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Editor's Page

The Society has embarked upon two new activities this year. One is the appearance of a monthly four to six page, one article per issue, publication called "Physiology for Physicians" designed not for the experienced physiologist but for the practicing physician. The Journal of the American Medical Association in its review states - "This new monthly bulletin indicates a wholly admirable trend which should be encouraged. Technical knowledge need not be stuffy. It can be well written and easily understood if the authors will make sufficient effort to suit their expositions to their audience. In the issues so far published, the editor, Dr. Julius H. Comroe, Jr., has achieved his avowed purpose, which is "to inform - not to mystify---to educate - not to overwhelm."

The subscription price of this publication is a modest $3.00 per year. If by the end of the first year we receive between 4 and 5000 subscriptions the venture will become self-supporting. As of May 1, 1963 there were just under 3000 subscribers. Members of APS are encouraged to make this publication known to their physician friends.

The other new activity is the Visiting Scientist Program supported by a grant from NIH. This program permits experienced physiologists to spend one to three days on a college campus assisting staff members in whatever problems they may have, discussing advanced training and opportunities with students, and giving informal talks on physiology, research and teaching. The response to this program has been beyond our expectations. Over 550 scientists from the memberships of APS, Society of General Physiologists and the Comparative Physiology Division of the American Zoological Society have agreed to make such visits. So far approximately 200 colleges have requested visits by scientists. In arranging the visits scientists are matched to the needs of the particular college in so far as possible. Up to May 1, 1963 approximately 50 colleges have been visited. Both the colleges and the visiting scientists have been very enthusiastic about the program. Not only do the colleges gain but the scientists feel they have learned much of the problems of the undergraduate schools. The program is tending to bring these two groups closer together.

DUES NOTICES

Members will be receiving dues notices for the year July 1963 to July 1964. Please send separate checks for dues and do not combine payments for journals or other material you may be ordering from the Society or the Federation. Dues payments are to be sent to the APS Central Office whereas subscriptions to journals are to be sent to the Federation Business Office. Members are no longer required to subscribe to one of the Society s journals. Journal subscriptions run from January to January but dues run from July to July.

ACTIONS TAKEN AT SPRING MEETING

April 16-20, 1963

ELECTIONS. John R. Pappenheimer was elected to the position of President-Elect. K. S. Cole was elected to a four-year term on the Council. Robert E. Forster was elected to fill the two-year unexpired term of John Pappenheimer on the Council. All candidates nominated by Council were elected to membership (See Newly Elected Members - this issue).

APPOINTMENTS. The following appointments were made to replace persons who had served terms on the various committees.

Publications Committee - Robert Forster
Finance Committee - Hiram Essex
Education Committee - Charles Wilber and Walter Randall. R. R. Ronkin was reappointed.
Membership Committee - Harold Green
Program Committee - Robert Berne was reappointed.
Use and Care of Animals Committee - Paul MacLean
Porter Fellowship Committee - Donald Rennie
Senior Physiologists Committee - Philip Bard. Edward Adolph was reappointed.
Representative to AIBS - John Pappenheimer

PORTER FELLOW. Mr. Marshall Elzinga of the University of Illinois was appointed Porter Fellow. He will work under the supervision of Dr. Clyde Manwell of the Dept. of Physiology and Biophysics.

MEMBERSHIP. The matter of foreign membership in the Society was sent back to the Membership Committee for further study and will come up for final decision at the Fall business meeting.

PROGRAM. The action of the Society at its meeting in April 1962 to enforce the rule that a person's name could appear only once on abstracts sent to the Society for programming did not result in fewer 10-minute papers (See Spring Meeting Statistics). The matter of possible ways to limit the number of 10-minute papers at the Spring meeting was referred back to the Program Committee for further study. A report will be made at the Fall business meeting.

PUBLICATIONS. The Publications Committee recommended and Council approved the directive that the references in the American Journal of Physiology and the Journal of Applied Physiology carry full titles. This will be expedited as soon as possible.

Dr. W. O. Fenn has written a history of the Society, covering the last 25 years, which will be ready for distribution about the time of the Fall meeting, the 75th anniversary of the Society. Free copies will be mailed to all members.

The new monthly publication, Physiology for Physicians is well

under way and is being well received by physicians.

The matter of information communications and retrieval was discussed. It was recommended that all members should read "Science, Government and Information" by the President's Science Advisory Committee, January 10, 1963. It can be obtained for 25 cents from the Superintendent of Documents, U. S. Printing Office, Washington 25, D. C.

FINANCES. The fiscal reports for 1962 appear in this issue. The budgets for 1963 were approved.

FEDERATION. For the year July 1963 to July 1964, Dr. H. S. Mayerson of the Physiological Society will become chairman of the Federation Advisory Committee and the Federation Board.

In 1964 the September-October issue of Federation Proceedings (the Federation Directory) will become a separate publication. It will be issued free to all members and sold as a separate publication to all others.

The Federation Board approved the following registration fees for the 1964 Spring meeting: Non-members, $20; Members, $15; Graduate Students, $10.

