerebellar Purkinje cells recorded with single and double microelectrodes. J. Neurophysiol. 32: 1044-1055, 1969.
11. Bennett, M. V. L. Physiology of electrotonic junctions. Ann. N.Y. Acad. Sci. 137: 509-539, 1966.
12. Bennett, M. V. L. A comparison of electrically and chemically mediated transmissions. In: Structure and Function of Synapses, edited by G. D. Pappas and D. P. Purpura. New York: Raven Press, 1972, p. 221-226.
13. Berthoz, A., and R. Llinás. Afferent neck projection to the cat cerebellar cortex. Exptl. Brain Res. (In Press).
14. Bloedel, J. R., and W. J. Roberts. Functional relationship among neurons of the cerebellar cortex in absence of anesthesia. J. Neurophysiol. 32: 75-84, 1969.
15. Bloedel, J. R., and W. J. Roberts. Action of climbing fibers in cerebellar cortex of the cat. J. Neurophysiol. 34: 17-31, 1971.
16. Braitenberg, V., and R. P. Atwood. Morphological observations on the cerebellar cortex. J. Comp. Neurol. 109: 1-34, 1958.
17. Bruggencate, G. ten, R. Teichmann, and E. Weller. Neuronal activity in the lateral vestibular nucleus of the cat. III. Inhibitory actions of cerebellar Purkinje cells evoked via mossy and climbing fiber afferents. Pflügers Arch. 337: 147-162, 1972.
18. Cannessa, M. Effect of hallucinogen harmaline on sodium active transport in giant squid axon. Arch. Biol. Med. Exp. 7: R7, 1970.

19. Chan-Palay, V., and S. L. Palay. Interrelations of basket cell axons and climbing fibers in cerebellar cortex of rat. Z. Anat. Entwickl.-Gesch. 132: 191-227, 1970.
20. Chan-Palay, V., and S. L. Palay. The synapse en marron between Golgi II neurons and mossy fibers in the rat's cerebellar cortex. Z. Anat. Entwickl.-Gesch. 133: 274-287, 1971.
21. Chan-Palay, V., and S. L. Palay. The stellate cells of the rat's cerebellar cortex. Z. Anat. Entwickl.-Gesch. 136: 224-248, 1972.
22. Chan-Palay, V., and S. L. Palay. High voltage electron microscopy of rapid Golgi preparations. Neurons and their processes in the cerebellar cortex of monkey and rat. Z. Anat. Entwickl.-Gesch. 137: 125-152, 1972.
23. Collewijn, H. Dysmetria of fast phase of optokinetic nystagmus in cerebellectomized rabbits. Exptl. Neurol. 28: 144-154, 1970.
24. Crill, W. E. Unitary multiple-spiked responses in cat inferior olive nucleus. J. Neurophysiol. 33: 199-209, 1970.
25. Crosby, E. C., T. Humphrey, and E. W. Lauer. Correlative Anatomy of the Nervous System. New York: Macmillan, 1962.
26. Eccles, J. C., M. Ito, and J. Szentágothai. The Cerebellum as a Neuronal Machine. Berlin-Heidelberg-N. Y.: Springer-Verlag, 1967.
27. Eccles, J. C., R. Llinás, and K. Sasaki. The excitatory synaptic action of climbing fibres on the Purkinje cells of the cerebellum. J. Physiol. (London) 182: 268-296, 1966.
28. Eccles, J. C., R. Llinás, and K. Sasaki. The inhibitory interneurones within the cerebellar cortex. Exptl. Brain Res. 1: 1-16, 1966.
29. Eccles, J. C., R. Llinás, and K. Sasaki. Parallel fibre stimulation and responses induced thereby in the Purkinje cells of the cerebellum. Exptl. Brain Res. 1: 17-39, 1966.
30. Eccles, J. C., R. Llinás, and K. Sasaki. The mossy fibre-granule cell relay of the cerebellum and its inhibitory control by Golgi cells. Exptl. Brain Res. 1: 82-101, 1966.
31. Eccles, J. C., R. Llinás, and K. Sasaki. Intracellularly recorded responses of the cerebellar Purkinje cells. Exptl. Brain Res. 1: 161-183, 1966.
32. Eccles, J. C., N. H. Sabah, R. F. Schmidt, and H. Táboříkova. Cutaneous mechanoreceptors influencing impulse discharges in cerebellar cortex. III. In Purkyně cells by climbing fiber input. Exptl. Brain Res. 15: 484-497, 1972.
33. Farquhar, M. G., and G. E. Palade. Junctional complexes in various epithelia. J. Cell Biol. 17: 375-412, 1963.
34. Fox, C. A. Personal Communication.
35. Fox, C. A., D. E. Hillman, K. A. Siegesmund, and C. R. Dutta. The primate cerebellar cortex: a Golgi and electron microscopical study. Progress in Brain Res. 25: 174-225, 1967.
36. Fox, C. A., K. A. Siegesmund, and C. R. Dutta. The Purkinje cell dendritic branchlets and their relation with the parallel fibers: Light and electron microscopic observations. In: Morphological and Biochemical Correlates of Neural Activity, edited by M. M. Cohen and R. S. Snider. New York: Harper & Row, 1964, p. 112-141.
37. Fuchs, A. F., and H. H. Kornhuber. Extraocular muscle afferents to the cerebellum of the cat. J. Physiol. (London) 200: 713-722, 1969.

38. Gray, E.G. The granule cells, mossy fiber synapses and Purkinje spine synapses of the cerebellum: Light and electron microscope observations. J. Anat. 95: 345-356, 1961.
39. Hámori, J., and J. Szentágothai. The crossing over synapse: An electron microscope study of the molecular layer of the cerebellar cortex. Acta Biol. Hung. 15: 95-117, 1964.
40. Hámori, J., and J. Szentágothai. The Purkinje cell baskets: ultrastructure of an inhibitory synapse. Acta Biol. Hung. 15: 465-479, 1965.
41. Hámori, J., and J. Szentágothai. Participation of Golgi neurone processes in the cerebellar glomeruli: An electron microscope study. Exptl. Brain Res. 2: 35-48, 1966.
42. Hillman, D.E. Morphological organization of the frog cerebellar cortex: A light and electron microscopic study. J. Neurophysiol. 32: 818-846, 1969.
43. Hillman, D.E. Neuronal organization of the cerebellar cortex in amphibia and reptilia. In: Neurobiology of Cerebellar Evolution and Development, edited by R. Llinás. Chicago: Am. Med. Assn. 1969, p. 279-325.
44. Hillman, D.E., M. Chujo, and R. Llinás. Quantitative computer analysis of the morphology of cerebellar neurons. I. Granule cells. Anat. Rec. (In press).
45. Ito, M., M. Yoshida, and K. Obata. Monosynaptic inhibition of the intracerebellar nuclei induced from the cerebellar cortex. Experientia 20: 575-576, 1964.
46. Ito, M., M. Yoshida, K. Obata, N. Kawai, and M. Udo. Inhibitory control of intracerebeilar nuclei by the Purkinje cell axons. Exptl. Brain Res. 10: 64-80, 1970.
47. Jansen, J., and A. Brodal. Aspects of Cerebellar Anatomy. Oslo: Johan Grundt Tanum Forlag, 1954.
48. Kaiserman-Abramof, I. R., and S.L. Palay. Fine structural studies of the cerebellar cortex in mormyrid fish. In: Neurobiology of Cerebellar Evolution and Development, edited by R. Llinás. Chicago: Am. Med. Assn., 1969, p. 171-205.
49. Kornhuber, H.H. Motor functions of cerebellum and basal ganglia. Kybernetik 8: 157-162, 1971.
50. Lamarre, Y., C. de Montigny, M. Dumont, and M. Weiss. Harmaline-induced rhythmic activity of cerebellar and lower brain stem neurons. Brain Res. 32: 246-250, 1971.
51. Larramendi, L.M.H., and T. Victor. Synapses on the Purkinje cell spines in the mouse: An electron microscopial study. Brain Res. 5: 15-30, 1967.
52. Leicht, R., M.J. Rowe, and R.F. Schmidt. Inhibition of cerebellar climbing fiber activity by stimulation of precruciate cortex. Brain Res. 43: 640-644, 1972.
53. Llinás, R. (Editor). Neurobiology of Cerebellar Evolution and Development. Chicago: Am. Med. Assn., 1969.
54. Llinás, R. Neuronal operations in cerebellar transactions. In: The Neurosciences: Second Study Program, edited by F.O. Schmitt. New York: Rockefeller Univ. Press, 1970, p. 409-426.
55. Llinás, R., R. Baker, and C. Sotelo. Electrotonic coupling between neurons in the cat inferior olive. Submitted for publication.

56. Llinás, R., J. R. Bloedel, and D. E. Hillman. Functional characterization of the neuronal circuitry of the frog cerebellar cortex. J. Neurophysiol. 32: 847-870, 1969.
57. Llinás, R., and D. E. Hillman. Physiological and morphological organization of the cerebellar circuits of various vertebrates. In: Neurobiology of Cerebellar Evolution and Development, edited by R. Llinás. Chicago: Am. Med. Assn, 1969, p. 43-73.
58. Llinás, R., and C. Nicholson. Electrophysiological analysis of alligator cerebellum: A study on dendritic spikes. In: Neurobiology of Cerebellar Evolution and Development, edited by R. Llinás. Chicago: Am. Med. Assn., 1969, p. 431-465.
59. Llinás, R., and C. Nicholson. Electrophysiological properties of dendrites and somata in alligator Purkinje cells. J. Neurophysiol. 34: 532-551, 1971.
60. Llinás, R., W. Precht, and M. Clarke. Cerebellar Purkinje cell responses to physiological stimulation of the vestibular system in the frog. Exptl. Brain Res. 13: 408-431, 1971.
61. Llinás, R., and R. A. Volkind. The olivo-cerebellar system: Functional properties as revealed by harmaline-induced tremor. Exptl. Brain Res. 18: 69-87, 1973.
62. Llinás, R., and J. W. Wolfe. Single cell responses from the cerebellum of Rhesus preceding voluntary, vestibular and optokinetic saccadic eye movements. Soc. for Neuroscience 2: 201, 1972.
63. Llinás, R., and J. W. Wolfe. Eye movement-related, Purkinje cell activity from the posterior vermis of awake Rhesus monkeys. Submitted for publication.
64. Lorente de Nó, R. Action potential of the motoneurons of the hypoglossus nucleus. J. cell comp. Physiol. 29: 207-288, 1947.
65. Lundberg, A. Function of the ventral spino-cerebellar tract. A new hypothesis. Exptl. Brain Res. 12: 317-330, 1971.
66. Maekawa, K., and J. I. Simpson. Climbing fiber responses evoked in vestibulo-cerebellum of rabbit from visual system. J. Neurophysiol. 36: 649-666, 1973.
67. Massion, J. Intervention des voies cérébello-corticales et cortico-cérébelleuses dans l'organisation et la régulation du mouvement. J. Physiol. (Paris) 67: 117A-170A, 1973.
68. Matsushita, M., and M. Ikeda. Olivary projections to the cerebellat nuclei in cat. Exptl. Brain Res. 10: 488-500, 1970.
69. Matsushita, M., and M. Ikeda. Spinal projections to the cerebellar nuclei in the cat. Exptl. Brain Res. 10: 501-511, 1970.
70. Montigny, C. de, and Y. Lamarre. Rhythmic activity induced by harmaline in the olivo-cerebello-bulbar system of the cat. Brain Res. 53: 81-95, 1973.
71. Mugnaini, E. The histology and cytology of the cerebellar cortex. In: The Comparative Anatomy and Histology of the Cerebellum: The Human Cerebellum, Cerebellar Connections and Cerebellar Cortex, by O. Larsell and J. Jansen. Minneapolis: Univ. of Minnesota Press, 1972, p. 201-262.
72. Murphy, M. G., J. L. O'Leary, and D. Cornblath. Axoplasmic flow in cerebellar mossy and climbing fibers. Arch. Neurol. 28: 118-123, 1973.

73. Nicholson, C., and R. Llinás. Field potentials in the alligator cerebellum and theory of their relationship to Purkinje cell dendritic spikes. J. Neurophysiol. 34: 509-531, 1971.
74. Oscarsson, O. Functional organization of spinocerebellar paths. In: Handbook of Sensory Physiology, Vol. II, edited by A. Iggo. Berlin-Heidelberg-N. Y. : Springer-Verlag, 1973, p. 339-380.
75. Palkovits, M., P. Magyar, and J. Szentágothai. Quantitative histological analysis of the cerebellar cortex in the cat. III. Structural organization of the molecular layer. Brain Res. 34: 1-18, 1971.
76. Pappas, G.D., and M.V.L. Bennett. Specialized junctions involved in electrical transmission between neurons. Ann. N.Y. Acad. Sci. 137: 495-508, 1966.
77. Pellet, J. Contribution à l'étude de l'électrogenèse spontanée du cortex cérebélleux vermien au cours des états de veille et de sommeil. Thèse présentée a la Faculté des Sciences de l' Université d'Aix-Marseille.
78. Precht, W., and R. Llinás. Functional organization of the vestibular afferents to the cerebellar cortex of frog and cat. Exptl. Brain Res. 9: 30-52, 1969.
79. Ramón y Cajal, S. Histologie du système nerveux de l'homme et des vertébrés, Vol. 1. Paris: Maloine, 1909.
80. Ramón y Cajal, S. Histologie du système nerveus de l'homme et des vertébrés, Vol. 2. Paris: Maloine, 1911.
81. Revel, J.P., and M.J. Karnovsky. Hexagonal array of subunits in intercellular junctions of the mouse heart and liver. J. Cell Biol. 33: C7-C12, 1967.
82. Robertson, J.D. The occurrence of a subunit pattern in the unit membranes of club endings in Mauthner cell synapses in goldfish brains. J. Cell Biol. 19: 201-221, 1963.
83. Robinson, D.A. A note on the oculomotor pathway. Exptl. Neurol. 22: 130-132, 1968.
84. Robinson, D.A. On the nature of visual-oculomotor connections. Investigative Ophthalmology 11: 497-503, 1972.
85. Ron, S. A quantitative study of eye movements evoked by cerebellar stimulation in the alert monkey. Federation Proc. 30: 711A, 1971.
86. Sigg, E.B., L. Gyermek, R.T. Hill, and H.C.Y. Yen. Neuropharmacology of some harmine derivatives. Arch. int. Pharmacodyn. 149: 164-180, 1964.
87. Simpson, J.I., and K.E. Alley. Trigger features for the visual climbing fiber input to rabbit vestibulo-cerebellum. Soc. for Neuroscience 3: 152a, 1973.
88. Simpson, J.I., and K.E. Alley. Direction specificity in the visual climbing fiber input to rabbit vestibulo-cerebellum. Submitted for publication.
89. Smolyaninov, V.V. Some special features of organization of the cerebellar cortex. In: Models of the Structural-Functional Organization of Certain Biological Systems, edited by I.M. Gelfand with V.S. Gurfinkel, S.V. Fomin, and M.L. Tsetlin. Cambridge, Mass.: M.I.T., 1971, p. 251-325.
90. Snider, R.S., and A. Stowell. Receiving areas of the tactile, auditory and visual systems in the cerebellum. J. Neurophysiol. 7: 331-357, 1944.

91. Sotelo, C. Ultrastructural aspects of the cerebellar cortex of the frog. In: Neurobiology of Cerebellar Evolution and Development, edited by R. Llinás. Chicago: Am. Med. Assn., 1969, p. 327-371.
92. Sotelo, C., R. Llinás, and R. Baker. Structural study of the inferior olivary nucleus of the cat. Morphological correlates of electrotonic coupling. Submitted for publication.
93. Spira, M. E., and M. V. L. Bennett. Synaptic control of electrotonic coupling between neurons. Brain Res. 37: 294-300, 1972.
94. Szentágothai, J., and K. Rajkovits. Ueber den Urspring der Kletterfasern des Kleinhirns. Z. Anat. Entwickl.-Gesch. 121: 130-141, 1959.
95. Thach, W. T. Discharge of cerebellar neurons related to two maintained postures and two prompt movements. II. Purkinje cell out-out and input. J. Neurophysiol. 33: 537-547, 1970.
96. Thach, W. T. Cerebellar output. Properties, synthesis and uses. Brain Res. 40: 89-97, 1972.
97. Villablanca, J., and F. Riobo. Electro-encephalographic and behavioral effects of harmaline in intact cats and in cats with chronic mesencephalic transection. Psychopharmacol. 17: 302-313, 1970.
98. Wann, D. F., T. A. Woolsey, M. L. Dierker, and W. M. Cowan. An on-line digital computer system for the semi-automatic analysis of Golgi-impregnated neurons. IEEE Trans. BME 20: 233-248, 1973.
99. Westheimer, G., and S. M. Blair. Oculomotor defects in cerebellectomized monkeys. Investigative Ophthalmology 12: 618-621, 1973.
100. Wolfe, J. W. Relationship of cerebellar potentials to saccadic eye movements. Brain Res. 30: 204-206, 1971.
101. Wolfe, J. W., C. A. Rawlings, and R. Llinás. A procedure for chronic microelectrode recording from cerebellar cortex in the awake cat and monkey. Physiology & Behavior. 10: 967-970, 1973.

PHYSIOLOGY IN MEDICINE

In the September 3, 1970 issue of the New England Journal of Medicine an editorial that introduced the series "Physiology in Medicine" to the readers of the Journal ended with the statement:

> "The American Physiological Society and the Journal continue the promulgation of science in medicine not because science solely determines the quality in medical practice, but because science offers a unique and trusty framework for the practice of rational medicine. Science in medicine cannot be allowed to exist by itself, but neither can a scientific recession in absolute terms - a calculated sacrifice for example of a series such as "Physiology in Medicine" - be defended as advantageous to the doctor's work."

With this statement as a guide the editors and editorial board have tried to provide a series of personal essays that are useful to the more than 140,000 subscribers to the Journal.

Topics of the more than two dozen papers that have appeared have varied as the following list of those published during the first part of 1973 indicates:

1. Physiological Basis of Premature Beats and Sustained Tachycardias by Gordon K. Moe and Carlos Mendez

2. Color Vision by Charles R. Michael

3. Cheyne-Stokes Breathing by Neil S. Cherniack and Guy S. Longobardo

4. Gene De-Repression by John H. Frenster and Paul R. Herstein

5. The Cellular Basis of Metabolic Bone Disease by Howard Rasmussen and Phillippe Bordier

6. Mechanisms of Lithium Action by Irwin Singer and Donald Rotenberg

We believe that such papers have been useful to doctors who completed their formal training some time ago as well as younger students and residents. We further suspect that research physiologists have gained from seeing these clear presentations of the application of basic research.

Dr. Alfred P. Fishman has served as Editor of the series since its beginning. He has been aided by an Editorial Board, presently composed of A. Clifford Barger, Donald S. Fredrickson, Alfred Gellhorn, Kenneth L. Melmon, Samuel O. Thier, and Hibbard E. Williams, and an Executive Editor, Stephen R. Geiger. All wish to express their appreciation to Dr. Franz J. Ingelfinger, Editor of the New England Journal of Medicine for his support and for allowing the American Physiological Society to be guests in his journal.

THYROID

Volume III, Thyroid, of the Handbook of Physiology section on endocrinology is designed to present an overview of current basic information about the thyroid gland. Although the primary orientation is toward thyroid physiology, clinical aspects of thyroid disease are elaborated whenever they are pertinent to the development of concepts about physiological processes in the gland.

The organization of topics and chapters is designed to enhance the volume's usefulness to the interested novice as well as the expert looking for specific background information. Chapters are grouped under the following headings: Developmental and Anatomical Aspects, Thyroid Metabolism, Extrathyroidal Metabolism of Iodoamino Acids and Related Compounds, Factors Influencing Thyroid Function, and Actions of Thyroid Hormones.

The volume editors, Monte A. Greer and David H. Solomon, have provided an introductory chapter that includes an overview of the synthesis and secretion of iodinated thyroid hormones and of major iodine pathways in the body. This chapter also contains a list of abbreviations frequently used by thyroidologists publishing in current scientific journals, along with definitions and comments. Chapter cross references have been provided throughout the volume. With such help the reader should be able to enter the volume at various places with proper orientation to the total scope of the book.