ANIMAL CARE. There was considerable discussion of the pending animal care and utilization legislation. At the time of the meetings there were 7 bills in Congress. They are - S-533, Clark; S-1041, Randolf; HR-4856, Randall; HR-4620, Ashley; HR-5430, Ashley; HR-4840, Fogerty; and HR-4843, Roberts. The Fogerty and Roberts bills are identical and are essentially non-restrictive. Various opinions were expressed by members of the Animal Care Panel, the National Society for Medical Research, and others. Some felt that there should be no legislation recommended by scientists; others that a joint resolution was preferable to a bill since it could not be amended on the floor of Congress; and still others felt that a positive constructive bill or bills emphasizing animal care should be recommended by scientists.

Various persons urged all scientists to write to their congressmen expressing their opinions regarding the pending bills. Various methods of informing congressmen and the public of the scientists views, their interest in animal care, and objection to restrictive measures were outlined.

All members of the Society will be sent a new publication by the Public Health Service titled, "Guide for Laboratory Animal Facilities and Care" which has been prepared by the Animal Care Panel.

SPRING MEETING STATISTICS

	1962	1963
Total attendance	14,549	17,339
Total number of sessions	285	313
Intersociety sessions	54	52
Movies	9	9
Simultaneous sessions	31	34
Total number of papers	2,986	3,138
APS Abstracts		
Total received	847	933
Transferred to other societies and intersociety	219	219
Received from other societies	80	56
Total number of sessions programmed by APS(including Intersociety Sessions on Endocrines)	75	79
APS simultaneous sessions	5-7	7

Note: The ruling of having a person's name appear only once did not reduce the number of abstracts received.

FUTURE MEETINGS

1963 - Fall Meeting, Univ. of Miami, Coral Gables, Fla., Aug. 26-30;
Dr. Gordon Ring, Local Committee
Celebration of 75th Anniversary of the American Physiological Society

1964 - Spring Meeting, Chicago, Ill., Apr. 10-14

1964 - Fall Meeting, Brown Univ., Providence, R.I., Sept. 8-11;
Dr. Walter Wilson, Local Committee
200th Anniversary of Brown Univ.

1965 - Spring Meeting, Atlantic City, N.J., Apr. 10-15

1965 - Fall Meeting, UCLA

1965 - International Physiological Congress, Tokyo, Japan

1966 - Spring Meeting, Atlantic City, N.J., Apr. 11-16

MEMBERSHIP STATUS

April 1, 1963

Active members	2131
Retired members	129
Honorary members	16
Associate members	164
	2440

SUSTAINING ASSOCIATES

Abbott Laboratories, Inc.
Ayerst Laboratories
Beckman Instruments Co.
Burroughs Wellcome & Co.
CIBA Pharmaceutical Products
Ethicon, Inc.
Gilford Instrument Laboratories
Gilson Medical Electronics
Grass Instrument Co.
Harvard Apparatus Co.
Hoffman-LaRoche, Inc.
Lakeside Laboratories
Eli Lilly & Co.
Merck Sharp & Dohme Research Laboratories
Norwich Pharmacal Co.
Charles Pfizer & Co.
Phipps & Bird, Inc.
Precision Scientific Co.
Riker Laboratories, Inc.
A. H. Robins Co.
Sherman Laboratories
Smith Kline & French Laboratories
Squibb Institute for Medical Research
Tektronix
The Upjohn Co.
Warner-Lambert Research Institute
Wyeth Laboratories

DEATHS SINCE SEPTEMBER 1962

Gordon A. Alles
J. G. Edwards
Dorothy Fetter
J. Frederick Gudernatsch
Harry H. Hines
Paul D. Lamson (R)
Howard S. Liddell
Frank C. Mann (R)
Walter J. Meek (R)
David J. Sandweiss
Harold G. Struck
Robert D. Taylor
L. M. Tocantins

50-YEAR MEMBERS

Samuel Amberg (R)
Harold C. Bradley (R)
Percy M. Dawson (R)
Joseph Erlanger (R)
George Fahr (R)
Mabel P. Fitzgerald (R)
Alexander Forbes
Charles C. Guthrie (R)
Philip B. Hawk
R. G. Hoskins (R)
Paul E. Howe (R)
Dennis E. Jackson (R)
Israel S. Kleiner
Frank P. Knowlton (R)
Henry Laurens (R)
Edward Lodholz (R)
David Marine (R)
J. F. McClendon (R)
Hugh A. McGuigan (R)
Frederick R. Miller (R)
Victor H. K. Moorhouse (R)
Eugene L. Opie (R)
W. J. V. Osterhout
Alfred N. Richards (R)
Andrew H. Ryan
Charles D. Snyder (R)

Torald Sollmann (R)
George H. Whipple (R)
Carl J. Wiggers (R)
Shiro Tashiro (R)

NEWLY ELECTED MEMBERS

The following, nominated by the Council, were elected to membership in the Society at the Spring meeting, 1963.