This volume of 500 pages and 216 figures will be available in March 1974. It will regularly sell for $38, but will be available to members of the Society for $31, when ordered directly from the APS Business Office, 9650 Rockville Pike, Bethesda, Maryland 20014.

ASPECTS OF THE ELECTROPHYSIOLOGY OF CORTICAL PROCESSES RELATED TO THE DEVELOPMENT AND PERFORMANCE OF LEARNED MOTOR RESPONSES*

CHARLES D. WOODY
UCLA Medical Center
Los Angeles, California

Introduction

Recent attempts to advance our understanding of possible physiologic bases of learning and memory have turned increasingly to investigations of simple models (3, 4, 6, 11, 19, 28, 32) or simple systems (8, 17, 18, 22). One rationale for this approach is that re-definition or partitioning of otherwise complex processes may permit physiologically meaningful experimental analyses.

The experiments to be described in this article were designed accordingly. They concern investigations of classically conditioned (Pavlovian) facial reflexes in the cat, such as that resulting from pairing a 60-70db click-CS with tap to the glabella (US). After several hundred pairings a blink response (CR) is elicited by the originally neutral click-CS.

Several features characterize this type of behavior. First, there is motor specificity. A specific motor response is elicited by the click. That is, the cat blinks its eyes to the click rather than producing some other extraneous movement.[1] Second, there is stimulus specificity. As will be shown later, the CS is rather specific in eliciting the conditioned motor response. Thus, a cat trained to blink to a click sound will not blink to a hiss sound except, perhaps, for the first few presentations. This appears to differ somewhat from other forms of conditioning in which there is stimulus generalization. Third, some persistent change occurs during the course of training. That is, the animal responds after training to the same physical stimulus that failed to produce a consistent response before training. One infers that there must have occurred some persistent change(s) in the CNS corresponding to the alteration in the response of the CNS to that stimulus.

Conditioning, Sensitization or Pseudoconditioning

Blink reflexes as described above appear to represent conditioned as opposed to sensitized or pseudoconditioned responses. Attempts to separate those phenomena by careful definition (20, 30) have not been entirely successful, perhaps because of certain commonalities in their underlying physiologic mechanisms. However, some operational separation is possible.

---

* Taken from the introductory remarks given at the session on Brain and Behavior at the 1973 Federation Meetings.

[1] This is, physiologically, something of an oversimplification. The observed movement is specific, although EMG activity to a lesser degree than present in "target" musculature may be produced in other muscle groups.

First, sensitization and pseudoconditioning phenomena do not ordinarily show the extinction curves and extent of learnings-savings seen with our blink CR's with reversal and re-reversal of the CS-US pairing order (39). Second, sensitization and pseudoconditioning phenomena do not ordinarily show the "slow" learning curves of blink CR's to click-tap pairing. Third, sensitization and pseudoconditioning phenomena do not ordinarily show stimulus specificity (9, 20, 37). Fourth, our conditioned blink response does not develop after pairing click with glabella tap in a paradigm employing a randomized CS-US interval in which either stimulus may be the first of the pair (recent, unpublished observations).

Involvement of "Motor" Cortex in Classical Blink Conditioning

Many areas of the brain may be activated in the course of learned motor performance (7, 12, 25). In addition, conditioning is associated with many phenomena besides learning including fear, arousal and motor control per se (10, 14, 24). Thus, some evidence is required to demonstrate any specific involvement of a particular area of the CNS such as the coronal - pericruciate or "motor" cortex with the persistent changes, motor specificity and, perhaps, the stimulus specificity that characterize blink conditioning in the cat.

1. Effect of Ablation of "Motor" Cortex on Blink Conditioning

Ablation of the cortical areas shown in Figure 1 results in impairment of acquisition of a conditioned blink response to a click stimulus. These motor areas include the principal cortical regions known to produce an eye blink following their electrical stimulation in the cat (13, 23, 34). The areas also contain somato-sensory receptor neurons and neurons that respond with short latencies to visual and auditory stimuli as well as those that more directly effect contraction of the peripheral musculature (31, 34). Ablation of comparable magnitude of more posterior cortical regions does not result in impaired acquisition of blink conditioning of this type.

The impairment following ablation of cortical motor regions is profound (Fig. 2). It persists for at least three months, the period over which some of these animals were studied. Ablation is also followed by a rise in threshold for eliciting unconditioned facial responses by loud (80-100db) auditory stimuli. However, the impairment in acquisition of click-conditioned behavior cannot be attributed simply to deafness since pinna response to low intensity sound is preserved and since one animal with a comparable auditory threshold increase following ablation of a smaller portion of rostral cortex (cat No. 6, Fig. 1) achieved some partial level (35%) of blink CR performance.

2. Correlation Between Unit Activity and Behavior

The pattern of click-evoked unit activity recorded at the coronal - pericruciate cortex is correlated with the development of conditioned behavior. Averaged PST histograms of such unit activity show increases after conditioning in the magnitude of the response to click compared with that seen in naive animals (Fig. 3). The increases disappear after

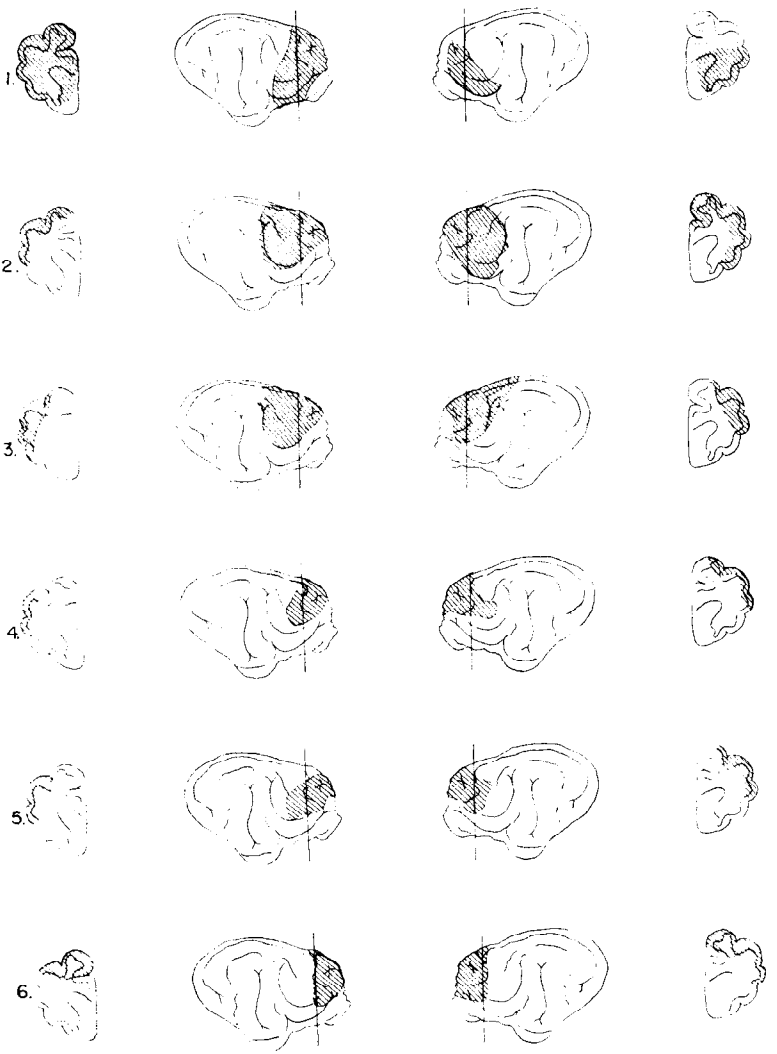


Fig.1. Areas (shaded) of cortex removed from six lesioned cats. Examples are also shown of the sections taken at stereotaxic frontal plane A 24 (27). Data from cats 1-5 shown in Fig.2.

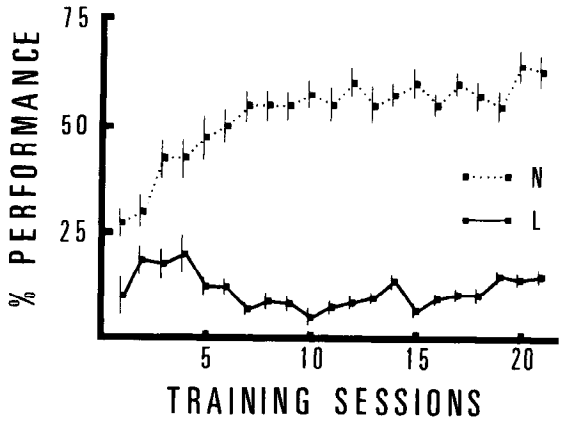


Fig.2.Performance levels of normal(N) and lesioned(L) cats, n=6 and n=5 respectively, during training of classically conditioned eye blink. Group averages and standard deviations shown are compiled from averages of response performance by each animal for the respective training session. Each training session consisted of 150 trials of paired CS and US. The CS-US interval was 400 msec; the intertrial interval was 10 sec.

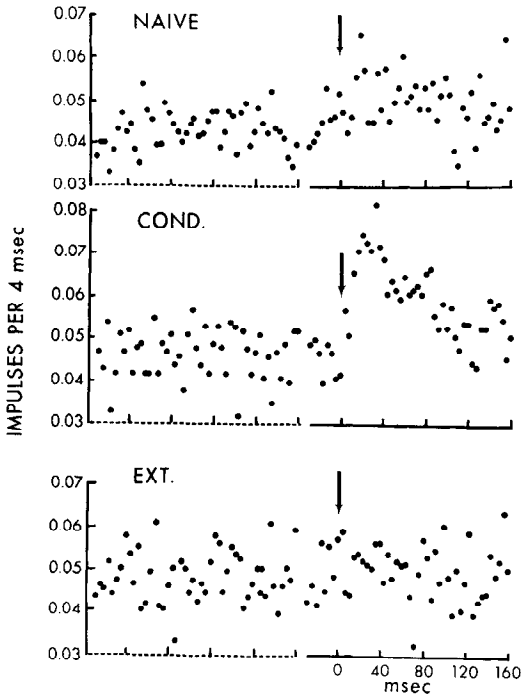


Fig.3. Averages of unit activity for cells at areas of coronal - pericruciate cortex projecting ultimately to blink musculature in naive, conditioned and extinguished cats.N= 51,56,and 38, respectively. Activity to the left of each plot, overlying the broken line, represents the averaged spontaneous activity for the respective group of cells. On the right is the averaged evoked activity following the click stimulus(arrow, 0 msec). (From Woody et al., 1970).

extinction of the CR. The latter was accomplished by repeated presentation of the CS and US in reversed order such that the US preceded the CS by 500-800 msec. The decrement in unit response following this procedure also suggests that the enhanced unit response in the blink-conditioned animal is not simply a matter of arousal by the US. Analogous changes may be found in the activity of single units. An example is shown in Figure 4. The frequency of discharge of the illustrated neuron during the period immediately preceding blink initiation approximates that of neurons in motor cortex in monkeys performing conditioned hand movements (10), although the duration of the increase is not so protracted just as the blink movement is not so protracted.

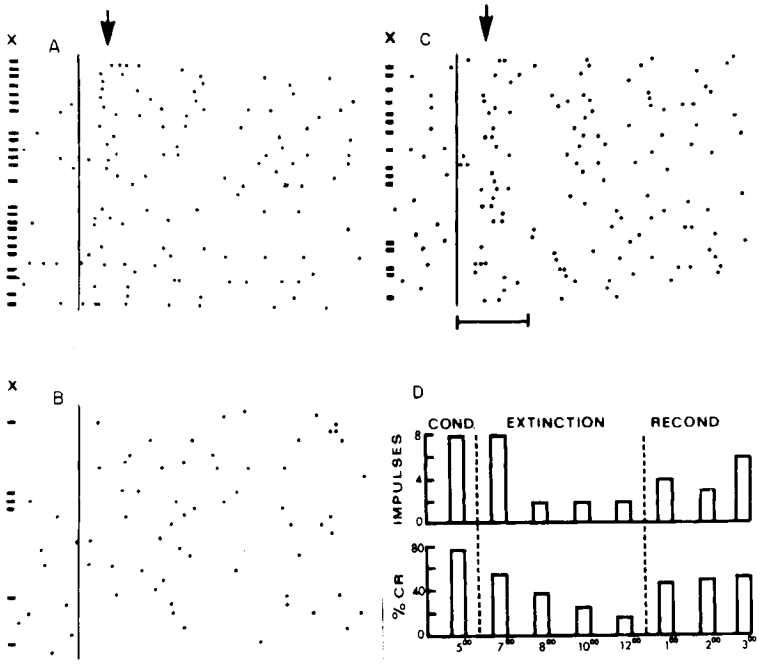


Fig.4. Study of click-evoked discharge of a single unit through extinction and reconditioning of blink. A: 32-sweep dot raster of evoked activity in conditioned animal. B: activity after extinction. C: activity after reconditioning. Initial bars designate conditioned blink response on that sweep. Solid line corresponds to click-CS presentation. Arrows show increased unit response. 40-msec time calibration as shown in C. D: number of impulses above spontaneous rate per 32 sweeps in 8- to 28-msec period after click, averaged and shown at real time intervals during extinction abd reconditioning (above), and compared with corresponding percent conditioned response performance (below). In contrast to D, note the noisy and inconsistent response of the unit on single trials. (From Woody et al., 1970).

3. Appropriate Latency of Unit Response

In trained animals the latency of the above unit activation should precede the initiation of the conditioned EMG response in blink musculature by a time appropriate to conduction delay along efferent pathways from cortex to periphery. As shown diagrammatically in Figure 5, this does in fact appear to be the case. The onset of neuronal activation at motor cortex following click is 4 msec earlier than that at facial nucleus. Allowing for a probable interneuron at the brainstem level (5), this is consistent with independent measurements of conduction delays along the pyramidal pathway in the cat (15). Similarly, the difference in latencies between facial nucleus and periphery is consistent with expected conduction and transmission delays between brainstem and periphery (21, 36).

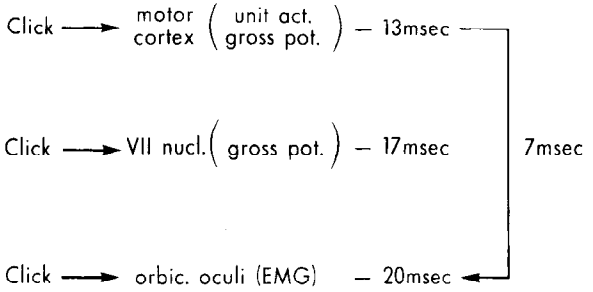


Fig.5. Response onset latencies at different loci along efferent pathway for production of conditioned blink response. Standard deviations of 3-4 msec are associated with the above means.

4. Polysynaptic Connectivity Between Cortical Units and Peripheral Musculature

Establishment of a relationship between populations of units of motor cortex and specific peripheral musculature may be quite useful in investigations of phenomena concerned with motor specificity. For the case of linkage through polysynaptic transmission, relationships can be easily determined by the microstimulation technique of Asanuma and colleagues (2). That is, by delivering current extracellularly (Fig. 6) or intracellularly (Fig. 7) through a unit-recording electrode and by monitoring the subsequent, peripherally evoked EMG activity, it is possible to classify populations of units, so treated, on the basis of their ultimate motor projection.

Certain technical limitations confine such classification to stochastically treated populations rather than to single units. For the case of extracellular electrical stimulation, it is estimated (29) that as many as 28 neurons in the area surrounding the electrode tip may be activated by currents of 1-10 μA. Thus, identification of the ultimate projection of the stimulated micro-region need not necessarily be equivalent to that of the recorded unit. However, it appears reasonable to assume that,

while the ultimate projection of any single recorded unit may be in doubt, grouped data from large numbers of such units, so identified, will accurately reflect activity leading to the activation of specific muscle groups. For the case of intracellular stimulation with currents of 0.5 - 6 nA, it is unlikely that neighboring units are activated by ephaptic spread of the injected current. However, the muscle response evoked by intracellular stimulation of a single cortical unit is sufficiently small and inconsistent (averaging must be performed to identify the response) that one cannot be certain of the ultimate projection of any single unit and population stochastics must again be invoked to study differences in motor projection. Note also that possible projection to other muscle groups than those from which EMG is recorded cannot be excluded with either technique.

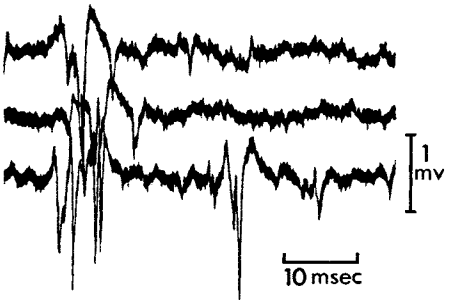


Fig.6. Three successive (bipolar) EMG responses in orbicularis oculis muscle evoked by electrical microstimulation at ipsilateral coronal - precruciate cortex. Beginning of stimulation coincident with beginning of trace. Response onset latencies 7-9 msec. (From Woody et al., 1970).

Insights into questions concerning the functional organization of the motor cortex (1) may derive from use of the intracellular stimulation technique. The ability to provoke some measurable peripheral EMG response by firing a single cortical unit indicates that a single cortical neuron can significantly influence muscle contraction in a relatively direct manner. However, the pattern of EMG activity produced by electrically evoked discharge of the cortical unit may differ from that produced by spontaneous spike activation in the same unit (cf. Fig. 7). Hence some potential exists for the control of movement by the introduction of additional "extrinsic" information into the final efferent pathway, presumably, by the usual mechanisms of anatomic and electrophysiologic integration. Just as the receptive properties of many single units of rostral cortex in the cat may be characterized as polysensory, so may the properties of their effectuation be characterized as poly-motor. (Note the large numbers of "both" units in Table I where EMG activity of but two peripheral muscle groups was sampled.) Thus the stochastics of interactions within cellular ensembles making up a particular projective field may be of particular interest in studies of motor control as well as of learned motor performance. Some small hint of functional organization of these stochastics with regard to motor control is given by the observation that in the populations of cortical units shown in Table I, classification of ultimate projection by the EMG response to intracellular stimulation correlated positively (correlation coefficient $=+0.52$) with classification by EMG activity associated with spontaneous spike discharge (35).

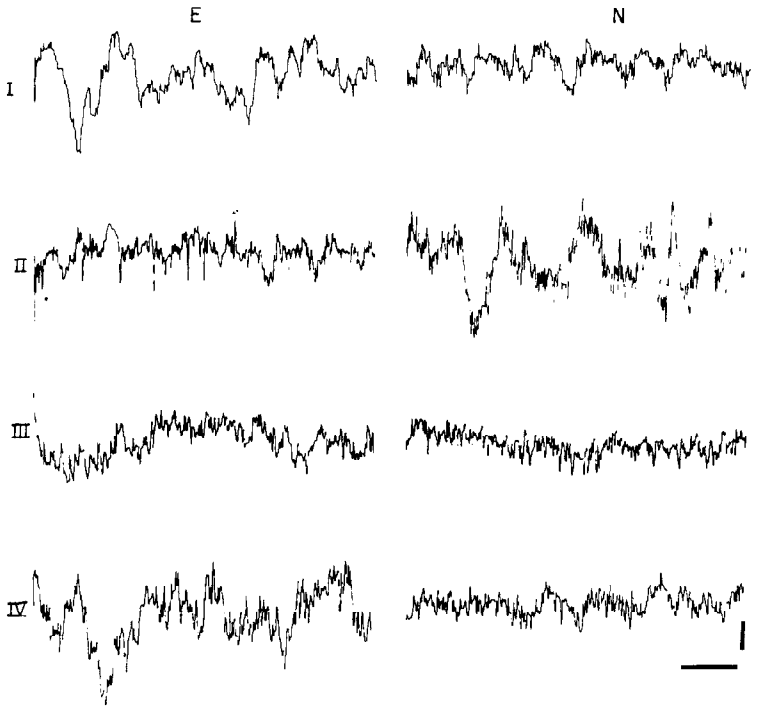


Fig.7. Averaged (bipolar) EMG activity evoked by intracellular electrical stimulation (10 msec current pulse of 0.5 - 6 nA delivered at start of trace) of three different cortical units (I-III). E = response in ipsilateral orbicularis oculis muscle, N = response in ipsilateral levator oris muscle. Numbers of responses averaged equal 100, 200 and 180 respectively. Units classified as follows: I) eye muscle projection, II) nose muscle projection, III) "other" projection, IV) average of EMG activity (180 responses) synchronous with spontaneous discharges of same unit as in III. Amplitude calibration = 20 μV; time calibration = 10 msec. (From Woody and Black-Cleworth, 1973).

5. "Direct" Conditioning

Further support for the direct involvement of motor cortex with blink conditioning is afforded by the ability to introduce an effective electrical conditional stimulus directly into such an area during training. That is, a conditioned blink response can develop from pairing an electrical current pulse to the coronal -pericruciate cortex with glabella tap (Fig. 8). Presumably, the motor cortex participates in the elaboration of the persistent change with conditioning. The short latency of the ensuing conditioned blink response to the electrical CS (less than 12 msec) suggests that more remote areas of the brain are bypassed during initiation of the conditioned movement. Ablation of caudal or

sensory receptor cortex does not adversely affect performance of this conditioned reflex. These experiments do not exclude the possibility of the additional participation of CNS extrinsic to cortical motor areas during the acquisition process.

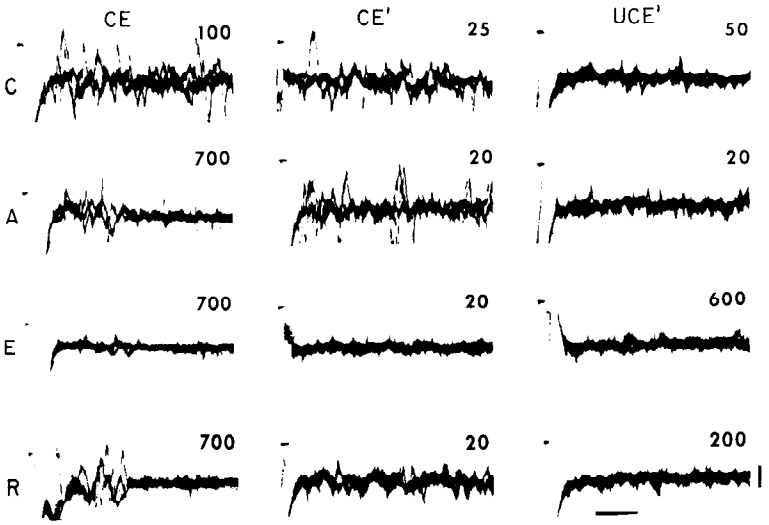


Fig.8. Orbicularis oculi EMG responses to electrical CS (extracellular) at conditioned electrode loci (CE) and unconditioned electrode loci (UCE) in two animals after conditioning (C), then after ablation of cortex posterior to coronal - precruciate region (A), then after extinction of conditioned response by reversing order of CS-US pairing (E), and then after retraining of response by returning to original order of CS-US presentation (R). CE loci are loci 1.5 mm deep into coronal - precruciate cortex at which cathodal electrical CS pulse train was paired with glabella tap during training. Adjacent UCE loci received no pairings. Electrodes were Teflon-coated stainless steel wires of 0.1 mm diameter, cut at the tip and referenced to a neck electrode. Each trace represents three superimposed EMG responses. Stimulus current in microamperes shown upper right; 2-msec stimulus pulse artifact at left of the traces. 50 μV and 10 msec calibrations as shown. (From Woody and Yarowsky, 1972).

Coding of Motor Specificity

By the above criteria, neurons in the motor cortex of the cat appear to be directly involved with the elaboration of conditioned blink responses of the type studied. Hence, one might ask if the pattern of activation of these cortical units could encode information required for initiation of the specific conditioned blink movement.

TABLE I

Characteristics of Intracellular Recordings for Units of Coronal-Pericruciate Cortex in Awake Cats Conditioned to Eye Blink

Cell Projection	# Cells	Membrane Potential (mV) Resting	Action	Current Firing Threshold (nA)	Latency Driven Spike (msec)	Spontaneous Firing Rate (Impulses per sec)
Eye	74	50 ± 20	33± 9	1.3 ± 0.9	2.7 ± 1.0	18.3 ± 17.4
Nose	30	46 ± 20	33± 9	1.9 ± 1.3	2.9 ± 1.2	21.6 ± 15.8
Both	46	51 ± 30	33± 9	1.7 ± 1.1	2.7 ± 1.3	20.0 ± 14.8
Other	71	53 ± 25	*33± 9	1.8 ± 1.2	3.0 ± 1.0	18.3 ± 20.1

* Coincidence, not typographical error

1. Unit Response Partitioned According to Unit Projection

As shown earlier, the magnitude of the mean unit response to click at motor cortex is enhanced after conditioning. Should the resulting increase in evoked activity be confined to units projecting ultimately to the target muscle of the CR and be absolutely greater than the activity evoked in units of different muscle projection, an obvious means would be provided for encoding, neuronally, information required to produce the initiation of a specific movement. This possibility can be examined by comparing averages of PST histograms of unit activity from two populations of cats trained to perform different movements (Fig. 9). One population was trained to perform a conditioned nose twitch by pairing air puff to the nostrils with an auditory CS (9, 38). The other population was trained to blink by pairing click with glabella tap. Unit activity was subdivided according to unit-area projection as determined by extracellular microstimulation via the same electrode from which unit activity was recorded. In cats trained to nose twitch, the CS-evoked activity of units from cortical areas projecting ultimately to nose musculature was selectively increased. CS-evoked activity from unit-areas of different ultimate projection was lower. However, in the blink trained cats, such activity was not selectively increased in unit-areas projecting to blink musculature. On the basis of the magnitude of mean unit activity, these animals should have been twitching their nose rather than blinking their eyes to the click CS. Obviously, some further basis than the magnitude of mean unit activity evoked by the CS must encode the contribution of these units to initiation of the specific conditioned blink movement.

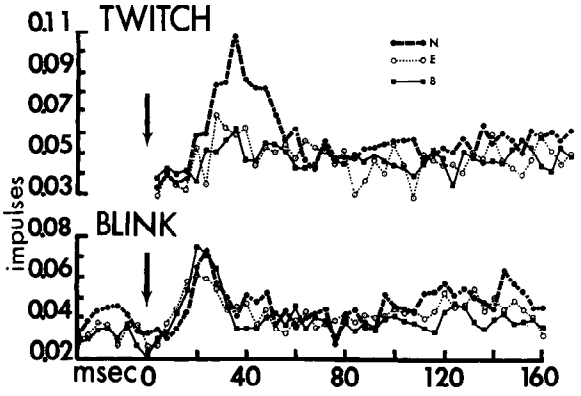


Fig.9. Mean activity of units from nose (N), eye (E), and both (B) projective areas of coronal -pericruciate cortex as determined by extracellular microstimulation. Activity associated with production of conditioned nose twitch is compared with that associated with production of conditioned eye blink. Numbers of units averaged: twitch -N(63), E(18), B(60); blink -N(39), E(68), B(75). Delivery of hiss and click CS for twitch and blink CR's, respectively, is indicated by arrows at 0 msec. Activity preceding stimulus delivery is shown for blink group. Ordinate is mean impulses per 4 msec per unit. (From Woody and Engel, 1972).

2. Response Sub-Partitioned According to Unit Projection and Spontaneous Firing Rate

Further partitioning of the above units according to their rate of spontaneous firing provides additional insights into their possible functional properties. Arbitrary division of units into low (less than 5 impulses per sec) and high (greater than 5 impulses per sec) spontaneous discharge rate suggests that the enhancement of unit response to the CS after conditioning could be preferentially mediated by the units of low discharge rate (Fig. 10). Comparison, after conditioning, of the activity of units of low and high discharge rate separated according to their ultimate muscle projection (Fig. 11) reveals 1) that units of low discharge rate of target muscle projection (eye only) have a greater degree of increase of evoked activity relative to their spontaneous firing level than those projecting to non-target muscles (nose only), 2) that the envelope of their evoked activity during the period of response initiation is greater than that of units projecting to non-target muscles, and 3) that the maximum level of firing in response to the CS is still no greater in units projecting to the target muscle than in those projecting elsewhere. Thus, units of low spontaneous discharge rate that project to the target muscle of the CR may show a selectively enhanced response to the CS, but the magnitude or degree of enhancement per se is still not sufficient to encode initiation of the specific motor act.

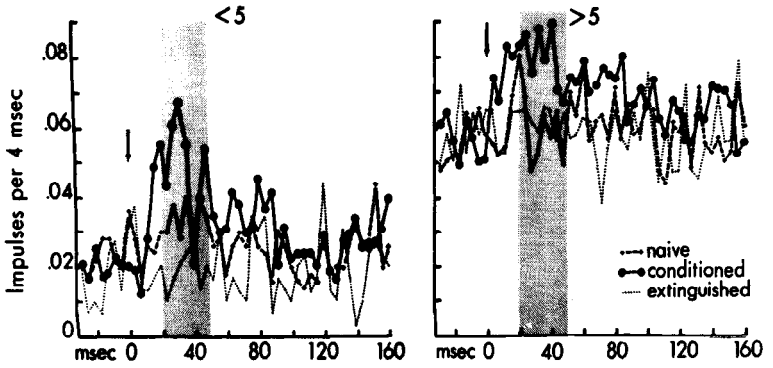


Fig.10. Averaged activity from units in Fig. 3 separated according to rate of spontaneous discharge (< 5 vs. > 5 impulses per sec). Arrows designate click presentation. Shading indicates time at which conditioned blink muscle response occurs. (From Woody et al., 1970).

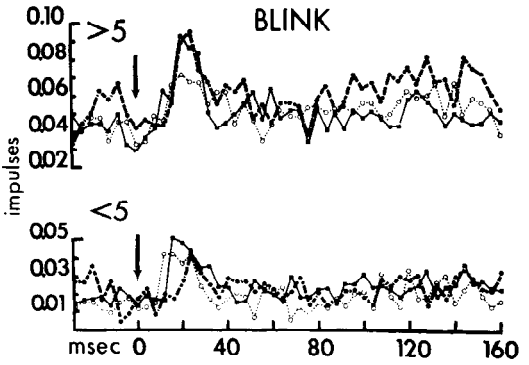


Fig.11. Mean activity of units in Fig. 9, blink, divided into groups with high (>5/sec) and low (<5/sec) rates of spontaneous discharge. Coding of projective types, time of stimulus delivery, and ordinate as in Fig.9. (From Woody and Engel, 1972).

Further support for making a functional distinction between units of low vs. high spontaneous discharge rate can be found. Figure 12 compares spontaneous discharge rate before and after series of 32 click-CS presentations in naive and conditioned animals. The object was to see if serial presentation of the unreinforced CS had an effect on spontaneous unit activity. No effect was found in naive animals, but in the conditioned animals serial click presentation (reinforced after series) was followed by an increase in spontaneous discharge both in units that were classified as projecting ultimately to target musculature (PC) and those that were classified as projecting elsewhere (UPC). The increase in spontaneous discharge rate was mediated preferentially by units of high spontaneous discharge rate and was greater in units that did not project to the target musculature. The possibility is suggested

that cells of low discharge rate that project to the target muscle of the CR selectively mediate initiation of specific conditioned facial movements, while those of higher spontaneous discharge rate that do not project to target musculature selectively mediate other processes such as non-specific arousal associated with CS presentation.

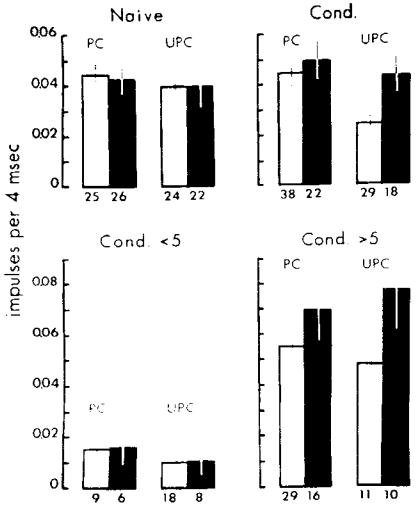


Fig.12. Averaged spontaneous activity rates before (light bar) and just after (dark bar) period of 32 serial click presentations for cells projecting to blink musculature (PC) and cells of other projection (UPC) in naive and blink-conditioned animals. Conditioned animal cell groups separated below into < 5/sec and > 5/sec spontaneous discharge rates. Dotted line designates cutoff point for < 5 grouping. Numbers of cells in each category are shown below each bar. (From Woody et al., 1970).

3. Prevalence of Projective Units As A Function of Muscle Response Conditioned

The number of unit-areas of a particular motor projection encountered in the coronal - pericruciate cortex by a penetrating microelectrode changes as a function of the type of motor response that is conditioned (Fig. 13). In the case of twitch-trained cats, more areas projecting to nose musculature are found than areas projecting to eye musculature. In cats trained to blink, the reverse is true. Larger numbers of "eye" vs. "nose" cells are also found at the motor cortex by use of the intracellular method for determining projection in blink conditioned animals (35). As will next be discussed, this finding may be of use in understanding the way in which initiation of the learned movement might be coded neuronally.

4. Coding of the Initiation of Movement By An Ensemble Average Process

The stochastics of ensemble average processes have been elegantly described by Siebert (26). Let us consider an intuitively appealing example of such a process. Take the process of coin tossing to determine the probabilities of occurrence of a head and a tail. One can empirically approach this problem by selecting an unbiased coin at random, flipping it a large number of times and averaging, over time, the number of

heads and tails flipped. In contrast with the time average, one can take a large number of coins and flip them once, all at the same time. The same probabilities can be determined from averages of the flipped ensemble as from the average, over time, of flipping one representative coin. However, consider what happens if the population of coins is not homogeneous. That is, for example, if 30% of the coins are biased. In this case, in practice, it may not be possible to select a single, representative coin and the time average may differ from the ensemble average. We view neurons much as biased coins. Analytically, functional ensembles or sets are defined, at motor cortex, on the basis of common motor projection, the latter being determined by intracellular or extracellular microstimulation.

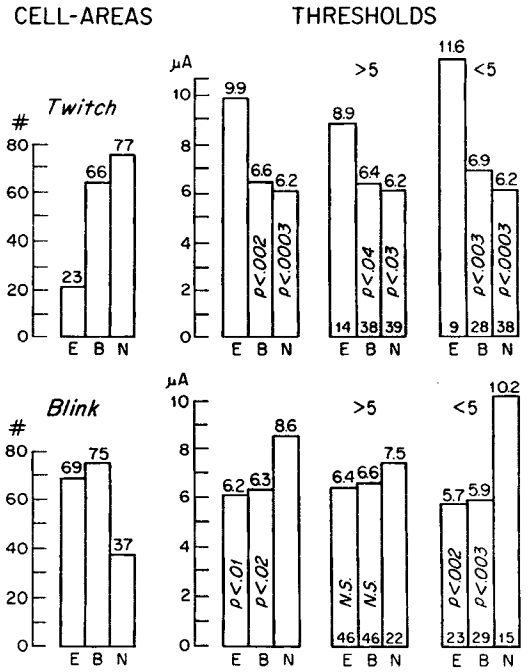


Fig.13. Far left: numbers of cell-areas receiving microstimulation and classified according to projection that were encountered in twitch-trained animals and blink-trained animals. E: eye muscle projection, N: nose muscle projection, B: both eye and nose muscle projection. Center: averaged thresholds (μA) for eliciting EMG response by extracellular microstimulation of cortical areas at which cells on left were identified. These areas were subdivided (right) into two groups according to the level of the spontaneous discharge rate (greater than 5 impulses/sec or less than 5 impulses/sec) of the associated units. The average thresholds were then determined for the eye, nose, and both subgroups within each of these classes. The sample numbers are given at the bottom of each of the bars. Significance of differences in thresholds between B and N versus E cell areas (twitch) or E and B versus N cell areas (blink) as shown. Differences not significant (NS) in >5 blink group. (From Woody and Engel, 1972).

The correlation between the time average of the activity of the unit shown in Figure 4 and behavioral performance might lead one to the oversimplified and erroneous conclusion that the magnitude of the unit response per se provides a sifficient basis for encoding the initiation of a specific motor act of the type studied. Examination of the mean activities of ensembles of such units, classified according to ultimate projection and taking into account the prevalence of encountered units of a particular projective type, leads to a somewhat different conclusion. The coding of initiation of the learned movement appears to derive in part from the number of units over a particular ensemble that are brought to discharge within a narrow time period of a few milliseconds rather than from some longer, temporally ordered, characteristic pattern of single unit discharge. Thus, if one multiplies the number of units encountered of a particular projective classification by their respective mean activity in response to the CS, a basis is provided by which initiation of the learned blink movement might be neuronally controlled. In fact, a basis exists by which to account, neuronally, for small myographic variations in the type of movement produced. The latter is illustrated in Figure 14.

Coding of CS Specificity in Terms of Unit Response at Motor Cortex

The unit response at the motor cortex to a CS that has been repeatedly paired in close temporal association with a US (i.e., a stimulus of conditioning significance) is selectively enhanced after acquisition of classically conditioned facial reflexes of the type studied. Figure 15 compares the mean PST histogram response of cortical units to a CS with that of the same units to a stimulus of neutral significance. Units have been separated according to their ability to respond to either or both stimuli. The selective enhancement of the unit responses to the CS is consistent with the observed behavior in that cats trained in this way do not ordinarily show stimulus generalization, that is, do not perform the conditioned response to other stimuli of comparable intensity and sensory modality to the CS (9, 37).

Despite the above enhancement in unit response to the CS, it is again clear that the absolute response level (impulses per unit time) is not a satisfactory means by itself for encoding the ability to discriminate between stimuli of conditional vs. non-conditional significance. In the click-blink conditioned animals of Figure 15, the magnitude of the unit response to the click CS is no greater than that to a neutral hiss in the same units (Fig. 15 1, C vs. 2, M). However, the prevalence of units of a particular receptive category appears to change as a function of conditioning. That is, more hiss responding units are found at the motor cortex in cats trained to a hiss CS, while more click responding units are found at the same cortical area in animals trained to a click CS (9). The increased overall number of activated CS-responding units results in greater total activity along motor efferent pathways from the cortex following the CS than following the neutral stimulus. Hence, stimuli of differing conditioning significance would have different consequences on motor function. This provides an indication that neurons at the level of the motor cortex transmit neuronally encoded information permitting discrimination between sensory inputs of different significance, the coded transmission

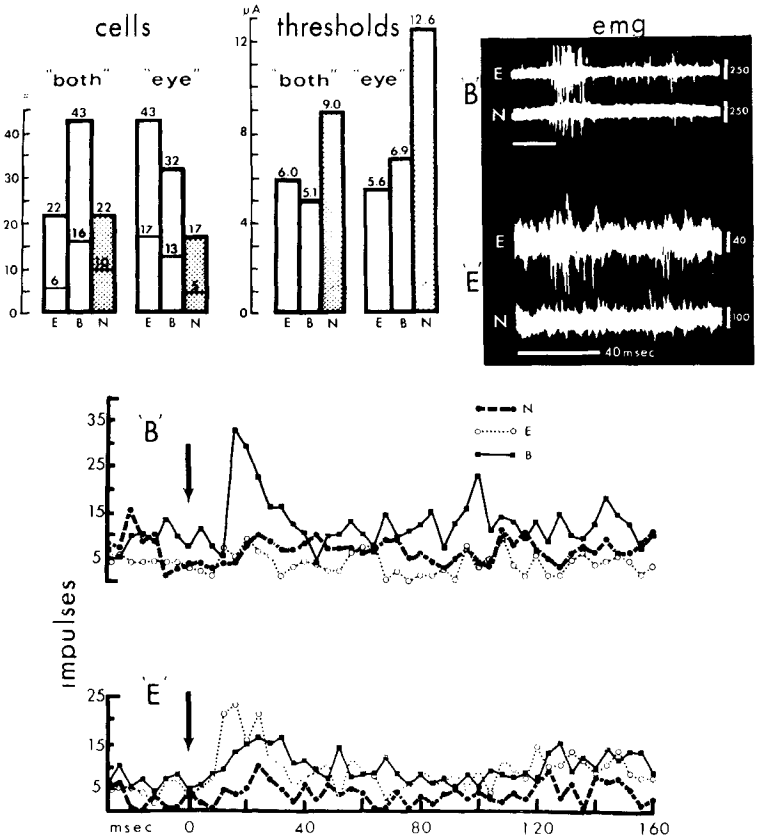


Fig.14. Prevalence, thresholds, and total activity of unit-areas in blink-trained cats with CR in both eye and nose muscles ('B') versus blink-trained cats with pure eye muscle CR ('E'). Examples of bipolar EMG traces associated with the respective types of CR shown upper right. E: electrode pair in eye muscles; N: electrode pair in nose muscles. Click CS delivery at start of sweeps. Amplitude in microvolts. 40-msec time calibrations indicated; note different sweep speed of upper pair of traces. Upper left shows total number of cell areas encountered of each projective classification (extracellular microstimulation) as well as number of areas encountered with associated units of low spontaneous rate (numbers in lower portion of bars). Averaged thresholds (bar graph, above, center) and total activity (line graph, below) of only the low-rate unit-areas are shown. Note that for graphs of total unit activity, impulses refers to the total number of impulses found in each 4-msec epoch in all low rate units encountered as opposed to the impulses per 4 msec per unit shown in previous figures. Times of CS delivery and other labeling as in previous figures. (From Woody and Engel, 1972).

depending not only on a selective enhancement of the response of receptive units to the CS, but also on the response-recruitment of cells which have the potential to respond.