FULL MEMBERS

ABBOTT, Ursula H.: Asst. Prof. Poultry Husb., Univ. of California.
ABBOUD, Francois M.: Asst. Prof. Internal Med. State Univ. Iowa.
ACKERMAN, Eugene: Assoc. Prof. Biophys., Mayo Clinic.
ARMSTRONG, David T.: Res. Assoc. Anat., Harvard Sch. Dent. Med.
ARMSTRONG, William McD.: Visiting Res. Assoc., Univ. of Rochester.
BALL, Wilmot C., Jr.: Instr. in Med., Johns Hopkins Univ.
BARR, Lloyd: Asst. Prof. Physiol., Univ. of Michigan.
BLATTBERG, Benjamin: Assoc. Res., St. Vincent Hosp., Cleveland.
BOYARSKY, Saul: Asst. Prof. Surg. in Urol., Albert Einstein Coll.
BRALOW, Saul P.: Asst. in Med., Temple Univ.
CHOBANIAN, Aram V.: Instr. Med., Boston Univ.
CUMMINGS, Edmund G.: Physiologist, Army Chemical Ctr.
DINGMAN, Joseph F.: Dir. Med. Res., Robert B. Brigham Hosp.
EKBERG, Donald R.: Physiologist, Gen. Elec. Co., King of Prussia, Pa.
ELLISON, Robert G.: Prof. Med., Med. Coll. of Georgia.
ELSNER, Robert W.: Asst. Res. Physiologist, Univ. California, La Jolla.
FALES, John T.: Asst. Prof. Environ. Med., Johns Hopkins Univ.
FISKE, Virginia M.: Assoc. Prof. Zool. & Physiol., Wellesley College.
FLEMING, Warren R.: Assoc. Prof. Zool., Univ. of Missouri.
FRAZIER, Howard S.: Assoc. Med., Massachusetts Gen. Hosp.
FREIS, Edward D.: Chief, Cardiovascular Res. Lab., Georgetown Univ.
FRENCH, Gordon N.: Instr. Med., Univ. of Pennsylvania.
FRY, Edith G.: Instr. Physiol., Yale Univ.
GLASSER, Richard L.: Asst. Prof. Physiol., Univ. of North Carolina.
GLASSER, Stanley R.: Asst. Prof. Radiation Biol., Univ. of Rochester.
GLICK, Bruce: Poultry Physiol., Mississippi State Univ.
GOODKIND, M. Jay: Asst. Prof. Physiol., Yale Univ.
GORDON, Paul: Instr. Pharmacol., Chicago Medical School.
GREENSPAN, Kalman: Instr. Physiol., State Univ. of New York.
HALL, James C.: Prof. Physiol., Rutgers - The State University.
HIX, Elliott L.: Assoc. Prof. Pharmacol., Kirksville Coll. Osteo. & Surg.
HOLLANDER, William: Asst. Prof. Med., Boston Univ.
HOOVER, George N.: Res. Assoc., Ohio State Univ.
HOYLE, Graham: Res. Prof. Biol., Univ. of Oregon.
HUMPHREY, Edward W.: Assoc. Surg., Univ. of Minnesota.
JACOBS, Harry L.: Assoc. Prof. Physiol., Psychol., Univ. of Illinois.
KAHN, Arthur J.: Asst. Prof. Physiol., Seton Hall College.
KALEY, Gabor: Asst. Prof. Pathol., New York Univ.
KATZMAN, Robert: Assoc. Prof. Neurol., Albert Einstein College.
KAVALER, Frederic: Asst. Prof. Physiol., State Univ. of New York.
KEYL, Milton J.: Assoc. Prof. Physiol., Univ. of Oklahoma.
KITAY, Julian I.: Asst. Prof. Med. & Physiol., Univ. of Virginia.
LIPKE, Herbert: Biochemist, Army Chemical Center.

LYNCH, Peter R.: Asst. Prof. Physiol., Temple Univ.
MACK, Robert E.: Assoc. Prof. Med., Wayne State Univ.
MENDELSTAM, Paul: Asst. Prof. Med., Univ. of Kentucky.
MILIC-EMILI, Joseph: Res. Fellow, Harvard Sch. Public Health.
MULROW, Patrick J.: Asst. Prof. Med., Yale Univ.
NATHAN, Paul: Asst. Prof. Physiol., Univ. of Cincinnati.
NEVILLE, James R.: Aviation Physiologist, Brooks Air Force Base.
O'DELL, Roberta: Asst. Prof., Tulane Univ.
PACKER, Lester: Asst. Prof. Physiol., Univ. California, Berkeley.
PITTMAN, Constance S.: Instr. Med., Univ. of Alabama.
RANKIN, John: Assoc. Prof. Med., Univ. of Wisconsin.
RAWSON, Robert O.: Asst. Fellow, John B. Pierce Fndn.
ROSENTHAL, Fred: Asst. Res. Physiol., Univ. California, Berkeley.
SAID, Sami I.: Asst. Prof. Med., Med. Coll. Virginia.
SAVITSKY, J. Philip: Res. Assoc., Montefiore Hosp.
SHORE, Bernard W.: Asst. Prof. Physiol., Washington Univ.
SHORE, Virgie C.: Asst. Prof. Physiol., Washington Univ.
STEMLER, Fred W.: Res. Physiologist, U.S. Army Chemical Ctr.
STOLWIJK, Jan A.J.: Assoc. Fellow, John B. Pierce Lab.
STRISOWER, Edward H.: Res. Assoc., Donner Lab., Univ. California, Berkeley.
SULLIVAN, Lawrence P.: Asst. Prof. Physiol., Univ. of Kansas.
TING, Er Yi: Instr. Med., Albert Einstein College.
TOOLE, James F.: Prof., Neurol., Bowman Gray Sch. of Med.
TORRES, Joseph C.: Instr. Physiol., Boston Univ.
TURINO, Gerard M.: Asst. Prof. Med., Columbia Univ.
URQUHART, John: Investigator, Natl. Heart Inst.
VALTIN, Heinz: Asst. Prof. Physiol., Dartmouth Med. Sch.
VAN LIEW, Hugh D.: Asst. Prof. Physiol., Stanford Univ.
WHITE, Robert J.: Asst. Prof. Neurosurg., Western Reserve Univ.
WIEDERHIELM, Curt A.: Res. Instr. Physiol., Univ. of Washington.
WILSON, Russell H.: Dir. Research, VA Hosp., Dallas.
WINTERNITZ, William W.: Assoc. Prof. Med., Univ. of Kentucky.
WOLBACH, Robert A.: Asst. Prof. Physiol., Univ. of Utah.
WOLF, Robert L.: Res. Asst. Med., Mt. Sinai Hosp., New York.
WOOLLEY, Dorothy E.: Lecturer Physiol., Univ. California, Berkeley.
YU, Paul N.: Assoc. Prof. Med., Univ. of Rochester.

ASSOCIATE MEMBERS

ABBRECHT, Peter H.: Medical Intern, UCLA Hosp.
ABERLE, Mary Ann: Predoctoral Fellow, NIH.
AGERSBORG, Helmer P.K.: Mgr., Tox. & Comp. Pharm., Wyeth Labs.
BEACH, Vivian L.: Scientist, Warner Lambert Res. Inst.
BOND, Ted P.: Grad. Student, Univ. of Texas.
COLEMAN, Bernell: Grad. Student, Stritch Sch. Med., Loyola Univ.
CROSS, Cecil E.: Investigator, NHI, St. Joseph's Hosp., Burbank.
HAYWARD, James N.: Sr. Instr. Med. & Pediat., Univ. of Rochester.
NELSON, Phillip G.: Physiologist, NIH.
RULON, Russell R.: Instr. Physiol., Univ. of Iowa.
STOREY, Arthur T.: Grad. Student, Univ. of Michigan.

HONORARY MEMBER

GRANIT, Ragnar: Karolinska Institutet, Stockholm, Sweden.

1962 FISCAL REPORTS

SOCIETY OPERATING FUND

INCOME	
Regular Membership Dues	$24,370
Associate Membership Dues	702
Sustaining Associates	6,550
Interest on Savings Accounts	1,450
Fall meeting, net	926
Officer tours, net	17
Reimbursement from Federation Spring meeting	11,228
Physician's Course, net	4,870
Reimbursement from Grants (overhead)	4,854
Miscellaneous Income	56
Total Income	$55,023
EXPENSES	
Dues to Federation	$10,029
Dues to AIBS	1,987
Dues to National Society for Medical Research	250
Salaries, Soc. Security, Ins. and Pensions	14,660
Travel	924
Addressing, Mailing and Shipping	882
Telephone and Telegraph	170
Supplies and Duplicating	762
Equipment	1,883
Depreciation on Equipment	371
Repairs and Maintenance	190
Rent	481
Fire Insurance (3 yrs.)	69
Bowditch Lecture	500
Legal and Consulting Fees	500
Advance to Physiology for Physicians	5,785
Incidental Expenses	88
Business Office Service Charge	3,257
Total Expenses	$42,788
Excess of Income over Expenses	$12,235
Amount in Savings & Loan as of Dec. 31, 1962	$40,000

PUBLICATION OPERATING FUND

INCOME	
Subscriptions	$220,192
Sale of Reprints	64,275
Other Publication Sales	15,343
Advertising, net	7,074
Page and Article Charges	39,606
Author Charges	4,773
From Grants for Special Projects	12,425
Other Income from Special Projects	54,720
Total Income	$418,408

EXPENSES	
Salaries, Soc. Security, Ins. and Pensions	$70, 283
Section Editors	10, 648
Redactorial Expense	20, 273
Printing and Engraving	172, 290
Cost of Reprints and Books Sold	47, 328
Supplies and Duplicating	1, 960
Communications, Shipping and Travel	33, 471
Promotion Expenses	3, 480
Depreciation on Furniture and Equipment	1, 564
Rent	5, 825
Incidental Expenses	2, 035
Business Office Service Charge	31, 036
	$400, 193
Less Allocations to Publication Inventories	18, 070
Total Expenses	$382, 123
Excess of Income over Expenses	$36, 285
Transfer from Publications Service Center Grant	5, 553
Net Income	$41, 838

JOURNAL OF NEUROPHYSIOLOGY

Balance Dec. 31, 1961	$8, 646
Receipts	$31, 901
Expenses	$41, 082
Deficit Dec. 31, 1962	(535)

PUBLICATION CONTINGENCY AND RESERVE FUND

Balance Dec. 31, 1961	$588, 976
Gain on Sale of Securities	22, 282
Dividends & Interest Paid to APS	21, 134
Principle Paid to APS*	50, 000
Balance Dec. 31, 1962	$582, 392

*Capital fund for Physiology Handbooks

SOME COMPARISONS

Scientific Manpower Study of 1960 National Register of Scientific and Technical Personnel

The National Science Foundation publication NSF 62-43 has reported some interesting figures taken from the National Register. Below are some comparisons extracted from this report that may be of interest to physiologists.