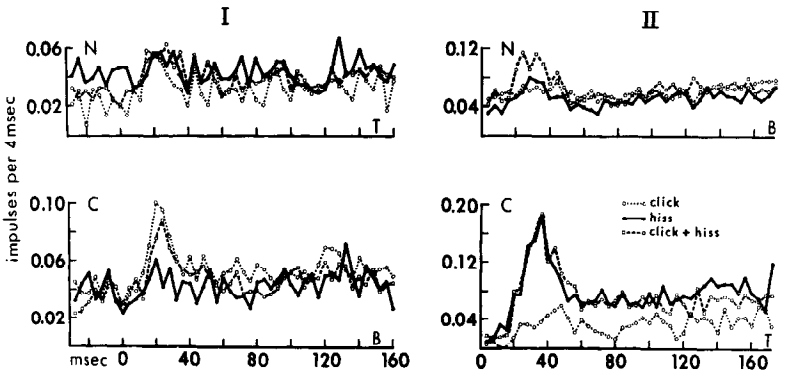


Fig.15. Averaged unit activity evoked by click (I) and hiss (II). Units in each group are grouped separately as showing a response to click, hiss, or click and hiss. N = response to neutral stimulus without conditioning significance; C = response to conditional stimulus; I T and II T same cells, I B and II B same cells. All stimuli presented at time 0; activity to left of 0 in I is spontaneous. Ordinate is mean impulses per 4 msec per unit. In I T and II T the response of the same units is compared to a click of neutral significance and a hiss of conditioning significance, respectively. (The animals were trained to perform a nose twitch in response to the hiss-CS). In II B and I B,unit response is compared to a hiss of neutral significance and a click of conditioning significance, respectively. (The animals were trained to perform a blink in response to a click-CS.) The results show that the unit response to the stimulus of conditioning significance is enhanced after conditioning. (From Engel and Woody, 1972).

Mediation of a Persistent Change with Conditioning

Persistent changes in excitability can be demonstrated, after conditioning, at areas of the motor cortex that are involved with initiation of conditioned motor responses of the type studied. As shown in Figure 16, the amount of extracellularly injected current required to produce an EMG response at unit-areas that project to the target muscle of the CR is less after conditioning. Cortical excitability also changes as a function of the type of motor response that is conditioned. For example (Fig. 13), in cats trained to nose twitch, unit-areas projecting to nose musculature require less current for production of an EMG response than unit-areas projecting to blink musculature. In blink trained cats, the reverse is true. Unit-areas projecting to blink musculature require less current to produce an EMG response than do unit-areas projecting to nose musculature. Interestingly, these differences are still more pronounced in unit-areas from which cells of low spontaneous discharge rate are recorded. Further, less intracellularly injected current is required to initiate an action potential in units projecting to the target muscle of the blink conditioned reflex than in units projecting elsewhere (Fig. 17).

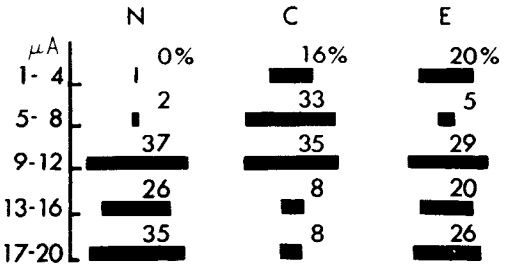


Fig.16. Thresholds for eliciting an EMG response in blink musculature by cortical extracellular microstimulation in naive (N), blink-conditioned (C), and blink-extinguished cats (E). Bars show % of unit-areas found to respond at threshold ranges shown on left. Lower thresholds were required to produce EMG responses in the conditioned animals. Numbers of cell-areas sampled are 54, 62, and 41 for N, C, and E groups respectively.

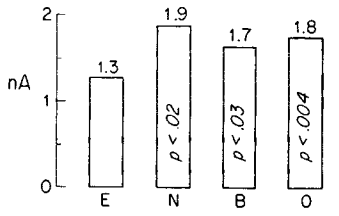


Fig.17. Averaged current required to produce an action potential by intracellular electrical stimulation of cortical cells of "eye" (E), "nose" (N), "both" (B) and "other" (O) muscle projection in awake, blink-conditioned cats. Statistical significance of difference in means vs. that of the "eye" cells as indicated. See Table I for numbers if cells sampled. Mean current thresholds are lower in cells (E) projecting to the target muscle of the CR.

An argument can be made that such excitability increases must be mediated postsynaptically. The intracellularly injected currents of 0.5 - 6nA are too small to directly excite presynaptic regions, and the latencies of the initiated spikes are not compatible with their being initiated presynaptically indirectly through recurrent collateral systems (Table I). The possibility that tonic presynaptic influence is responsible for the excitability increases is also unlikely since no persistent changes in membrane potential or in synaptic PSP's can be demonstrated, nor are the rates of spontaneous firing altered in such cells. It is important to consider this possibility in light of experiments by Wall and colleagues in spinal cord (33) and Kandel, Tauc and others in Aplysia (16, 17). Our results are consistent with previous experiments of Voronin in rabbits (32) in which it was not possible to demonstrate any persistent changes in membrane potential or in synaptic PSP's following cortical conditioning.

We suggest that motor specificity and a persistent change in neuronal firing properties relative thereto seen with conditioned reflexes of the type studied are subserved by persistent postsynaptic excitability increases in cells that project ultimately to the target muscle of the CR. A possible basis for the mediation of such persistent postsynaptic excitability increases by means of local increases in dendritic membrane resistance is discussed elsewhere (35). Postsynaptic excitability in-

creases of this type do not appear to be correlated with the sensory receptive properties of neurons in the motor cortex. Hence, cellular changes subserving the development of CS specificity in conditioning of this type, though reflected in the unit activity at the motor cortex, are either mediated by a different mechanism or are located at some other region of the CNS.

ACKNOWLEDGEMENT

I gratefully acknowledge the collaboration in this research of my colleagues as referenced. I also thank P. Black-Cleworth and S. Jordan of UCLA for constructive review of the manuscript.

This research was supported in part by USPHS HD-05958, HD-04612, and the Department of Mental Hygiene, State of California.

REFERENCES

1. Asanuma, H. Cerebral cortical control of movement. Physiologist 16: 143-166, 1973.
2. Asanuma, H., S. D. Stoney, Jr., and C. Abzug. Relationship between afferent input and motor outflow in cat motorsensory cortex. J. Neurophysiol. 31: 670-681, 1968.
3. Buchwald, J. S., and K. A. Brown. Subcortical mechanisms of behavioral plasticity. In: Efferent Organization and the Integration of Behavior, edited by J. Maser. New York: Academic Press, 1973, p. 100-136.
4. Buerger, A. A., and A. Fennessy. Longterm alteration of leg position due to shock avoidance by spinal rats. Exper. Neurol. 30: 195-211, 1971.
5. Chambers, W. W., and C-N Liu. Cortico-spinal tract of the cat. An attempt to correlate the pattern of degeneration with deficits in reflex activity following neocortical lesions. J. Comp. Neurol. 108: 23-55, 1957.
6. Cohen, D. H. Development of a vertebrate experimental model for cellular neurophysiologic studies of learning. Conditional Reflex 4: 61-80, 1969.
7. Disterhoft, J. F., and J. Olds. Differential development of conditioned unit changes in thalamus and cortex of rat. J. Neurophysiol. 35: 665-679, 1972.
8. Eisenstein, E. M., and M. J. Cohen. Learning in isolated prothoracic insect ganglion. Animal Behavior 13: 104-108, 1965.
9. Engel, J., Jr., and C. D. Woody. Effects of character and significance of stimulus on unit activity at coronal - pericruciate cortex of cat during performance of conditioned motor response. J. Neurophysiol. 35: 220-229, 1972.
10. Evarts, E. V. Pyramidal tract activity associated with conditioned hand movement in the monkey. J. Neurophysiol. 29: 1011-1027, 1966.
11. Farel, P. B., and A. A. Buerger. Instrumental conditioning of leg position in chronic spinal frog: before and after sciatic section. Brain Res. 47: 345-351, 1972.
12. Galambos, R., and G. C. Sheatz. An electroencephalograph study of classical conditioning. Am. J. Physiol. 203: 173-184, 1962.

13. Garol, H. W. The "motor" cortex of the cat. J. Neuropathol. Exp'l. Neurol. 1: 139-145, 1942.
14. Hall, R. D., and R. G. Mark. Fear and the modification of acoustically evoked potentials during conditioning. J. Neurophysiol. 30: 893-910, 1967.
15. Humphrey, D. R. Re-analysis of the antidromic cortical response. I. Potentials evoked by stimulation of the isolated pyramidal tract. Electroenceph. clin. Neurophysiol. 24: 116-129, 1968.
16. Kandel, E., V. Castellucci, H. Pinsker, and I. Kupferman. The role of synaptic plasticity in the short-term modification of behavior. In: Short-Term Changes in Neural Activity and Behaviour, edited by G. Horn and R. A. Hinde. Cambridge: Univ. Press, 1970, p. 281-321.
17. Kandel, E. R., and L. Tauc. Mechanism of prolonged heterosynaptic facilitation. Nature 202: 145-147, 1964.
18. Kennedy, D., W. H. Evoy, and J. T. Hanewalt. Release of coordinated behavior in crayfish by single central neurons. Science 154: 917-919, 1966.
19. Khananashvili, M. M. Some conclusions and perspectives of development of Pavlov's ideas concerning problems of higher nervous activity. Vestnik. AMN USSR No. 9: 49-58, 1972.
20. Kimble, G. A. Hilgard and Marquis' Conditioning and Learning. New York: Appleton-Century-Crofts (2nd Ed.), 1961.
21. Kitai, S. T., T. Tanaka, N. Tsukahara, and H. Yu. The facial nucleus of cat: antidromic and synaptic activation and peripheral nerve representation. Exp. Brain Res. 16: 161-183, 1972.
22. Krasne, F. B., and J. S. Bryan. Habituation: regulation through presynaptic inhibition. Science 182: 590-592, 1973.
23. Livingston, A., and C. G. Phillips. Maps and thresholds for the sensorimotor cortex of the cat. Quart. J. Exptl. Physiol. 42: 190-205, 1957.
24. Mark, R. G., and R. D. Hall. Acoustically evoked potentials in the rat during conditioning. J. Neurophysiol. 30: 875-892, 1967.
25. Olds, J., J. F. Disterhoft, M. Segal, C. L. Kornblith, and R. Hirsh. Learning centers of rat brain mapped by measuring latencies of conditioned unit responses. J. Neurophysiol. 35: 202-219, 1972.
26. Siebert, W. M., and Communications Biophysics Group. Processing Neuroelectric Data. Cambridge, Mass.: Technology Press, 1959.
27. Snider, R. S., and W. T. Niemer. A Stereotaxic Atlas of the Cat Brain. Chicago: Univ. of Chicago Press, 1961.
28. Spencer, W. A., and R. S. April. Plastic properties of monosynaptic pathways in mammals. In: Short-Term Changes in Neural Activity and Behaviour, op. cit.
29. Stoney, S. D., Jr., W. D. Thompson, and H. Asanuma. Excitation of pyramidal tract cells by intracortical microstimulation: Effective extent of stimulating current. J. Neurophysiol. 31: 659-669, 1968.
30. Thompson, R. F. Foundations of Physiological Psychology. New York: Harper and Row, 1967.
31. Towe, A. L. Sensory-motor organization and movement. Neurosci. Res. Prog. Bull. 9: 40-48, 1971.
32. Voronin, L. L., and E. I. Solntseva. After-effects of polarization of single cortical neurons. Intracellular recording. Pavlovian J. Higher Nervous Activity. 19: 828-838, 1969.

33. Wall, P. D. Habituation and post-tetanic potentiation in the spinal cord. In: Short-Term Changes in Neural Activity and Behaviour, op. cit.
34. Woody, C. D. Conditioned eye blink: gross potential activity at coronal -precruciate cortex of the cat. J. Neurophysiol. 33: 838-850, 1970.
35. Woody, C. D., and P. Black-Cleworth. Differences in excitability of cortical neurons as a function of motor projection in conditioned cats. J. Neurophysiol. (In press).
36. Woody, C. D., and G. Brozek. Gross potentials from facial nucleus of cat as an index of neural activity in response to glabella tap. J. Neurophysiol. 32: 704-716, 1969a.
37. Woody, C. D., and G. Brozek. Changes in evoked responses from facial nucleus of cat with conditioning and extinction of an eye blink. J. Neurophysiol. 32: 717-726, 1969b.
38. Woody, C. D., and J. Engel, Jr. Changes in unit activity and thresholds to electrical microstimulation at coronal - pericruciate cortex of cat with classical conditioning of different facial movements. J. Neurophysiol. 35: 230-241, 1972.
39. Woody, C. D., N. N. Vassilevsky, and J. Engel, Jr. Conditioned eye blink: unit activity at coronal - precruciate cortex of the cat. J. Neurophysiol. 33: 851-864, 1970.

30th Brazilian Cardiology Meeting

The XXX Congresso Brasileiro de Cardiologia (the 30th Brazilian Cardiology Meeting) sponsored by the Brazilian Society of Cardiology will be held from July 7th to 13th, 1974 in the Convention Hall of the Hotel Nacional-Rio, in Rio de Janeiro.

This important event will be attended by all Brazilian Specialists, as well as the most important physicians and surgeons from abroad, who will discuss the most varied matters, showing the advanced technological and scientifical stage of Cardiology. Over 2,500 people are expected to participate.

This Congress, in the same manner as the previous ones, will be comprised of round-tables, lectures, symposia, conferences, lunch meetings, discussion of free matters, several courses, etc., during which the participants will be able to exchange ideas and present works developed in the field of their specific activities, thus contributing to update and enrich their knowledge.

All correspondence should be addressed to Professor Nelson Botelho Reis - President of the XXX Congresso Brasileiro de Cardiologia (the 30th Brazilian Cardiology Meeting), Executive Secretaryship at Rua 19 de Fevereiro, 76 - Rio de Janeiro - GB - Brazil.

ANNOUNCEMENT

THE JOHN F. PERKINS, JR. MEMORIAL AWARDS

The American Physiological Society invites applications for the John F. Perkins, Jr. Memorial Fellowships. The fund is designed to provide supplementary support for the families of foreign physiologists who have arranged for fellowships to carry out scientific work in the United States. Applications by U.S. physiologists, who require supplementary assistance to work abroad will also be considered.

It is the interest of the Perkins Fund to develop the full potentialities for cultural benefit associated with scientific exchange. Preference will be given to physiologists working in the fields of respiratory physiology, neurophysiology and temperature regulation.

Each application will be made by both the visiting scientist and his host. Ordinarily, the joint applicants will have made financial arrangements for the visiting scientist before applying to the Perkins Fund for family support. The application will contain an account of these arrangements together with a description of the proposed scientific work, and a brief account of how the visitor and his family intend to make use of the cultural benefits.

The amount available for each award will be in the range of $2,000-$5,000, depending upon the estimated needs of the family over and above the amount already available to the visiting scientist. Crdinarily, 2-4 awards will be available in any one year.

Application forms for host and visiting scientist may be obtained from Dr. Orr Reynolds, Executive Secretary, American Physiological Society, 9650 Rockville Pike, Bethesda, Maryland 20014, U.S.A.

STATISTICS ON APS MEMBERSHIP

(As of December 1973)

Distribution by Employment

Medical Schools	2238	56.11%
Physiology Departments	(972)	(24.37%)
Other Preclinical Departments	(324)	(8.12%)
Clinical	(881)	(22.09%)
Administration	(61)	(1.53%)
Hospitals and Clinics	392	9.83%
Veterinary Schools	33	.83%
Dental Schools	29	.73%
Public Health & Graduate Schools	118	2.96%
Undergraduate Schools	284	7.12%
Commercial Companies	82	2.06%
Government (Inc. V.A.)	258	6.47%
Institutes and Foundations	292	7.32%
Private Practice	60	1.50%
Emeritus or Inactive	202	5.07%
	3988	100.00%

Distribution by Degree

	%
Ph.D.	47.25
M.D.	39.38
Ph.D. & M.D.	10.16
D.Sc	.96
Ph.D. & DVM	1.08
Ph.D. & DDS	.26
Other Degrees	.91
	100.00

Distribution by Specialty

	%
Cardiovascular	16.40
Neurophysiology	15.42
Endocrines and Reproduction	12.60
Electrolyte and Water Balance	10.54
Respiration	6.51
Renal	4.40
Muscle and Exercise	4.40
Gastrointestinal, Food & Nutrition	4.28
Environmental	4.26
Cellular & Tissue	3.97
Blood	3.24
Comparative	1.94
Energy Metabolism & Temperature Regulation	1.80
All other Categories (none above 1.5%)	10.24
	100.00

COMPUTER TEACHING SESSION REPRINTS

Reprints of "Computer Assisted Education" which appeared in the November 1973 issue of The Physiologist are available at $1.00 each from: APS Education Office, 9650 Rockville Pike, Bethesda, Maryland 20014.

ON BLOOD PRESSURE CONTROL*

GUNTER N. FRANZ
Department of Physiology and Biophysics
West Virginia University Medical Center
Morgantown, West Virginia

Part 1: Set Point and Gain

The application of system analytic concepts to blood pressure regulation by baroreceptor reflexes has brought with it the use of terms such as "resetting of the set point", "open-loop gain", "closed-loop gain", etc. (e.g., 15). It is often not understood that the use of these concepts may imply (a) linearization, (b) a certain equivalent model of the system, (c) a system more "intact" than warranted by the experimental procedures, etc. It is the purpose of this section to review and clarify the use of "set point" and "gain" in the quantitative description of the baroreceptor control system.

1. Operating point vs. set point.

The essential features of the baroreceptor control loop are given in Figure 1. The curves in this figure depict only the steady state behavior of the baroreceptor reflexes; all pressures are mean pressures; the functions of carotid sinus and aortic baroreceptors are lumped together; pulsation effects are neglected.

The curve in block "1" of Figure 1 represents the relationship between systemic arterial pressure (P_a) and pressure at the baroreceptors (P_b) during an open-loop experiment, i.e. the baroreceptor areas are connected to external reservoirs at varying pressure levels. This open-loop characteristic, the equivalent of Koch's (14) "Blutdruckcharakteristik", indicates the whole range of regulatory ability of the baroreceptor reflex.

In block "2" of Figure 1 baroreceptor pressure (P_b) as a function of systemic arterial pressure (P_a) is given for the intact, closed-loop state. With the assumption that hydraulic pressure drops are negligible and that no hydrostatic pressure differences exist (recumbent position), this closed-loop condition is described by a straight line through the origin with a 45^0 slope.

The circular arrangement of the two blocks in Figure 1, where P_a and P_b alternate in the roles of "input" and "output" can be considered a "minimal" representation of the control system in the intact closed-loop state. The functional relationships of blocks "1" and "2" are both satisfied by only one pair of values for the two pressures as defined by

---

*Taken from the introductory remarks given at the session on Blood Pressure Control at the 1973 Federation Meetings. Investigations reported here were in part supported by Public Health Service Grants HE-1315 and GM-739, National Aeronautics and Space Administration Grant NGL-49-001-001, and National Science Foundation Grant GB-27642.

the intersection of the two curves (P_{a1}, P_{b1}; Figure 1, right). The pressure P_{a1} is, in fact, the mean blood pressure existing in the normal, closed-loop state. The point of intersection is therefore appropriately called the steady state operating point of the system (12). Mathematically, it represents the solution of two independent simultaneous equations. Functionally, it can be considered a "compromise" or "dynamic equilibrium" point reconciling open-loop behavior and closed-loop condition.