Distribution of Doctorates

	Total*	Total Doctorates		Ph.D.		M.D.	
		#	%**	#	%	#	%
Physiology	2797	2366	84.5	1498	53.5	868	31.0
Biochemistry	5625	3686	65.5	3408	60.5	278	4.9
Pharmacology	1402	1033	73.6	807	57.5	226	16.1

*Total number in each discipline reported in the register.

**Percentages in this and following tables are of the total number reported in the register.

Type of Employer

	Educational Institution		Government Including Military		Non-Profit Organizations		Industry	
	#	%	#	%	#	%	#	%
Physiology	1904	68.0	333	11.9	247	8.8	260	9.2
Biochemistry	2681	47.6	981	17.4	738	13.1	1078	19.1
Pharmacology	553	39.4	185	13.1	84	5.9	558	39.8

Work Activity

	Research		Teaching		Management and Administration	
	#	%	#	%	#	%
Physiology	1523	54.4	766	27.3	238	8.5
Biochemistry	3757	66.7	667	11.8	716	12.7
Pharmacology	788	56.2	201	14.3	292	20.8

Years of Experience

	Physiology		Biochemistry		Pharmacology	
	#	%	#	%	#	%
1 Year	44	1.5	175	3.1	30	2.1
2-4	383	13.6	839	14.9	171	12.1
5-9	754	26.9	1461	25.9	382	27.2
10-14	595	21.2	1185	21.0	297	21.1
15-19	281	10.0	638	11.3	154	10.9
20+	686	24.5	1150	20.4	339	24.1

Age Distribution

Age	Physiology		Biochemistry		Pharmacology	
	#	%	#	%	#	%
20-24	50	1.7	231	4.1	32	2.2
25-29	249	8.9	728	12.9	154	10.9
30-34	583	20.8	1255	22.3	295	21.0
35-39	632	22.5	1232	21.9	298	21.2
40-44	437	15.6	830	14.7	224	15.9
45-49	308	11.0	522	9.2	164	11.6
50-54	230	8.2	337	5.9	116	8.2
55-59	145	5.1	219	3.8	63	4.4
60-64	90	3.2	139	2.4	26	1.8
65-70	39	1.3	63	1.1	13	0.9
70+	23	0.8	29	0.5	8	0.5

SYMPOSIUM ON THE EXPLORATION OF MARS

The first national symposium devoted to the scientific, technical, management and economic resources needed for exploring Mars will be held at the Hilton Hotel, Denver, Colo., June 6 and 7, 1963. The symposium is being presented by the American Astronautical Society and co-sponsored by the American Institute of Biological Sciences, the American Astronomical Society, the American Rocket Society, the Institute of Aerospace Sciences and the National Aeronautics and Space Administration. The symposium will include the life science aspects of the Mars trip. For further information write Dr. George W. Morgenthaler, The Martin Company, P. O. Box 766, Littleton, Colo.

REFRESHER COURSE
FALL MEETING 1963

Dr. Charles E. Lane of the Institute of Marine Science of the University of Miami has arranged a Refresher Course on Comparative Physiology. The following will participate in the presentation.

B. T. Scheer, Univ. of Oregon - Comparative view of homeostasis
A. W. Martin, Univ. of Washington - Invertebrate circulation and excretion
L. H. Kleinholz, Reed College - Comparative endocrinology
W. J. Gross, Univ. of California - Ion regulation in crustacea
A. Riggs, Univ. of Texas - Comparative physiology and biochemistry of respiratory pigments
J. L. Larimer, Univ. of Texas - Stress-induced reflexes modifying gas transport in crustacea
K. Johansen, Univ. of Oslo - Comparative cardiovascular physiology of vertebrates

This promises to be an intensive and interesting session. It is hoped a large number of medical school physiologists as well as comparative and general physiologists will attend. This will be a unique opportunity for many to learn of work in comparative physiology.

BOWDITCH LECTURE

President Mayerson has chosen Dr. Eugene M. Renkin to deliver the Bowditch Lecture at the 1963 Fall Meeting in Coral Gables, Florida. The title of his lecture will be "Transport of Large Molecules across Capillary Walls."

Dr. Renkin was born in Boston, October 21, 1926. He received his undergraduate degree from Tufts College, graduating summa cum laude in 1948. He took his graduate work under Dr. John Pappenheimer at Harvard and received his Ph.D. degree in 1951. He has held positions at the Brookhaven National Laboratories, National Heart Institute of NIH and is at present professor of physiology at George Washington University School of Medicine, Washington, D.C. He was a postdoctoral fellow at Karolinska Institute, Stockholm in 1960-1961. He became a member of the American Physiological Society in 1954. His primary research interest has been capillary permeability and transcapillary exchange.

THE SOCIETY'S 75th ANNIVERSARY MEETING
CORAL GABLES, FLORIDA
AUGUST 27-30, 1963

The Local Committee at the University of Miami extends a warm invitation to all members and friends of the American Physiological Society to attend the Fifteenth Fall Meeting of the American Physiological Society, in Coral Gables, Florida.

The Program Committee has plans for several important symposia, presentation of scientific papers, and visits to several departments and research facilities. The Refresher course in Comparative Physiology, under the chairmanship of Dr. Charles E. Lane of the Institute of Marine Sciences, is expected to attract a wide range of interested physiologists. The Bowditch Lecture will be delivered by Dr. Eugene Renkin.

The Local Committee is planning a Luau, an outdoor tropical dinner feast, as well as the Annual Fall Banquet, both to be held in settings appropriate to the Miami subtropical scene.

Social activities planned will include boat trips, bus tours of the Vizcaya Gardens, the Parrot Jungle and the Seaquarium, by prearrangement. These are particularly designed for the pleasure and edification of the families.

Housing will be available on campus in modern dormitories or in nearby luxury motels with swimming pool facilities at modest, off-season rates, according to the needs of the individual and his family.

Announcements with abstract forms, applications for housing, and requests for paid tours or boat trips will be mailed to the membership shortly. These are to be returned not later than June 19, 1963.

The Local Committee urges all members and friends to make this seventy-fifth Anniversary Fall Meeting a successful and pleasant one by their most welcome attendance.

REPORT OF DIVISION OF MEDICAL SCIENCES OF NRC

R. W. GERARD

The Division of Medicine of the National Research Council has continued its many useful activities during the year since the last report to the Council of the American Physiological Society, and has initiated or contemplates initiating some important new activities. These latter include a careful study on medical and hygenic problems of the tropics and the recommendation of a permanent advisory organization and information center in this area; a conference was held on the role of universities, industry, and government in recruiting and training students for service in environmental health fields; the Division is cooperating with the Federation on a plan for a depth study of the resources and needs for scientific communication, especially at the scientist-to-scientist level-- a welcome opportunity to bring the Society and the Council into more vigorous and effective interaction than has ordinarily been possible through a single delegate.

At the Fall meeting of the Division, on November 26, 1962, most of the day was devoted to a conference on "The Responsibilities of Investigators and of Government Agencies in the Development, Evaluation and Release of New Drugs." The theme of the conference, organized by Dr. Alfred Gilman, was the course that a new drug takes from the laboratory, through various phases of animal and clinical testing, to its acceptance--and recall when necessary. This topic was well chosen and highly timely, in view of the effects of the "drug amendments of 1962"-the first case in Congressional legislative history in which a law was passed without a dissenting vote in either chamber. The five main presentations were: Animal Testing, by Karl Beyer of Merck, Sharpe & Dohme; Clinical Evaluation, by John Clark of Smith, Kline and French; Physician Responsibilities to the Patient, Louis Lasagna, of Johns Hopkins University; The Decision to Release a Drug, by Alfred Gilman, Albert Einstein College of Medicine; and Recall of a Drug, by Chester Keefer of Boston University School of Medicine. The problems were presented in balanced and judicial manner and were further examined during a discussion period.

The question was left for further study as to whether an NAS-NRC committee on drug evaluation should be created.

REPORT OF DIVISION OF BIOLOGY AND AGRICULTURE OF NRC

J. H. LEATHEM

Each of forty national biological societies nominates a representative to the Division of Biology and Agriculture of the National Research Council. This division is currently headed by Dr. T. C. Byerley of USDA. I have served as the representative of the American Physiological Society to this division for the past two years and have attended the annual meetings of the National Research Council in Washington held April 1-3, 1962 and April 9 and 10, 1963. As representative, the members may act to advocate or defend a position taken by the Society and especially to assist the National Research Council in improving or strengthening a scientific field. The American Physiological Society has not made a direct request and therefore my actions have been as an individual. The representative may be asked to serve on suitable advisory committees. In this regard, I accepted appointment to the Advisory Fellowship Panel for the Committee of International Exchange of Persons and have examined 6-10 applications each year. The representative serves to transmit information provided to him by the National Research Council to his Society and it is in this scope that I shall summarize the actions taken or reports given at the annual meetings.

The NRC annual meeting held in 1962 included a plenary session entitled "Science in International Cooperation"(by Harrison Brown, Edward Fei, and Walsh McDermott). The general tone was to help a country by planning with that country to gain the goals they set for themselves.

A session entitled "Role of Sciences in Government Policy" was presented by Wiesner, Beckler, and Revelle. While the first two speakers spoke broadly of organization, Revelle thought that government considered a scientist as one who should be on tap but not on top and that a bureaucrat could not care less for his advice.

The volume of published material was of concern to Emery and others and they urged the societies to initiate steps to cut the volume.

The Divisions of Medical Sciences, Engineering and Biology and Agriculture met jointly to consider "Effective Communications." While films, computers and human understanding and education were discussed, the tone of awareness of the problem was more predominant than a precise program.

The 1963 annual meeting included several plenary sessions:

A report by the Atomic Bomb Casualty Commission (Cannan, Finch, Francis, Neel) indicated that the program was going very well as cooperation was very good with 85% returnees and at death 50% came to autopsy. By 1950 it was evident that no major effects were to be noted and even today there has not been an increase in non-tumor disorders. An increase in thyroid tumors, leucemia, and cataracts is indicated but an effect on sex ratio is equivocal.

A report on Natural Resources has resulted in publications on renewable water, mineral and energy resources. Coal, oil and gas reserves seems adequate for 500 years but population poses a major threat.

A discussion, "Effect of Governmental Support on Science and the Universities" (Brooks, Dryden, Goddard, McElroy, Shannon, and Waterman) considered summer salary, fellowship pay, but stressed that the university should not permit available research funds to divert the goals set for the university.

A report on Fellowship Selection indicated that NRC administered 20 programs. The report indicated that grades, GRE, and references all aid in selection with the former as least indicative and that a panel of three serves to provide a good balance in making a choice. While our current Ph. D. production has returned to a 10% level only a small number of very good students complete the degree. High School students with a top I. Q. complete a doctorate in only one of five cases.