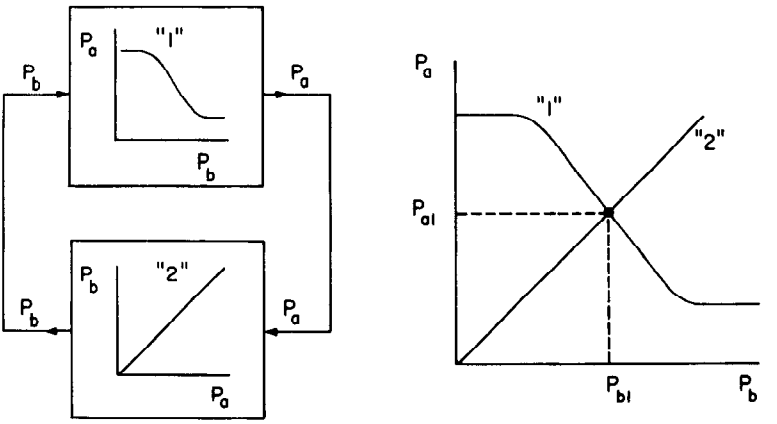


Fig.1. Minimal representation of the baroreceptor control system. P_a-systemic arterial pressure, P_b-baroreceptor pressure. Curve "1"-open-loop characteristic, Curve "2" - closed-loop condition. P_{a1}, P_{b1}-intersection of curves "1" and "2" or operating point of the system. All pressures are mean pressures, baroreceptor regions are lumped, pulsation effects are neglected.

Frequently, the operating point (i.e. the "normal" blood pressure) is called the "set point" of the system (e.g., 15). This is unfortunate. For one, it suggests that blood pressure is controlled rigidly, somewhat in analogy to the action of a thermostat, when, in fact, it does fluctuate according to the demands of the organism. Secondly, it fosters the idea that the barostatic reflexes spring into action only whenever the blood pressure deviates from this set point or "normal" level; they are, of course, tonically active and thus maintain a dynamic equilibrium. This notion of a set point also differs from the more common one of the set point being a reference input to a control system. It does, however, provide a physiological correlate for the set point, which is more than can be said of set point "generators" postulated for other systems.

A "fictitious" set point variable may arise from certain modelling procedures. This is demonstrated in the next section.

2. The linearized system.

The nonlinear open-loop curve in Figure 1 can be linearized around the operating point. This linear approximation is given by the tangent at the operating point. The tangent has a slope -G and a P_a-axis intercept $P_{ao}=GP_o$ (Figure 2, equ. 1). The second equation in Figure 2, describes the closed-loop condition. (In this case we can set H=1). The simultaneous solution of the two equations in Figure 2, i.e. the operating point, is then given by the third equation.

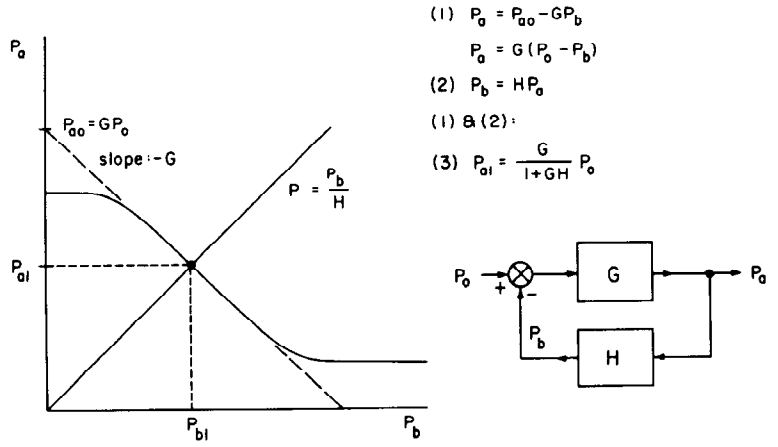


Fig.2. Linearization of the open-loop characteristic around the operating point defines a gain (-G) and a fictitious set point ($P_o=P_{ao}/G$). The equations for the open-loop curve (equ. 1) and the closed-loop condition (equ. 2) can also be symbolized by the canonical block diagram for a single-loop feedback system. Equation 3 defines the operating point as a function of the fictitious set point.

These manipulations result in the reduction of the system to the basic or canonical form of a single-loop feedback control system as symbolized by the block diagram in Figure 2. The block diagram can be interpreted as follows: An "input" or "set point" P_o is "compared" with P_b; the difference is "amplified" with "gain" G to yield the "output" P_a (equ. 1 in Fig.2). In the closed-loop state, the output is "fed back" to the comparator as P_b (equ. 2 in Fig.2; in this case, H=1).

The following is worth noting:

(a) The "set point" variable is P_o ($=P_{ao}/G$) and not the resultant P_{al} (operating point).
(b) The open-loop gain or loop gain, the amplification for a signal traversing the complete feedback loop once, is

$G_{OL} = -GH$ or
$G_{OL} = -G$ for H=1 ("unity feedback")

(c) The closed-loop gain, the net amplification between input and output, is $G_{CL} = G/(1+GH)$ from equ. 3 in Figure 2.

For unity feedback (H=1) we have

$$G_{CL} = G/(1+G) \text{ and}$$

$\lim_{G \to \infty} G_{CL} = 1$, i.e. if the loop gain becomes very large the output will practically equal the input. However, the open-loop gain of the blood pressure control system is quite modest.

(d) Set point (as defined by P_{ao}/G) and gain (slope, incremental gain) are the results of a linearization procedure. Their values depend on the location of the operating point on the nonlinear open-loop curve.

(e) The "explicit" set point (input) in the block diagram is at best an "implicit" set point in the actual system (4, 12). As with most other biological control systems, there is no evidence for a physiological variable providing an explicit set or reference point for the blood pressure control system.

(f) The notion of a fictitious set point could be of some use in the case of a regulator system designed to keep a physiological variable fixed. However, the purpose of blood pressure control is to hold pressure to an appropriate level.

3. Response to perturbations.

Since the closed-loop system exhibits negative feedback (slope of open-loop characteristic is negative), we should expect that the effects of disturbances are less pronounced than in the open-loop case. Let us assume then that a disturbance ΔP is added to the systemic pressure (Fig. 3., equ. 1 and block diagram), and that the gain G remains unchanged. The blood pressure control system will make a partial correction for the disturbance and establish a new operating point. (Fig. 3, equ. 3). The original disturbance ΔP is now attenuated by the factor $1/(1+GH)$ (Fig. 3, equ. 4). From such an experiment the open-loop gain can be computed (Fig. 3).

Since the curve for the closed-loop condition remains unchanged (Fig. 3, equ. 2), the new operating point (P_{a2}; equ. 3 in Fig. 3) must lie on it too. The shift of the operating point by ΔP_a is then equivalent to a parallel displacement (G = const.) of the open-loop characteristic. This implies, however, a change of the fictitious set point level to $P_0 + (\Delta P/G)$, but, especially for modest disturbances, one would hardly expect an actual change of the system characteristics. It should also be clear that the new open-loop curve in Figure 3 actually represents the combined behavior of the control system and the separate system causing the disturbance.

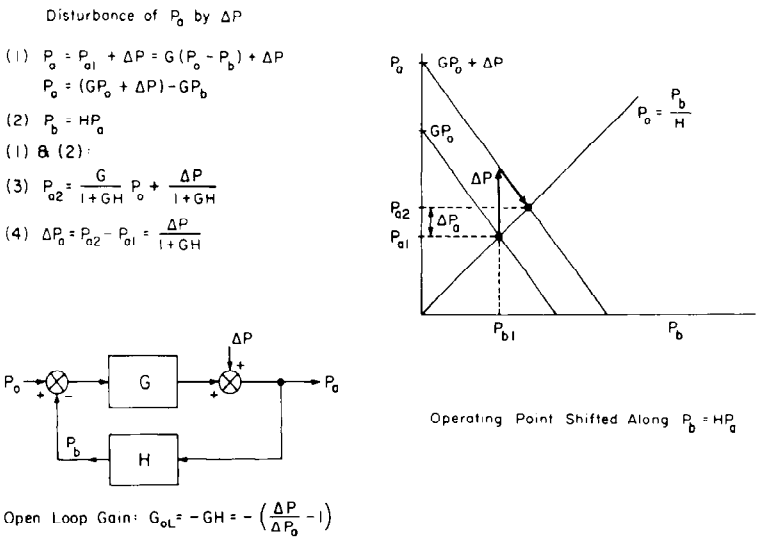


Fig.3. Attenuation of an output disturbance by negative feedback. Both operating point and fictitious set point are shifted (P_O+ (ΔP/G)).

The operating point may also be shifted along the open-loop curve as, for instance, in a change from the recumbent to the upright position resulting in a hydrostatic pressure drop Δ P at the carotid sinuses (Fig. 4, equ. 2). In this case we note:

(a) The attenuation of the disturbance is less effective than in the previous example (compare equ. 4 in Fig. 3 with equ. 3 in Fig. 4).

(b) Although there is no shift of the open-loop curve, the equivalent of a set point shift has taken place (P_O+Δ P); in fact, for large values of G, ΔP_a approaches the magnitude of the additional "input" P(Fig. 4, equ. 3).

(c) The closed-loop gain is easily calculated from such an experiment (Fig. 4).

In the two examples discussed, one can postulate, on purely formal grounds, a shift of the fictitious set point variable for the simple equivalent system (non-adaptive, with constant parameters) in combination with the external disturbing system. But not much physiological insight can be derived from these set point shifts. Nevertheless, true resetting of the adaptive blood pressure control system does occur. For example, it is appropriate that blood pressure be adjusted during exercise. With a number of simplifications (recumbent position, no slope changes, neglect of pulsation effects, etc.) we can assume a simple parallel shift of the open-loop curve resulting in a modest rise in systemic pressure (Fig. 5).

If the same increase in blood pressure were accomplished by a postural change alone, an entirely different carotid sinus pressure would be needed ($P_{b1}-\Delta P_b$ vs. $P_{b1}+\Delta P_b$). Quite obviously, a functional adaption of the control system has taken place.

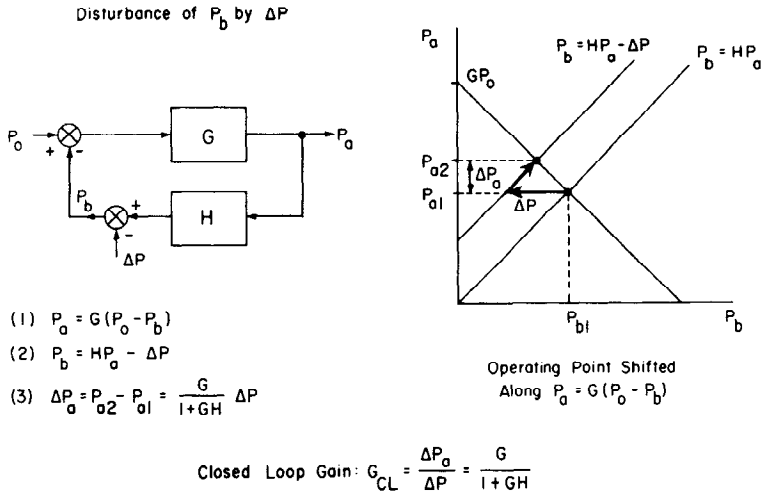


Fig.4. Attenuation of a disturbance of the feedback signal. See text.

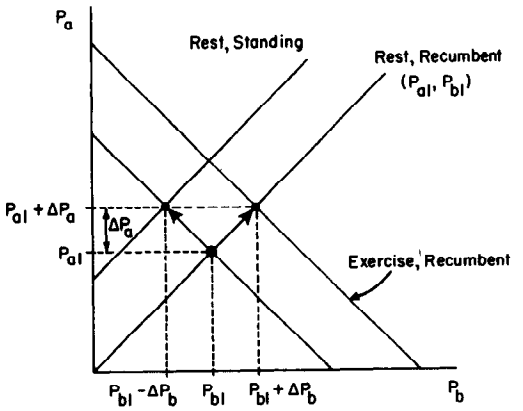


Fig.5. Comparison of true and fictitious changes in system parameters. See text.

4. Gain.

Published values for open-loop and closed-loop gains for the blood pressure control system of a given species vary greatly (e.g., 16, 18, 19, 20, 22). This variation is not only due to differences in anesthesia, severity of trauma inflicted by the experimenter, etc., but also due to generally overlooked methodological problems. Generally accepted techniques for inducing pressure perturbations especially in unanesthetized, "intact" preparations can lead to erroneous results. This is obvious from the following derivation of the simplified general gain formula.

The net driving pressure of the systemic circulation (A-V pressure difference) equals the product of total peripheral resistance and cardiac output (Figure 6). Cardiac output is the product of stroke volume and heart rate. The discussion is simplified if we assume that, in the range of interest, stroke volume stays constant and venous pressure is much smaller than arterial pressure (Fig. 6). Then an increment in arterial pressure (ΔP_a) due to increments in heart rate (ΔHR) and peripheral resistance (ΔR) will be given by the formula in Figure 6 (higher-order products of incremental quantities neglected). If the increments of the "effector" quantities (HR and R) are in turn reflexly governed by decrements in baroreceptor pressure (ΔP_b), we may define the "partial" gains G_{HR} and G_R. From Figure 6 it is now evident that the overall gain (6) of the baroreceptor reflex system is (in this simplified form) a function of the partial gain as well as heart rate and resistance. Consequently, maneuvers such as opening of large A-V shunts, inflation of aortic cuffs, injection of epinephrine, etc. will lead at least to partial "clamping" (i.e. removal from reflex control) of some of the variables in the gain formula. This, however, is equivalent to a change in system parameters, and the resultant gain values are not those of the "intact" animal.

$$P_a - P_v = R \times CO = R \times HR \times SV$$

with $P_v \approx \text{const.} \ll P_a$; $SV \approx \text{const.} = K$

$$\Delta P_a \approx K (R \times \Delta HR + HR \times \Delta R)$$

$$\Delta P_a \approx K \left(R \frac{\partial HR}{\partial P_b} + HR \frac{\partial R}{\partial P_b} \right) \Delta P_b$$

$$G = \frac{\Delta P_a}{\Delta P_b} \approx K (R \times G_{HR} + HR \times G_R)$$

Fig.6. Derivation of a simplified gain formula for the baroreceptor reflex. P_a- systemic arterial pressure, P_V- venous pressure, R-peripheral resistance, CO- cardiac output, HR- heart rate, SV- stroke volume, P_b- baroreceptor pressure, G- total gain, G_{HR}- partial gain for heart rate, G_R- partial gain for peripheral resistance.

The point of the preceding remarks is that even the most basic notions of control theory need to be applied with care if they are to serve any purpose in the description of blood pressure control.

Part II: Properties of Baroreceptors.

Many contributions to the quantitative analysis of the blood pressure control system have been made. In the following discussion I shall consider only the description of the properties of the feedback transducers

of the system or, more specifically, the characteristics of single baroreceptor fibers.

In Figure 7 we see a representative set of static input-output curves for single baroreceptor fibers from rabbit, cat and dog (2, 6, 9, 13, 17). The curves vary considerably in shape. They all show a minimum sustained firing frequency (between 10-30 pulses per second) for some threshold pressure and usually a saturation level if subjected to high pressure. The range in between is most economically described by piece-wise linear segments. Surprisingly, no hysteresis is evident, provided sufficient time for adaptation (50 seconds or more) is given and damaging stimulus levels are avoided. If the static firing rate of a whole bundle of baroreceptor fibers is measured, then typically a sigmoidally shaped characteristic is obtained (e.g., 13).

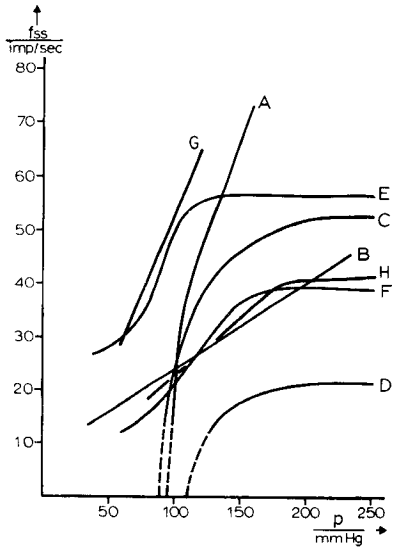


Fig.7. Static response of single baroreceptor fibers for several species. f_{ss}- steady state firing rate, p- carotid sinus or common carotid pressure. A,B,G, H- rabbit, carotid sinus nerve (2,6); C,D- cat, carotid sinus nerve (17); E- dog, carotid sinus nerve (13); F- cat, common carotid nerve (9).

The dynamic properties of baroreceptors can be investigated with step-wise pressure changes. The overshoots and undershoots of the single-fiber responses to such stimuli (Fig. 8) demonstrate the bidirectional (though asymmetric) rate sensitivity of these receptors. Analysis of unit step responses in the linear range shows that this "rate" sensitivity extends to higher-order derivatives of the pressure stimulus (Fig. 9). The differential equation for the particular response in Figure 9 is of third order for both input and output because at least three exponential terms were needed to fit the transient part of the response (6).

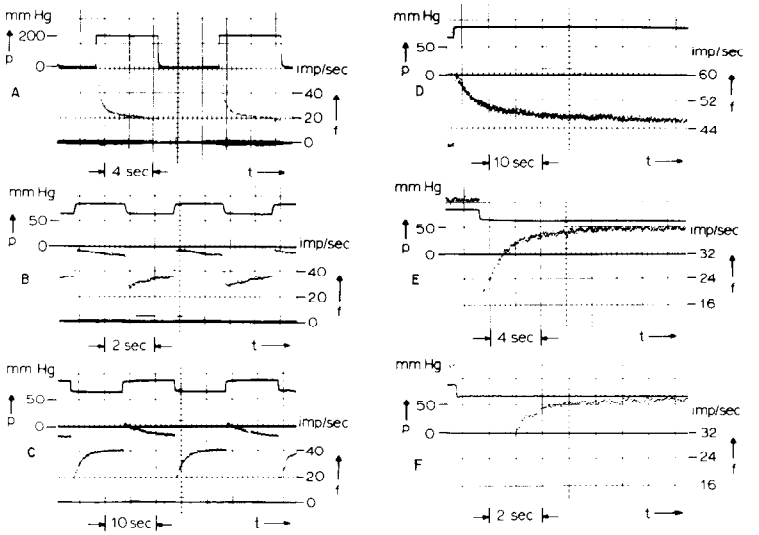


Fig.8. Single fiber responses to step-wise pressure changes; rabbit, carotid sinus nerve (6; reproduced with permission, J. Appl. Physiol.).

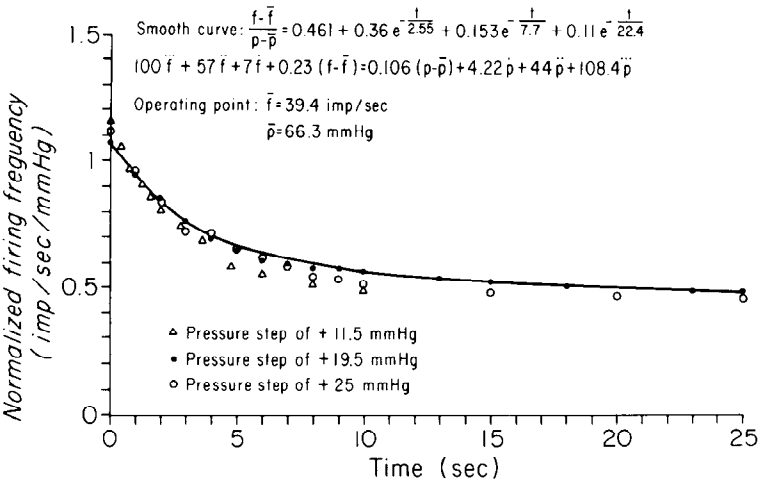


Fig.9. Unit step responses and differential equation based on data from the 19.5 mm Hg pressure step (6; reproduced by permission, J. Appl. Physiol.).

A partial explanation for the dynamic transient and the long adaptation time (Fig. 8) can be found in mechanical "filtering" which takes place before the stimulus reaches the receptor membrane proper (6). How such filtering can occur is evident from the idealized mechanical network in Figure 10 (5). In this schematic,the dendritic aborizations of a baroreceptor fiber are reduced to a single "equivalent" dendritic cylinder undergoing cross-sectional deformation. It is important to realize that the sensory dendrites cannot be rigidly coupled to the tissue substrate, and that the tissues involved are viscoelastic. This viscoelasticity is modelled in the network by elastic and viscous elements (springs and dashpots). Many such elements are needed because the dynamic behavior of tissues is characterized by many time constants (discrete approximation of a continuous spectrum of time constants; ref. 21).

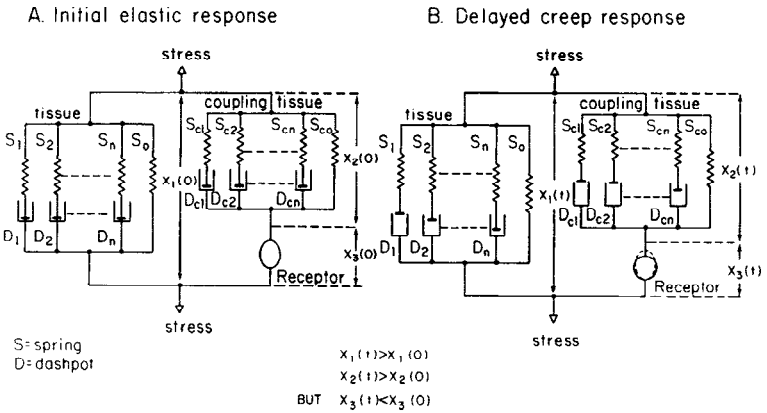


Fig.10. Network model for the receptor-tissue complex as an explanation of mechanical filtering of the pressure stimulus (5).

The initial response of the model network to a step-wise stress (isotonic) is purely elastic (dashpots "locked"; Fig. 10A); thereafter viscoelastic creep takes place (Fig. 10B). If we assume a faster creep rate for the coupling tissue than for the substrate, the deformation of the sensory dendrite will show an overshoot (Fig. 11A). This overshoot is even more pronounced during isometric deformation (Fig. 11B). Firing rate transients corresponding to Fig. 11A and B have been observed in stretch receptors (e.g., 23).

In general, creep of tissues proceeds roughly proportionally to log t (1, 7, 8, 10). Approximating the logarithmic time course with five exponential terms, a computer simulation of the isotonic response of the discrete model in Figure 10 was performed (5). The resultant receptor deformation (Fig. 12) can be translated into a surface area change (upper graph, Fig. 13) and a corresponding depolarization (lower graph, Fig. 13) of the sensory membrane. The depolarization has overshoot and adaptation similar to those observed for the firing frequency of baroreceptors

and other slowly adapting mechanoreceptors. Major assumptions underlying these successive transformations (deformation to surface area change to depolarization) are: (a) The elliptical deformation of the equivalent dendritic cylinder leads primarily to a change in surface area while the cross-sectional area stays practically constant; this has been confirmed for the Pacinian corpuscle (e.g., 11). (b) The graded sodium and potassium conductances of the sensory membrane are first-order functions of the surface area of the membrane (5).

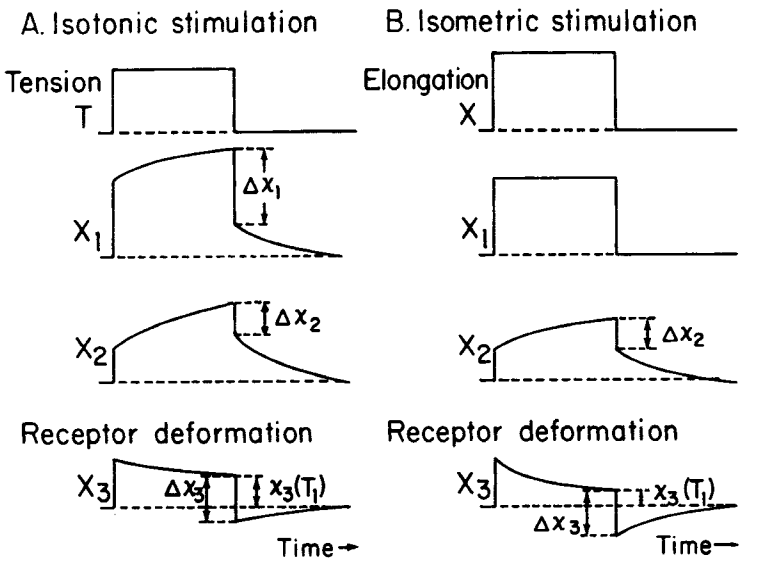


Fig.11. Expected receptor deformation if the model is subjected to isotonic or isometric deformation. Even with substrate (X_1) and coupling tissue (X_2) showing creep, the receptor deformation (X_3) has overshoot and adaptation (5).

The simulation of the response of the receptor-tissue complex to isotonic stress does, of course, not exactly correspond to step-wise pressure stimulation of the carotid sinus. In the latter case the dimensions of the sinus continue to change because of viscoelastic creep. Hence pressure-induced wall tension will not remain constant according to the Law of Laplace (3). The simulation does demonstrate that the decaying ("adaptive") transient of baroreceptor firing frequency is compatible with the creep transient of the sinus wall; unspecified "fatigue" processes need not be postulated.

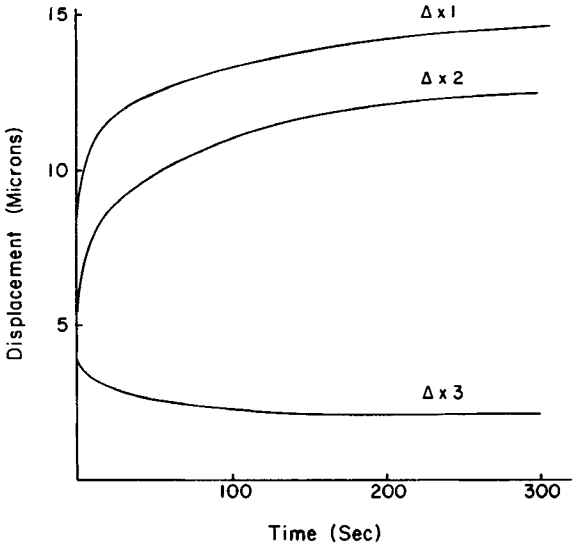


Fig.12. Result of a computer simulation of isotonic stress. ΔX_1, ΔX_2, ΔX_3: deformation of substrate, coupling tissue and receptor, respectively (5).

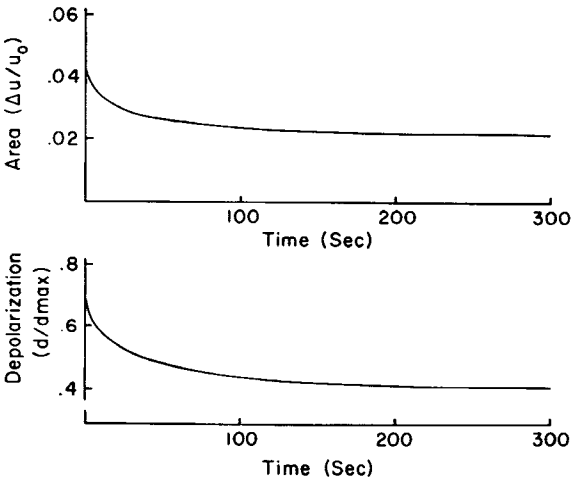


Fig.13. Result of a computer simulation of isotonic stress. Upper graph- normalized surface area of the sensory membrane; lower graph- normalized depolarization of the sensory membrane. See text (5).

The material presented in Part II provides an example for the application of system-analytic techniques of the "input-output" or "black box" variety. The result is a concise quantitative statement (here a differential equation) which is of great value if we wish to obtain the whole set of equations governing the complete control system. But such equations are also limited in that they often are "only" phenomenological descriptions, inviting the accusation that they represent at best "glorified curve fitting." Their very conciseness seems to incite such objections even if they are better behavioral descriptions than qualitative statements based on poor analytical strategies. Nevertheless, the perpetrators of "glorified curve fitting" ought to exhibit some curiosity about the contents of their "black boxes" even if the experimental difficulties are too great to obtain "hard" data. The mechanical network model of the receptor-tissue complex and the subsequent simulations represent my attempt to follow this dictum. The result is, in my opinion at least, a good hypothesis for transducer action applicable to many mechanoreceptors not just baroreceptors.

REFERENCES

1. Alexander, R. S. Viscoplasticity of smooth muscle of urinary bladder. Am. J. Physiol. 224 (3): 618-622, 1973.
2. Bronk, D. W., and G. Stella. The response to steady pressures of single end organs in the isolated carotid sinus. Am. J. Physiol. 110: 708-714, 1935.
3. Burton, A. C. Physiology and Biophysics of the Circulation. 2nd Ed. Chicago: Year Book Medical Publishers, 1972.
4. Engelberg, J. Physiological Regulation: The Steady State. The Physiologist 9(2): 69-88, 1966.
5. Franz, G. N., and D. G. Frazer. A model for the dynamic response of slowly adapting mechanoreceptors. (Abst.) Proc. Int. Union Physiol. Sci. 9: 185, 1971.
6. Franz, G. N., A. M. Scher, and C. S. Ito. Small signal characteristics of carotid sinus baroreceptors of rabbits. J. Appl. Physiol. 30(4): 527-535, 1971.
7. Galford, J. E., and J. H. McElhaney. A viscoelastic study of scalp, brain, and dura. J. Biomechanics 3: 211-221, 1970.
8. Goto, M., and Y. Kimoto. Hysteresis and stress-relaxation of the blood vessels studied by a universal tensile testing instrument. Japan. J. Physiol. 16(2): 169-184, 1966.
9. Green, J. H. Baroreceptor and chemoreceptor control of the circulation. Ph. D. Thesis, Univ. of London, England, 1954.
10. Hildebrandt, J. Comparison of mathematical models for cat lung and viscoelastic balloon derived by Laplace transform methods from pressure-volume data. Bull. Mathem. Biophysics 31: 651-667, 1969.
11. Il'inskii, O. B., N. K. Volkova, and V. L. Cherepnov. Structure and function of Pacinian corpuscles. Fiziologicheskii Zhurnal SSSR imeni I. M. Sechenova 54(3): 295-302, 1968. (Neuroscience Translations No. 6, pp. 637-643, 1968-69).
12. Jones, R. W. Physiological control systems. 16th Ann. Conf. Engl. Biol. Med. pp. 237-254, 1963.
13. Kalkoff, W. Pressorezeptorische Aktionspotentiale und Blutdruckregulation. Verh. Dtsch. Ges. Kreislaufforschg. 23: 397-401, 1957.

14. Koch, E. Die reflektorische Selbststeuerung des Kreislaufes. Steinkopff, Dresden, 1931.
15. Korner, P.I. Integrative neural cardiovascular control. Physiol. Revs. 51(2): 312-367, 1971.
16. Lamberti, J.J., Jr., J. Urquhart, and R.D. Siewers. Observations on the regulation of arterial blood pressure in unanesthetized dogs. Circulation Res. 23: 415-428, 1968.
17. Landgren, S. On the excitation mechanism of the carotid baroceptors. Acta Physiol. Scand. 26: 1-34, 1952.
18. Sagawa, K., and K. Watanabe. Summation of bilateral carotid sinus signals in the barostatic reflex. Am. J. Physiol. 209(6): 1278-1286, 1965.
19. Scher, A.M., and A.C. Young. Servoanalysis of carotid sinus reflex effects on peripheral resistance. Circulation Res. 12: 152-162, 1963.
20. Shubrooks, S.J., Jr. Carotid sinus counterpressure as a baroreceptor stimulus in the intact dog. J. Appl. Physiol. 32(1): 12-19, 1972.
21. Staverman, A.J., and F. Schwarzl. Linear deformation behavior in high polymers. Ch. 1 in: Die Physik der Hochpolymeren. Vol. IV, H.A. Stuart, Ed., Berlin: Springer-Verlag, 1956.
22. Stegemann, J., and H. Müller-Bütow. Zur regeltheoretischen Analyse des Blutkreislaufes (1). Pflügers Arch. 287: 247-256, 1966.
23. Wendler, L. Über die Wirkungskette zwischen Reiz und Erregung. Z. vgl. Physiol. 47: 279-315, 1963.

ENDOCRINE UROSCOPY: A PHYSIOLOGY LABORATORY EXERCISE

J. W. BAUMAN, JR. AND J. BULLOCK
Department of Physiology
College of Medicine and Dentistry of New Jersey
New Jersey Medical School, Newark

It is our purpose here to describe a teaching laboratory exercise in Physiology which has been successful in both medical and dental physiological laboratories. Our criteria for assessment of its success are the diligence displayed by the students during performance of the exercise, and, in the case of the current medical class, requests by some of the participating students for additional laboratory assignments.

The simple principle of this exercise derives from those organic chemistry laboratory final examinations, the identification of unknowns. It is probably only remarkable in that one of us was able to remember that far back. The exercise, which we call "Endocrine Uroscopy", for want of a better title, challenges the student to identify the type of endocrine abnormality from analyses of plasma and urine. Thus far we have asked students to identify such abnormalities as diabetes mellitus, diabetes insipidus, bilateral adrenalectomy and phlorizin-induced renal glycosuria. We provided the students with a brief assortment of testing material and equipment, including spectrophotometers and glucose kits, flame photometers and osmometers. As performed here, the exercise has another advantage, which made some organic chemistry "unknown" determinations interesting in that the results are quite clear-cut. Even including student technical error, which was considerable, there was no room for confusion. In fact, in our most recent use of the exercise with the medical class, only one student "diagnosis" was in error.

Diabetes mellitus was produced by intravenous injection of streptozotocin (62 mg per kg in citrate buffer, pH 4.5) two or three days before the experiment. Adrenalectomized rats were operated at least one week before the experiment to assure depletion of steroid stores, and maintained on 2% saline to provide a more bountiful urine flow as well as sustain them. Diabetes insipidus rats were obtained through the National Institutes of Health[1]. Renal glycosuria was produced by phlorizin treatment, 100 mg/kg in AM and 200 mg/kg in PM subcutaneously (1).

The data obtained by students in one exercise is given in Table I. As is evident in the table, differences between the animal preparations with respect to the measures used, are significant and obvious. The "diagnosis" of diabetes insipidus can be easily and positively established by all students on the basis of urine osmolality and volume. Adrenalectomized rats can be identified as easily from the rate of sodium excretion. Similarly diabetes mellitus and renal glycosuria can also be readily iden-

[1] In our earlier experience these rats were available from a commercial source, Carworth Farms, but at the present time no commercial supply is available, to our considerable distress.

tified. Some of the data shown in Table I is less dramatic than that seen in other student laboratories. Sodium and potassium excretion by the d. mellitus rats, for example, were somewhat higher in other studies. The lower rates shown here are presumably due to the short duration, 3 days, of the experimental "disease." There is no overlap between sodium excretion in d. mellitus and adrenalectomy, however, when the latter group is maintained on 2 per cent saline, even when the diabetic group is maintained on high carbohydrate diet. Urine osmolality was considerably lower than the average shown in the Table when diabetic rats were maintained on high carbohydrate diet.

TABLE I

URINE AND PLASMA VALUES IN RATS WITH ENDOCRINE LESIONS

RAT	U_{NA}	$U_{NA}V$*	U_K	U_KV*	U_{osm}	U_G	P_G
	mEq/l	μEq/hr.	mEq/l	μEq/hr.	mOsm/kg		mg %
NORMAL	66	24 ± 9	141	48 ± 15	1469 ± 174	0	
ADREX.	243	234 ± 63	53	55 ± 22	1064 ± 118	0-trace	165
D. MELLITUS	16	52 ± 18	39	126 ± 38	1085 ± 44	3+, 4+	398
D. INSIPIDUS	19	40 ± 9	32	69 ± 14	237 ± 29	0	
R. GLYCOSURIA	35	36 ± 5	62	68 ± 4	1251 ± 77	4+	186

All values shown are average values determined from data obtained by students. Sodium and potassium excretion and urine osmolalities include standard deviations.

* Since some experiments were 17 hrs. and others 24 hrs. these values are reported as uEq/hr to standardize for comparison.

The degree of difficulty attached to the program clearly depends on the amount of instruction given the student. With adequate preliminary instruction, the exercise is almost simple enough to be performed by biology students at the high school level. If, however, unknown samples are given out, and the students required to make up a flow chart subject to instructor's approval for differential "diagnosis" without further instruction, it represents more of a challenge. Instructors can even present obstacles in the form of superfluous tests offered the student. The degree of difficulty is also obviously determined by the point in the curriculum at which the laboratory is used. We have used it as a part of the Endocrinology sub-discipline, and more recently after the Renal subdiscipline. In this regard, it is a useful illustration of osmotic diuresis, and when plasma determinations of sodium and potassium have been included, a useful illustration of the constancy of the ECF and limitations of plasma levels in diagnosis.

We have used the program with several variations from requiring an established set of determinations, both plasma and urine, to issuing unknowns with the choice of tests to be determined by the students. Students, we suspected, are clever enough to use whatever clues are

available, and it was necessary, as well as laborious, in some programs, to make all rats appear to have been adrenalectomized. The choice of rat strain is limited also when students are permitted to see the diabetes insipidus rats, whose appearance is obviously different from Wistars or Sprague. The specific protocol is flexible; we suspect ours will undergo further changes from year to year. But we think it s worthwhile inclusion in our laboratory program, however modified.

Commentary

There is another reason for describing our student laboratory exercise. Recently R. F. Pitts argued for the preservation of the student laboratory in the teaching curriculum (2). We, too, are disciples of the Sophoclean admonition, "One must learn by doing the thing ...." But we suspect that some of the enthusiasm of the instructors for thirty and forty year old laboratory experiments can wane over the years, particularly when some of those exercises are often less than rewarding. There is the notion that this communication might stimulate via this journal, more innovative laboratory methods that meet the requirements of good laboratory exercises for teaching. We are aware, for example, of an interesting and informative laboratory procedure, of which we would like to know more, used by Paul Johnson and Bill Dantzler at Arizona for teaching membrane physiology and ion fluxes. If we are to make the laboratory survive, we suggest a start by making it more interesting to both faculty and student. We might even begin to move further away from illustrating the controversy between Galvani and Volta than the use of oscilloscopes, rather than kymographs, has permitted.

REFERENCES

1. Lotspeich, W. D. Metabolic Aspects of Renal Function. Springfield, Illinois: Charles C Thomas, p. 156, 1959.
2. Pitts, R. F. The Physiologist 15(2): 49, 1972.

NEWS FROM SENIOR PHYSIOLOGISTS

Recollections - Dennis E. Jackson
Born Ridgeport, Indiana, Sept. 3, 1878

Dr. Dill has asked me to write a brief description of my boyhood in Indiana, my experiences at Indiana University and my contacts with physiologists of long ago.

I had a younger brother. Our parents both died when we were quite young and we were mainly raised by our maternal grandfather and some of his grown children (our grandmother was dead). A number of years earlier our grandfather's family had taken a baby girl, Viola Nozler, to raise. She helped a good deal in caring for my brother and me. We lived in the country about forty miles from Bloomington where the University was located.

When I reached the age of six years it was decided that I should go to school. No one told me anything about school or what I would be expected to do. But I was bitterly opposed to the suggestion and everything connected with it. Nevertheless when the opening day came, Viola and I started together for the school, about one-half mile away, mostly through a tall dense woods. By the time we had gone half way to the school I had made one of my saddest physiological discoveries - my eyes were running over with tears. The thought of letting strangers see me with tears in my eyes was mortifying. I was confronted with a catastrophic problem for which I could see no possible solution. What to do?

On a cold, dark, rainy morning in the Spring of 1899 (or 1900) I entered Indiana University. I filled out the necessary papers in about ten minutes and paid my enrollment fee, one dollar ($1.00) which was labelled the library fee. I believe I did not enter the library during the term. I had attained financial stability (maybe, hopefully) and I had perhaps as much as one hundred dollars ($100) all in cold cash! So I faced the ten or twelve weeks term in the University with guarded assurance. I was strictly on my own. I had just finished teaching my first term in a one-room country school house, and I had made friendly connections which I believed assured me of employment for the following year (provided I passed the examination for a teacher's license - which I did repeatedly for five years in succession).