The Division of Biology and Agriculture heard a series of reports and proposals including:

A report from Dr. Ebert regarding the AIBS. Dr. Ebert made it quite clear that the problems had not been resolved and that the deficit was larger than was generally presumed but within his estimate of $500,000. Certain studies have been transferred or dropped and the staff decreased by 50% but the present operation will cost $250,000 per year. The unfavorable note has been the response of only 7,000 of a 37,000 total membership to the $10 dues request.

Dr. Edward Graham discussed an International Biological Program but the details were few and a vote to proceed with such a program found nearly 50% of the division membership abstaining.

The Food and Nutrition Board indicated that contamination of milk by radio activity was not a serious problem and that studies were progressing toward obtaining whole fish concentrate as a valuable food protein. Suggestions of secondary deficiencies have been made in countries given excess corn meal or skim milk suggesting that we can not provide a single food supplement which happens to be in excess in the USA.

Studies are being carried out with Argentina on foot and mouth disease to control this factor related to meat imports.

Discussion was given to the restoration of a Biology Council. The Council would consider all aspects of pure and applied biology except those directly concerned with human medicine and human behavioral science. Studies may be concerned with education, instrumentation, facilities, fields which require stimulation, etc.

The NRC is looking in to Trends in Agriculture as to curriculae in agricultural schools and potential future for graduates. Programs seem

very varied.

Finally, of interest to the Society are the seven to eight bills before the Congress relating to the use of animals in experimentation. While opposition was generally expressed toward all bills, B. F. Hill was not optomistic that all would be withdrawn. In fact he indicated that we may need to support the least burdensome bills.

SOCIETY OF GENERAL PHYSIOLOGISTS
MEETING SEPTEMBER 4-7, 1963

The 16th Annual Symposium of the Society is to be held in Woods Hole, Massachusetts, September 4 through 7, 1963 in connection with the annual Fall meeting. The subject for the symposium is "The Cellular Function of Membrane Transport." It is being organized by J. F. Hoffman. The basic idea of the symposium is that membrane transport is as much a characteristic of a cell as its metabolism, excitation, or replication, and therefore has an integral role in cellular activity. The purpose of the symposium will be to explore these interrelationships. There will be four sessions which will include the following speakers and topics.

R. Adrian - Membrane properties of striated muscle and the initiation of contraction
J. Dainty - Correlation of ion uptake with various physiological processes in plant cells and tissues
A. Fleckenstein - Metabolic aspects of the excitation-contraction coupling
K. Frank - Membrane properties of the molluscan ganglion cell
H. Halvorson - The role of the alphaglucoside permease on the induction of isomaltose
J. Orloff - The mechanism of action of antidiuretic hormones on epithelial structures
W. Rehm - Metabolism and membrane transport in the gastric mucosa

A. Rothstein - Membrane function and physiological activity of microorganisms
D. Tosteson - The role of the membrane in the regulation of cell volume
R. Whittam - The interdependence of metabolism and active transport
T. Wilson - Intestinal absorptive phenomena

For further information write Dr. David W. Bishop, Dept. of Embryology, Carnegie Institute of Washington, Baltimore 10, Maryland.

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ON
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July 12-13, 1963
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Dr. I. H. Page, Cleveland Clinic, Ohio - History of Subject, and Natural History of the Disease
Dr. W. S. Peart, St. Mary's Hospital, London, England - Etiology
Dr. L. J. McCormack, Cleveland Clinic, Ohio - Classification of Pathologic Lesions
Dr. J. Genest, Hotel-Dieu - De Montreal, Canada - Differential Diagnosis
Dr. O. M. Helmer, Lilly Laboratory, Indianapolis, Indiana - Bioassays of Renin and Renin Substrates
Dr. A. Rapoport, Toronto University, Canada - Diagnostic Individual Renal Function Tests
Dr. E. F. Poutasse, Cleveland Clinic, Ohio - Urographic and Aortographic Diagnostic Procedures
Dr. C. C. Winter, Ohio State University College of Medicine, Columbus - Selection of Patients for Surgery and Prediction of Outcome
Dr. P. T. DeCamp, Ochsner Clinic, New Orleans, Louisiana - Surgical Treatment
Dr. M. E. DeBakey, Baylor University College of Medicine, Houston, Texas - Surgical Techniques
Dr. I. H. Page - Summary of Presentations

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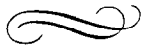

TOUR OF PRESIDENT-ELECT AND COUNCILMAN

HERMANN RAHN
JOHN PAPPENHEIMER

PHYSIOLOGY IN SCHOOLS OF VETERINARY MEDICINE

The interests and responsibilities of physiologists in schools of Veterinary Medicine are closely allied to those of physiologists in medical schools generally. However, schools of Veterinary Medicine in the United States have usually developed in association with agricultural colleges, rather than with medical schools, and this has been an important factor, tending to isolate physiologists working in Veterinary Schools from the main stream of physiology represented by the American Physiological Society. This artificial separation of interests has unquestionably had adverse effects on the development of physiology in Veterinary Schools: at the same time it has deprived the APS of a small, but potentially important source of strength contributing to the development of physiology as a whole. In England, Scandinavia and some continental countries, this potential has been more fully realized, as evidenced by the relatively large number of research publications from Veterinary Colleges which appear in the major physiological journals. Many general problems in physiology can best be approached using animals and facilities which are not ordinarily available outside the Veterinary Schools. In addition, there are interesting and important physiological problems which are unique to domesticated animals, but are not represented in work with conventional laboratory species.