I entered the University under circumstances which would now be considered, at least, something of a handicap. I had completed only one year in high school (taking beginning algebra, geometry and Latin) and I had to finish the remaining three years in the University. Courses were then offered by the University to accomodate such students. They constituted a kind of "lame duck" group from which not much could be expected. In due course my brother also entered the University. We each succeeded in getting three degrees from the University: A.B., A.M., and Ph.D., he in geology and I in physiology.

My ambition when I first got to Bloomington was to specialize in Latin. I hoped to be able to speak and write Latin as well as I could

speak and write English, and I expected to teach it in a high school. This ambition was gradually overshadowed by beginning moves on the part of the University to start a new medical school. Dr. William J. Moenkhaus had for some years been teaching a course in physiology in the Department of Zoology. I had taken this course and when the new departments were finally established, Dr. Moenkhaus became head of the Department of Physiology and I became his assistant. I also then began to take medical courses and I later finished work for my M.D. degree from Rush Medical College which was then affiliated with the University of Chicago. But I retained my teaching position at Bloomington.

When I first entered Indiana University the yearly enrollment was somewhere between 1,200 and 1,500 students. Most of us were rather proud of being in such a large institution. (I believe the enrollment now is between 30,000 and 40,000.) Students who did not live in or near Bloomington rented rooms and ate at boarding houses. There were no dormitories, no automobiles, no general parking lots on the campus and no movies. But there were a number of severely separated fraternity and sorority houses, and I could send a letter anywhere in the United States or Canada for two cents postage. There were but few telephones. Professor Foley, in one of his lectures (1901), predicted that some day an invention might make it possible for one who was talking on a telephone to see on a screen the person to whom he was speaking. (This has now been recently done.) Board (20 meals, only two on Sunday) cost $1.75 per week and a room (two students in a room) cost $1.00 each per week. These prices were slowly raised somewhat within a range of ten years when I left the University and went to St. Louis (1910).

Typhoid fever was always a risk in Bloomington when I lived there. A few students died of the disease, but they might have got it anywhere at that time. Malaria was common, penicillin had not been dreamed of, and appendicitis was just beginning to become popular. There were a lot of fine tall maple trees on the campus. I often thought what a splendid place that would be to make "tree molasses," a process with which I was entirely familiar. Once a great man came to the University and gave a public lecture in which he stated that the weight of the earth in tons was represented by the figure 6 followed by twenty-one cyphers. I was probably not the only one in the audience who did not see just exactly how he weighed the earth by juggling figures with but little experimental data, but we all probably got some notion of the vastness of science, simply by receiving many repeated small doses of greatly diluted "research."

With the beginning of the new medical school we got a new medical dean who made his approach to Bloomington by way of Bucknell and Johns Hopkins, and who soon demonstrated his medical sagacity and competence by marrying the daughter of one of the wealthiest and most prominent families in town.

There was then a good deal of competition (not always in the highest christian tradition) between Purdue University and Indiana University. Once a great ball game was scheduled to be played between the two teams at Indianapolis. I went by train with a large group from Bloomington.

But a great train wreck killed most of the Purdue players before they reached Indianapolis. The game was cancelled and all of those from Bloomington had to wait until late in the day for a train to return home. It was a sad day for both schools.

Of graduates whom I knew from the Indiana University medical school and who gained prominence in scientific or medical circles, I can recall only two names (both my students), Dr. Frank Charles Mann of the Mayo Clinics and Dr. Edward W. Koch who became dean of the medical school at Buffalo, New York. There should have been more but that was in the early days when the great medical schools and institutions of the central and western parts of the country had not yet been fully developed.

My first two summer terms in the University were spent at the biological station at Winona Lake in Northern Indiana. Professor Eigenmann had just succeeded in getting two wood frame buildings put up there just by the lake. A course in general zoology was taught in one building and embryology was taught in the other. The first summer I took zoology and the second summer embryology. Professor Slonaker was one of the teachers. We made trips to Lake Wawasee to dig turtle eggs out of the sand to study the embryos.

Not far from the biological station was the small town of Winona Lake which was a well-known summer resort at that time. The resort presented many lectures or other forms of entertainment for many people who came and stayed at Winona for longer or shorter periods. The University students attended as many of these lectures as they could. One evening I went to the auditorium, not knowing what the program was to be. I went in and sat down and presently the show started. I was dumbfounded as I suspect most of the rest of the audience must also have been. The whole program consisted of moving pictures. The pictures were clean cut and well made and the subject matter was familiar so everyone could understand. Apparently nothing quite like it had appeared anywhere else since the creation of the Garden of Eden and they both had much in common. I had just been studying the miracles of embryology but these seemed pale and insignificant in comparison with what could be presented with moving pictures. Morning could be seen just breaking out at 5 o'clock in the afternoon, but at that time (1901 or 1902) with no special crowing of the roosters at that hour (that came later).

Among members of the faculty at Bloomington, Professor C. H. Eigenmann (Zoology) was probably the most widely known. He was undoubtedly the world's greatest expert on blind fish. Other faculty members were Professors Sampson, Rothrock, Mottier, Bede, Bergstrom, Foley, Cummings, Myers, Pohlman, Kuensteiner, Miss Berry, Johnston, Brooks, Bryan, Lindley, Moenkhaus, Miller, and a number of others whose names I cannot at this moment recall.

I was elected to the Physiological Society about 1910. I had moved to the Washington University Medical School in St. Louis by that time. My first meeting of the Physiological Society was at Johns Hopkins Medical School. I presented a little paper (with lantern slides) on the physiological action of vanadium. It was well received. One man told me had never

before seen anything like it! In the discussion Dr. Meltzer asked where I had got the vanadium. I told him from Kahlbaum in Germany. That was probably the leading drug company in the world at that time and schools in this country could import drugs from abroad duty free. I usually bought about $200 worth (in small quantities) each year.

The Federation was formed in 1913. In the early days the meetings were small and each member could know nearly everyone present. We regularly had a dinner and after that we all sat around at the tables and talked till near midnight. That was the high point of the meetings and those talks can never be repeated again. I was sometimes surprised to see how quickly some great scientist could understand and appreciate my problems. (History tends to repeat itself).

Among the great men at the meetings in those days, Dr. S. J. Meltzer of New York was probably the most prominent. Others were W. B. Cannon, G. N. Stewart, W. H. Howell, Harvey Cushing, A. J. Carlson, Joseph Erlanger, W. E. Garrey, S. A. Mathews, and many others whom I knew in those days but whose names I cannot now recall.

In the early days a majority of the members of the whole group were physiologists but many were biochemists and four or five were pharmacologists. Almost all, if not all, of the people about whom I have written in this note have now passed away. My earliest students in St. Louis used to refer to them as "the wise men from the east."

On one occasion, probably about 1913, the officers of the Society asked the railroad officials for reduced fares for the members to attend the annual meeting between December 25 and 31. The officials agreed to do this if the Society would guarantee that 125 members would attend. The Society could not make this guarantee and we had to pay full fare.

It has been said that he who laughs last laughs best. I believe this rule hardly applies to retired University Professors, for if the Professor is really the last of his old group, then he may smile sadly or he may gloat, but no one laughs best when he laughs alone.

Marie Hinrichs is an active member of the birthday card group. In response to Hal's request she supplied the following synopsis of her career: Educational Background - Lake Forest College with an A. B. degree (Shield Honors, 1917), University of Chicago with a Ph. D., 1923, with Ralph Lillie, Rush Medical College with an M. D., 1934. Research Experience - was gained in cellular physiology and radiation physiology at the University of Chicago as research associate and National Research Fellow (2 years), also as research assistant at Nela Laboratory in Cleveland. Fifteen summers were spent in study and research at Woods Hole Marine Biological Laboratory and Friday Harbor. Publications - Total of approximately fifty published papers in radiation physiology and student health problems. Presently writing Health Column for "Retirement Living Magazine" (Formerly Harvest Years Magazine). Teaching Experience - Includes Chicago public schools at the elementary level; Southern Illinois University Laboratory School (supervisory at the high school level in

health education); on the college level, Vassar College in Zoology, Southern Illinois University, University of Illinois and Roosevelt University; summer workshops and extension classes for in-service teachers at Southern Illinois University, Indiana University and Roosevelt University, also, Chicago Teachers College. Other school health experiences include membership on state-wide health committees, working in cooperation with the Institute of Juvenile Research, Home Bureau, and PTA. Chairmanship, School and College Health Section, AAHPER, 1954. Clinical Experience - Private practice, Chicago, Illinois. Medical Director in boy's camp in Canada; Medical Officer in charge (civilian status) for the 69th College Air Force Detachment; College Health Services, University of Illinois, Southern Illinois University as Director (14 years), Director of Bureau of Health Services, Chicago Public Schools (4 years) Medical Consultant, The Child Guidance Clinic at Southern Illinois University; Medical Consultant, Department of Health Education, American Medical Association, 1960-to date. Editorial Experience - Editor-in-Chief, Journal of School Health, (7 years). Presently contributing Editor. Membership - AMA (Chicago Medical Society), Illinois Medical Society, American Physiological Society, Society for Experimental Biology and Medicine, AAHPER; Fellowship in APHA and ASHA. Membership, Nu Sigma Phi, Sigma Delta Epsilon (Past President, University of Chicago Chapter and Past National President). Listing in American Men of Science and several Who's Who publications. Citations - Lake Forest College, 1957 - Alumni Citation; American School Health Association, 1962 - Citation (Distinguished Service); American School Health Association, Howe Award, 1969; Honorary Societies - Phi Beta Kappa, Sigma Xi.

Jane Sands Robb Johnson wrote Maurice Visscher: It was pleasant to receive the greeting card which followed us from Cooperstown to our new home. Thank you and the Society committee. From time to time I hear from physiologists who are continuing work, for instance - Bill Amberson, Edward Adolph, Grayson McCouch, Hiram Essex and now yourself - more power to each of you. I have two "thorns in the flesh" which have limited my efforts. My hearing has deteriorated and even more my eyesight has failed. In the right eye I have no central vision. The corrective lens for my left eye is one of those abominations called "balanced." The focal distance is some 2-1/2 inches. I can still read but have to watch out for my nose. My husband and I find this climate more suitable. He is far from well - but fortunately his limitations are unlike mine. I help him walk and write and he helps me hear and see - so we get along nicely. We continue to find life interesting, even challenging - the days pass all too quickly. Between us we have six young families; seventeen grandchildren, eight of whom are in college. It is a bit confusing to have a grandson at Russell Sage and a granddaughter at Princeton. Perhaps it is the constant adaptation which prevents one's soul from becoming sere as the body ages. My best wishes to you and to others who can continue to be productive. Our new address is: Majestic Towers A 1101, 1255 Pasadena Ave., S, St. Petersburg, Fl. 33707.

Hal Davis received from Isolde Therese Zeckwer information about her career. Born in Philadelphia, she spent only a few years away from her birthplace. After an A. B. cum laude, Bryn Mawr, 1915 she received an M. D., cum laude Women's Medical College in 1919. Then her years away began as an interne and resident in the Mercy Hospital, Pittsburgh; 1919-1921, followed by a fellowship in Pathology, Mayo Clinic, research in Pathology under Wolbach, Harvard until 1926 and then a year of research in the Department of Physiology, University College, London. Then her climb up the professional ladder began at the University of Pennsylvania from Instructor in Pathology in 1927-1928 to a Professorship 1954-1958. Forty references range from a paper on "Senile Atrophy of the Liver" in 1924 when she was at Harvard, to several papers on parabiotic rats 30 years later.

Her honors include membership in American Society for Experimental Pathology, American Association of Pathologists and Bacteriologists, American Physiological Society, American Association for Cancer Research, Sigma Xi, Philadelphia Physiological Society and the Philadelphia Pathological Society (Secretary and Treasurer, 1929-1931).

Isolde has studied painting at Colorado Springs Fine Art Center and at the Museum of Art, Philadelphia. She has won awards for paintings exhibited at American Physicians Art Association. Her address is, Devon Manor, Devon, Pennsylvania 19333

Bruce Dill inquired from Rosalind Wulzen about her student days at Berkeley. Dr. Alice M. Bahrs, Rosalind's close friend for over 40 years replied. She reports that Rosalind's physical health is reasonably good but memories of student days are gone. Dr. Bahrs recalls that Rosalind studied with Jacques Loeb when he was working on balanced salt solutions. Rosalind invited Alice to live with her when her mother died in 1925 and now Rosalind lives with Alice who is in medical practice in Corvallis.

Lester Dragstedt replied to Maurice Visscher: Thank you very much for your note of September 28th last congratulating me on my eightieth birthday. You are very kind indeed to do this and I thank you and also the members of the American Physiological Society for this nice gesture on their part. I have indeed had a happy life and am most fortunate in being given the opportunity to continue research in the field of my great interest.

Hal Davis writes further about Honorary Member, Karl von Frisch who shared the 1973 Nobel Prize in Physiology or Medicine with Konrad Lorenz and Nikolaas Tinbergen. Professor Dr. von Frisch was honored particularly for his discovery of the "language" and orientation of the honey bee. The communication among the bees is by means of "dance" patterns that tell the distance and direction of a new-found source of food. Distance is coded by the type of dance and its duration. Direction is relative to the sun or to the plane of polarized light from the sky and is coded by the orientation of the dance relative to the sun, if the dance is on a horizontal surface, or to gravity if the surface is vertical. Earlier von Frisch had established that fish can hear and are not color-blind and that bees have excellent color vision and discriminate very well among many odors. Professor Dr. von

Frisch, now 87 years old, lives in Munich. He has written a most delightful autobiography entitled"Erinnerungen eines Biologen" (Springer-Verlag, Berlin 1957). The English translation is "A Biologist Remembers" (Pergamon Press, 1967).

Dr. Edward Adolph sent us an article about G. H. Whipple. Drs. G. H. Whipple and D. E. Jackson are believed to be the oldest members of the American Physiological Society.

George Hoyt Whipple attained the age of 95 years on August 28th, 1973. To mark the occasion, older friends and colleagues held an informal reception to him in the Medical History Room of the Library at the University of Rochester Medical Center. Dr. Whipple founded the School of Medicine and Dentistry here in 1921 as Dean. He was Dean until 1953. Rarely does a Dean survive his duties for fifty years.

Since the American Physiological Society was meeting in Rochester in the week before Dr. Whipple's birthday, four officers of the Society visited him in his office, and conveyed to him their congratulations. Dr. Whipple became a member of the Society 62 years ago.

He also received a citation from the American Society for Experimental Pathology, of which he was a founding member (1914) and a President (1925).

In June Dr. Whipple received the Distinguished Service Award of the American Medical Association for "outstanding contributions to the science and art of medicine." He was cited for his many achievements in teaching and research. In 1934 Dr. Whipple had received a joint Nobel Prize Award for his work on hemoglobin regeneration as influenced by diet and other factors.

The Whipple House in Ashland, New Hampshire, was in 1970 given by Dr. Whipple to the Town, in care of the Ashland Historical Society. This was his birthplace and boyhood home, built in 1837. It is a museum open to the public on certain afternoons during July and August.

The APS Central Office was happy to receive the following information from Ralph H. Kellogg: You may be interested to know that one of Mabel FitzGerald's two specially-constructed portable Haldane-type gas analyzers has just been donated by her heirs to the White Mountain Research Station as a museum piece. The accompanying letter says, "This I am sure would have been the wish of Miss FitzGerald herself in that she always took such a great interest in all of her American connections up to the time of her death."

SOME CARDIOVASCULAR PHYSIOLOGISTS IN THE FIRST QUARTER OF THE TWENTIETH CENTURY

LOUIS N. KATZ
Late Director Emeritus of the Cardiovascular Institute
Michael Reese Hospital and Medical Center*

In this account of some of the cardiovascular physiologists I have known, I have omitted mention of any still living, with the notable exception only of A. V. Hill who is retired and is now over 80 years old.

We are all familiar with the ancients and with our own contemporaries, but I believe that those who lived and worked in the first quarter of the 20th century, our immediate predecessors, are apt to be forgotten. Much that is flaunted today as new material actually was often established first by these people. For the most part, they worked simply, without large government grants and its associated evils: paper work on grant applications, frequent reports and the associated governmental bureaucracy.

The Circulation Group, American Physiological Society

The Circulation Group started in 1932, and the first three names that I am presenting here were present at the first meeting and were active in its functions until their deaths. The Circulation Group has had a profound effect on Cardiovascular Physiology in North America during the past four decades, and promises to continue to do so in the future. I have been proud to have been one of the members, together with Walter Meek and C. J. Wiggers, of its first Steering Committee. This group developed the tradition of forthright argument and debate, all within the atmosphere of a friendly search for truth and the avoidance of personal vindictiveness.

H. C. Bazett (1885-1950) arranged the first organization meeting of the Circulation Group in Philadelphia. He came to the University of Pennsylvania from England in 1921 as Professor of Physiology. He was interested in the peripheral circulation and in blood volume, and advocated performing experiments upon himself, inserting thermocouples into many of his own blood vessels in order to study temperature gradients. His work on the duration of systole led to the formulation of the

---

* This article, based on an address made by Louis N. Katz upon receipt of the C. J. Wiggers Award from the Circulation Group of the American Physiological Society on April 17, 1967, and a Nathanson Memorial Lecture given at the University of Southern California, Los Angeles on March 18, 1970, has been completed with the aid of hand-written notes. The biographies of several physiologists mentioned in the original manuscript for whom no personal comments were available have been omitted.

The article was edited by Arnold M. Katz, Philip J. and Harriet L. Goodhart Professor of Medicine (Cardiology), Mount Sinai School of Medicine.

Bazett formula, which I have used for many years. I knew him well, and since he was as truculent as I, we got on well together - enjoying the thrill of arguing with one another, and of joining forces to debate with others. Burton is a pupil of his. Bazett died suddenly in 1950, of a heart attack on board a boat taking him to Copenhagen for a meeting of the International Congress of Physiology, as President of the American Physiological Society. He never presided at a meeting of the Society.

D. R. Hooker (1876-1946) was a member of the Physiology Department of Johns Hopkins. He worked on venous pressure and the venous circulation. In 1933, he was elected to exercise editorial control of the "American Journal of Physiology," and became its Managing Editor the following year. He set the scientific, editorial and business aspects of the publications of the Physiological Society as his contribution to physiology. In 1935, he became the Executive Director and Treasurer of the Federation of American Societies for Experimental Biology. At the time of his death in 1947, the Publication Reserve Fund of the Physiological Society had grown to a quarter of a million dollars through his efforts. This was quite an accomplishment which I appreciated better after my tour of duty on the Finance Committee of the Physiological Society in the 1950's!

W. F. Hamilton (1893-1964) served the Circulation Group with a record six years on its Steering Committee - twice as long as anyone else; three of these years were during World War II, when the "meetings" were carried on exclusively by mail, and quite effectively. I can claim that Hamilton was once one of my "boys," since he spent a summer working with me at Michael Reese. It was a pleasant experience.

Dr. Hamilton made a number of important contributions during his lifetime. He established the dye dilution method for cardiac output early in his career. For many years, the Hamilton manometer for blood pressure recording replaced the Frank-Wiggers method. These tools gave him great insight into the hemodynamics of the circulation. He held the chair of Physiology at the University of Georgia for many years until his retirement in 1960; and he built a large school of followers, including the training of many students in his methods and views, with the help of a government training grant. He was Editor of the Section on Circulation of the "Handbook of Physiology," and died before the third volume of this Section was completed. He was President of the Society in 1955-56. He was a constant attendant of the cardiovascular sessions of the Society and of the basic science sessions of the American Heart Association. There were few papers presented which he did not discuss effectively - sometimes sharply. This was expected of him. He and I helped establish the Basic Science Council of the American Heart Association. Ours was a long, warm and varied association covering science, medical politics, and philosophy.

Western Reserve University, University of London, and University of Chicago

During my early impressionable years, I had the privilege of meeting many Cardiovascular Physiologists, and training with some of them.

I first met R. W. Scott (1888-1957) when I was a Freshman in Medical School at Western Reserve University (now Case-Western Reserve University). He was an instructor in the course on Physiology in 1917. He was then interested in respiratory physiology; but the following year he went to the Cleveland City Hospital (now the Metropolitan General Hospital) and became a cardiologist. It was under him that I had my internship and residency there, and he was my Clinical Preceptor.

J. J. R. MacLeod (1876-1935) also taught me first year Physiology in 1917 at Western Reserve. He was not a cardiovascular physiologist but won a Nobel Prize in 1923 for his work in insulin and since diabetes is closely associated with atherosclerosis he has had an impact there also. He was born in Scotland and died there, aged 59 years. He was President of the American Physiological Society from 1921-22 and he wrote a standard physiology textbook, "Physiology and Biochemistry in Modern Medicine" which was revised and reprinted for at least seven editions! He was educated in Aberdeen to which he returned in 1928, as Regius Professor of Physiology, and later became Dean (1930-1935). He got his DPh at Cambridge in 1902, and worked in London Hospital and Leipzig as a Lecturer at Cambridge and a Research Scholar of the Royal Society. He came to Cleveland in 1903, and went to Toronto in 1918. "Jakey" was a kindly soul. I remember well a bit of advice of his: "Do not repeat work of others, you won't do so well. Use a better method or, better still, a new approach."

Carl J. Wiggers (1883-1963) was my Physiology Preceptor and I was his first associate in the Cleveland period of his career. He came to Cleveland in 1918, and taught me second year Physiology that year. I took his elective in research and won a prize for thesis on the duration of systole resulting from that period. As a Summer Assistant of his at the end of my Junior year I was paid $25.00/ mo. I became an absentee Clinical Clerk in my Senior year in order to work with him on volume curves, and still got "A" for my clerkship. I continued my association with him (except for the one year abroad) even during my internship and residency until I left for Chicago in 1930.

He was a first-rate clinician. He decided to study normal cardiovascular physiology and go on to abnormal, but found so much to do in the former, that he did not do as much on the latter as he would have liked to. He was born in Davenport, Iowa, of German parents and died in Cleveland at age 80. He received his MD in Michigan in 1906; became Instructor in Physiology there in 1906-1911. Lombard, his chief at Michigan, who worked on the duration of systole, asked him to be Acting Director of the Department in 1911. After that, Wiggers moved to Cornell in the same year, and stayed there until 1918. Lusk, his chief, asked him to be Acting Director of the Physiology Department while Lusk and Murlin were away during part of World War I. He came to Western Reserve University in 1918, and served as Head of Physiology until 1953 (for 35 years) when he became Emeritus and continued his work at the Bunts Institute of the Cleveland Clinic (through the good offices of Irvine Page). In 1911, he spent some time with O. Frank in Munich. There he arranged with the mechanic, without Frank's knowledge, to have Frank manometers built to take back with him to Cornell. Thus, Wiggers

was Frank's "scientific" son, as well as that of Lombard and Lusk.

He became the Dean of Cardiovascular Physiologists and trained many of the important ones. Among them were more department heads and heads of research institutes than even W. Cannon had! He founded the journal "Circulation Research" in 1952, and was its Editor for five years. He was President of the American Physiological Society in 1949-1950. He was a member of the first Steering Committee of the Circulation Group of the American Physiological Society and was a prolific writer who published many volumes: A "Textbook of Physiology in Health and Disease" in 1934 - its 5th and last Edition appeared in 1949; "Pressure Pulses in the Cardiovascular System" in 1928 - (someone borrowed mine and lost it, and when Wiggers heard about it, he bound a working copy of it, autographed it and sent it to me, since it was out of print).

His work and that of his school contributed greatly to the fundamental background of clinical hemodynamics. His work on the vulnerable phase of the heart is of great practical importance. Among his studies were: duration of systole, dP/dt, volume curves of the heart and the pressures in its chambers (and that of the veins and arteries). He believed that instrumentation would help expand observation. He made extensive use of the recorded heart sounds and the electrocardiogram. He was hard working and meticulous. "Every disease", he said, "is an experiment that nature performs, and its signs and symptoms are manifestations of abnormal function."

Dr. Wiggers has always been a prolific writer. Many reports by his associates in which his name has not appeared as a coauthor or in a footnote acknowledgement, were nevertheless greatly influenced by his thinking in the planning of the experimentation and the writing of the article. He has always felt that when a young man in research has attained a certain stature, it is incumbent upon his chief not to "sign-in" or even to detract from the young man's promise by having the chief's name appear in a footnote. He has always felt that each research project is the work primarily of one, two, or at most three minds and not of a large group.

He was always devoted to his research and teaching. However, he considered administrative and committee work a necessary evil detracting from his primary objectives, research, teaching and the training of young investigators and teachers. He worked hard, putting in a full day at the school. Even after leaving the laboratory, he has been known to have worked in his library until the small hours of the morning on many occasions. Since he himself worked hard and was always prompt, Dr. Wiggers disliked tardiness, sloppiness, and "spoon-feeding" in others. An example of his industry and attitude is shown by the fact that before he went to South America on tour he learned Spanish within a few months so that he himself could lecture in that language rather than through an interpreter. He was frank and maintained his intellectual honesty; he has never compromised his views either privately or in public regardless of the persons involved. He has retained the devotion of his associates, the respect of his colleagues and the warm friendship of an extraordinary number of people.

He was very Germanic. He made me come back from England on the S.S. Leviathan so I could help clean equipment to prepare for the student's lab! He once said to me, "Katz, it is not what you believe but what you find that people are interested in."

G. N. Steward (1860-1930) was Head of Experimental Medicine (1907-1930) when I was in Western Reserve University, he worked with Rogoff and was an endocrinologist. But in 1897, he worked on electrical conductivity of the circulation using salt solutions; this was the background for the blood dilution technique of cardiac output. He also studied the brain circulation and measured circulation time. He was born in London, of Scotch parents, and soon moved to a small village in Scotland. He died in Cleveland at age 70. He was educated at Edinburgh where he received his A.M. in Mathematics in 1883; D.Sc. in 1887, and M.D. in 1890. He was a pupil of DuBois-Reymond, the great electrophysiologist. He taught at Manchester, Cambridge and Aberdeen, and came to Harvard in 1893 as an Instructor in Physiology. He then became Professor of Physiology and Histology at Western Reserve University from 1894-1903; Professor of Physiology at the University of Chicago from 1903-1907 (before returning to Western Reserve University).

He was very frugal and lived for many years in his laboratory. He believed in using inexpensive and simple equipment (what a contrast to today!). He wrote a classical text on Physiology (which I have used) in longhand. When he died, he left a large departmental reserve fund which his colleagues fought over, as well as the space of his department which was disbanded.

A. V. Hill (1886 -) was the man I went to work with in England as a National Research Fellow in 1924. Wiggers wanted me to work with Starling, but the latter said he could not teach me anything (which was not true!) and so it was decided that I study with A. V. Hill at University College. He assigned me to work with C. N. H. Long on lactic acid and glycogen, in heart and skeletal muscle, and with T. Keeridge on the pH glass electrode. Then I worked on the heat of the heart. For this purpose, I first went to Cambridge for two weeks to learn how to make thermocouples with Hartree, but the galvanometers which were then available, we found, were not sensitive enough to record the heat of the heart. When E. Fisher came to Hill's lab, soon after I left, the techniques had improved so much that he could accomplish the task. However, I have in my file one experiment with the proper level of turtle heart heat - so that I can say that I was first. I also worked on plurisegmental innervation of skeletal muscle with heat measurements.

Hill was trained in Cambridge and was a mathematician and physicist. He was Professor of Physiology at Manchester from 1920-1923; Jodnell Professor of Physiology at University College, London, from 1923-1925; and Fullerton Professor of the Royal Society from 1925 until he retired. His students included: Long, Gasser,- Fenn, Azuma, Gerard, Bramwell, Fisher, B. Katz, Hartree, Richie, Baldes Cattell, and Wilkie. He was "Foreign Secretary" of the Physiological Society. He wrote "Living Machinery" in 1927; "Trails and Trials in Physiology" in 1965.

He won the Nobel Prize in 1923; was a Fellow of the Royal Society; was in the British War Cabinet in the Second World War. His work on muscular traction is classical, and forms the basis of much of our modern knowledge of cardiac contractility. But he also used the hot-wire aneroid with Bramwell for pulse wave velocity. He developed the technique for measuring heat of muscular contraction. He studied the muscular work-load curve, speed of muscle shortening and efficiency, and the muscle load-velocity curve, active state (with Gasser); Fenn effect; heat of the heart (with Fisher); heat of nerve (with Gerard), etc.

E. H. Starling (1866-1927) was one of the great attractions at University College. His weekly teas were famous. His biography was recently written by Carl Chapman. Starling's modesty was shown by the fact that he asked me to revise the text of his classical book on "Principles of Human Physiology" in 1924, as far as the Section on Circulation was concerned. He wanted to get the latest of Wiggers' views. I did, and he accepted most of the revisions which were quite drastic.

He died aboard a boat at age 61. He was educated at Kings College, Guys Hospital and Leipzig. He was Lecturer in Physiology at the School of Medicine for Women from 1890-1899; became Jodnell Professor of Physiology of University College from 1899-1923, being succeeded by A. V. Hill, and then Fullerton Professor of the Royal Society. Among his students were Lovatt Evans, Anrep, Visscher,and Verney. He studied the heart of dog and man with the electrometer (with Bayliss) in 1892; the absorption of fluid from tissue spaces and the balance of forces between capillary pressure and plasma protein in 1896; the differential control of afferent and efferent arterioles of the kidney in 1912; the pulmonary and coronary circulation in 1913; the latter with the heart-lung preparation; the regulation of the heart beat (with Patterson and Piper) in 1914, the reflex vasodilation in the body (he was the first) by means of raising blood pressure in the head in 1925; the metabolism of the heart (with Visscher) in 1927. He also used the work-calculator; determined pressure-volume curves; cardiac output at different venous returns and aortic resistance; and lymph flow.

His Linacre Lecture on the Law of the Heart is a classic. I remember especially well one thing he told me: "Analytic study tells what can happen; synthetic, what does happen; balance the two properly."

Sir William M. Bayliss (1860-1924) had just died (at age 64) when I got to the laboratory at University College, and his reprints were available for those that wanted them. I prize those that I obtained then. He was educated at University College, London and became Professor of General Physiology. He had written a beautiful book on "Principles of General Physiology." He worked extensively with Starling (his brother-in-law). Burdon-Sanderson was his teacher. His most important work was on vasomotor reflexes. He reorganized the knowledge of the antidromic nerve supply. He put some orderliness into the nature of vasodilator fibers - now it is known that this is more complicated than he realized. He showed that passive distention of blood vessels led to a rise in vessel tone. His son (Leonard) continued in his father's footsteps in physiology until his own death recently, working.

Two facts of a personal nature should be mentioned. Bayliss was modest. Once when a visitor saw him and mistook him for a diener and asked, "My dear fellow, where is Professor Bayliss?" he told him he was not in! The other is the famous dog case. In 1903-04, he and Starling were sued by the antivivisectionists, and charged with cruelty to animals. Bayliss countered and sued for defamation of character and won the case.

Sir Thomas Lewis (1881-1945) was at University College Hospital when I came in contact with him in 1924; and I spent the last two months of my stay in London doing clinical work with him. George Pickering was working with him then, and so was Arthur Master. Lewis was nice to me when I revisited London in 1935, unlike his usual gruff manner. He came to the United States in the 1930's and visited my department at Michael Reese. I showed him my work (with Brams) on heart fibrillation which opposed his simple circus movement concept. He did not disagree with me then, but "kept on sinning" as before when he returned home to England. We also repeated and confirmed his work on intermittent claudication.

He was born in Wales and died in London, with Pickering and his physician, at age 64. He was a pupil of Sir James MacKenzie and, in turn, trained Wilson, White, Alfred Cohn, Feil, Pickering, Master, Grant of Guy's and Durrer of Holland. In fact, he trained almost every American cardiologist of that period. He was Director of Clinical Research at University College Hospital. His book, "Mechanisms of Graphic Registration of Heart Beat," in 1925, was a classic; and so were his monographs on "Blood Vessels of Human Skin" in 1927, and "Pain" in 1942.

He used the polygraph and electrocardiograph extensively. He studied cardiac arrhythmias; "Unipolar" leads; intrinsic deflections; spread of excitation in the atria, A-V junction and ventricles, and their refractory periods; circus movement; and concealed conduction. The controversy he had about the location of bundle branch block with Wilson was famous. After all this, he said, "The cream was removed from electrocardiography," so he returned to the study of the human skin circulation and color, and the physiology of pain in man. He introduced such terms as "P substance" and "H substance." He edited the journal "Heart", and later changed its name to "Clinical Science." He worked in a totally different manner as a clinician than as a clinical and experimental investigator.

His final illness was due to cardiac failure and the question of using digitalis, in which he did not believe, was raised. Two versions exist: 1) He acceded to Pickering's advice to use it and 2) He refused to yield. I must ask Pickering which is true.

A. J. Carlson (1878-1956) was the Head of Physiology at the University of Chicago when I came to Chicago in 1930. I was appointed to the staff of the Physiology Department at the University of Chicago by him. He was, for many years, a neighbor of mine on Greenwood Avenue in a row of Columbian World's Fair (1893) attached houses - known either as

"University Row" or "Morgue Row," because it was so peaceful there. He was a Swede and retained his delightful accent. He was born in Goteberg and came to the United States when he was 16 years old. He died in Chicago at the age of 81. He obtained his Ph.D. at Stanford in 1902, and came to Chicago in 1904 as an Assistant Professor. He became the head of the department in 1909, and retired as Emeritus in 1940, but continued to work. His teachers were J. Loeb, G. N. Stewart, and A. P. Matthews. His pupils included the Dragstedts, Ivy, Luckhardt, Gerard, and V. Johnson. His only research in circulation was on the Limulus heart.

He was a character! He was known as "Ajax." Stories about him are rampant. Most significant is: "Vat is the control?" or "Vat is the evidence?"

Other Physiologists

W. J. Meek (1878-1962) was a small, quiet, but effective man. He worked closely with J. A. E. Eyster, who was Professor of Physiology at Wisconsin. He also wrote an excellent review on tone of heart (now called compliance). He was born in Dillon, Kansas and died at the age of 84 in Florida. He got his Ph.D. in Kansas in 1909; was Instructor and rose to the rank of Professor of Physiology at Wisconsin from 1908-1949; he became Associate Dean, and Dean, 1920-1949, and Emeritus, 1949. The "History of the American Physiological Society" for the first fifty years (1887-1937) was edited by him. He was President of the Society from 1930-1932; and was on the first Steering Committee of the Circulation Group.

F. N. Wilson (1890-1952) was a Mid-Westerner; educated and taught in Michigan where he died at the age of 62. He had a farm and like Lewis, enjoyed it. Like Lewis also, he was interested in birds. He was primarily a self-taught, excellent, mathematician and physicist. His research was in electrocardiography, to which he contributed mightily. Especially noteworthy are: distribution of electrocardiographic forces in solid conductors; the central terminal; the ventricular gradient; the vectorcardiogram. His controversy with Lewis was mentioned earlier. Students of his were: H. Hecht, F. Johnston, Rosenbaum, etc. He was stubborn and a good debater. We loved to debate with each other. Once when I was a moderator on a panel of which he was a member, I was not argumentative enough with him. The next day, when we were walking down the street, he said, "Louis, were you sick yesterday?"

O. Frank (1865-1944) was a thoroughly nationalistic German. Master and I visited him in 1924, and he was nice to us. I saw him in Russia at the Physiology Congress in 1935. He sent me a reprint! I tried to follow his mathematics. He studied and learned mathematics and physics, especially classical mechanics. His solution of branched, pulsating, elastic vessels was difficult to follow. Alexander Kolin attempted it. His secretiveness was mentioned earlier in relation to Wiggers. He is my "scientific" grandfather. He was a student of Ludwig (his last) and of Volt. He had a few students, of which Wiggers and Broemser were his most prominent. He quarreled with the latter on a matter of priority. His field was

hemodynamics; he recognized dP/dt, the "family of curves", pressure-volume relationship, and "arbeit" of heart. In the isovolumic frog heart, he found that peak ventricular pressure rose and then fell as volume was increased. Frank's capsule and optical lever principle were major developments. He shares with Starling the credit for the Frank-Starling Relationship, also known as "Starling's Law of the Heart."

Y. Henderson (1873-1944) was a handsome Southerner, who settled at Yale in 1900, and rose to the rank of Professor of Physiology, from 1911-1938, and then to Emeritus. He was born in Louisville, Kentucky and died at the age of 71. His work included: "Uniformity of behavior of the heart", in 1906; filling and emptying of heart; and its afterload. He studied venous return and the effect of muscle tone and posture upon it. He recognized, in 1914, the balance between right and left ventricular output. He was interested in CO_2 and the vasomotor center, and ascribed shock to acapnia. He used a swing table for the ballistocardiograph. He was a good debater.

J. Erlanger (1877-1965), "Uncle Joe", was a pillar among physiologists. He was born in San Francisco and died in St. Louis, at the age of 91. He earned his M.D. at Johns Hopkins in 1899, and joined the Physiology Department there. He went to Wisconsin in 1904, and then to Washington University in 1910, as Head of the Department, where he stayed until his retirement. He won the Nobel Prize on nerve transmission (with Gasser) in 1944. He was President of the American Physiological Society from 1927-1929. Besides Gasser, his students included: Bramwell, Bishop, Davis, and Gilson. At first, he was a cardiovascular physiologist; worked on blood pressure in blood vessels, arterial sounds, stroke output as determined from pulse contour, A-V and intraventricular block, and the role of the vagus nerves.

I. P. Pavlov (1849-1936) was the hero of the 1935 International Physiology Congress in Leningrad and Moscow. Even though a Czarist, he was worshipped by the Communist Regime and became sort of a deity. There was a Gospel of Pavlov! He did some work on the nerve supply of the heart, but I have included him primarily because I believe his work on conditioned reflexes has had a tremendous impact on physiology including that of the cardiovascular system. He won the Nobel Prize in 1904 and lived to be 87 years old.

O. Loewi (1875-1961) was a lovable man, who has my particular affection because of his advice to my son, Arnold, at Woods Hole in 1952. He was born in Frankfurt, Germany and got his M.D. in Strassburg in 1896; taught at Marburg, Vienna, and Graz. He came to the United States in 1940, and joined the staff at New York University. He was a pharmacologist whose classical work on "vagusstoffe" by means of cross-circulation won him a Nobel Prize in 1936.

A Krogh (1874-1949) won the Nobel Prize in 1920 for his work on capillaries. His monograph on "Anatomy and Physiology of Capillaries" was classical. His wife, Marie, (1874-1943) was a collaborator of his, and his daughter, Bodil Schmidt-Nielsen, has continued to work in physiology. His other daughter, Madam Tijberg-Hansen, is married to a

physiologist. Landis is a pupil of his. Krogh studied venous return; physiology of exercise on circulation; cardiac output; foreign gas (N_2O) method for cardiac output; splanchnic venous reservoir. He used a cinema to study capillary blood flow. He learned how to insert a pipette into a blood capillary. He promulgated the pore theory for the exchange across the capillary membrane (with Landis). He used the quartz rod to illuminate coronary flow. At a physiology meeting when someone used statistics to "Prove" the presence of gamma glucose, he pointed out the fallacy of using statistics for such a purpose.

There are many more other distinguished Cardiovascular Physiologists of this period, but space does not permit me even to mention them. Some are still living and active; some are retired and others are dead.

I would hazard the guess that today among the group of living and active cardiovascular physiologists, there are a number who have already attained distinction. They in their turn will be included among the eminent workers in the last half of the 20th Century when someone summarizes the list 50 years hence. I am equally certain that there are a large number who have not yet gained prominence but will do so before the year 2000, and so will also be included in a summary, such as mine, made by someone else in 2070!

Finally, I hope you have not been too bored - I do not fall easily into the role of historian. I still believe there are a few more years of creative work ahead for me before I really begin to look backwards and spend my time entirely in reminiscences!

Editor's Note: My father, indeed, fulfilled his prediction. During his brief retirement he remained active as a teacher and he retained his capacity for critical scientific judgement until the end of his life, demonstrating on many occasions his ability to define gaps in the logic of a research project even when the subject concerned the newer aspects of molecular biology. He remained skeptical until the end - during our last conversation, which took place near the end of his final illness, he interrupted a slightly self-serving description of my opinion of the current state of a controversy in which I had been involved with the question "Are you sure that's not just New York talking?" His death at age 75 left my father no time for reminiscences; this article represents his sole historical legacy.