These are some of the considerations which led to our tour of selected Veterinary Schools, but the immediate purpose was simply to establish closer communications between the APS and individual members of physiology departments. We visited seven of the 18 schools of Veterinary Medicine in the United States. Our hosts at each institution received us with warm hospitality and provided us with ample opportunity to discuss research, teaching, publications and administrative matters with staff members in physiology and in related departments within the Veterinary and Agricultural Colleges. The discussions were frank and lively and they revealed both the need and the desire for closer affiliations with APS.

Teaching

A. Courses for veterinarians. The 18 schools admit about 1,000 students annually, usually after 3 years of undergraduate training; the average class therefore numbers some 50 students. Physiology is an important part of the four-year curriculum leading to the degree of Doctor of Veterinary Medicine (DVM). It is ordinarily taught as a full year course in the second year and involves comprehensive coverage of systemic physiology. Comparative aspects are specially important and the laboratory experience usually includes work with most of the domesticated animals. Endocrinology, reproductive physiology and physiology of ruminants are specially emphasized, but almost every aspect of classical physiology may be represented in the general coverage. The time devoted to physiology and the comprehensive nature of some of the courses

was of interest to us because physiology courses in many medical schools are being compressed to allow for instruction in newer aspects of the ancillary basic sciences. The need for initial thorough training in physiology is specially important in the Veterinary Schools because clinical teaching in the third and fourth years is not likely to be so well correlated with the basic sciences as it is in the medical schools.

At the present time there are no separate departments of biochemistry in the Veterinary Schools. Responsibility for instruction in biochemistry may be delegated to departments of chemistry, or biochemistry elsewhere in the university (often in the associated college of agriculture or college of arts and sciences). Alternatively, the professor of physiology may be responsible for appointing a senior staff member within his own department to provide a separate course in "physiological chemistry." Responsibility for instruction in pharmacology usually resides within the department of physiology. Finally, the professor of physiology may have to organize advanced courses in physiology for graduate students (candidates for the M.S. and Ph.D.) coming from many departments of agricultural science as well as from departments within the Veterinary School itself. Small wonder then that physiologists working in Veterinary Schools are often burdened with almost overpowering commitments to teaching.

B. Graduate training programs. Twenty years ago there were few if any graduate students within the Veterinary Schools who worked towards the degree of Ph.D. in physiology. In recent years this situation has altered radically. All the schools we visited now offer advanced training leading to the degree of Ph.D. Practically all the students who undertake this training come by way of the Veterinary Schools themselves and already have a DVM. New appointments to the senior staff are often selected from candidates having both the DVM and the Ph.D. but it is relatively rare for the "pure" Ph.D. to find a permanent home in physiology within a Veterinary School. It might be an important step forward if well trained physiologists with advanced degrees from outside the Veterinary Schools could be attracted to fill senior positions. This step occurred a generation ago in the medical school. Meanwhile, the development of graduate training programs within the Veterinary Schools is having a stimulating effect on research and scholarship. Requirements for the degree of Ph.D. are much the same as they are elsewhere and, in general, the combined DVM and Ph.D. symbolize a well-rounded training in classical physiology.

Research

As pointed out above, the responsibilities for teaching are very great and only in the last few years has it been possible, in some departments, to arrange time and facilities for research. Nevertheless, an excellent start has been made and we were introduced to many interesting studies representing a variety of fields in physiology. It would not be appropriate, even if space were available, to discuss individual projects in this report. However, we can point out certain topics which are specially suited for study in veterinary schools and which are of general interest.

1. Ruminant digestion and metabolism. The ruminant stomach is a vast factory for the breakdown of cellulose into short chain fatty acids. In a normal cow the volume of ingesta and fluid in the rumen is over 100 liters at any one time. Microbial metabolism of the ingesta produces hundreds of liters of carbon dioxide and methane per day and the digestive tract absorbs kilogram quantities of fatty acids and salts. Massive and highly integrated cyclic muscle contractions are responsible for mixing rumen contents, for eructation, for rumination and for passage of ingesta through the elaborate system of stomachs. The elucidation of nervous and chemical mechanisms controlling these integrated processes will provide challenging problems for many years to come.

The mechanisms involved in the absorption and transport of fatty acids and salts are largely unknown. The high amount of potassium and magnesium in the diet raises interesting questions concerning absorption and excretion of these ions. The renal capacity for active secretion of potassium is specially well developed and it seems likely that ruminants are the animals of choice in experiments relating to renal secretion of potassium.

The importance of small chain fatty acids in ruminant metabolism raises many interesting problems, biochemical, physiological and pathophysiological. Blood glucose may be reduced to less than 15 mg % (either experimentally or in ketosis) without inducing convulsions and this raises fundamental questions about the physiological regulation of carbohydrates versus fatty acid metabolism, especially in relation to the central nervous system.

The dependence of ruminants on normal microbial metabolism results in many pathological conditions of economic importance as well as of physiological interest. For example, a diet rich in carbohydrate, such as corn, results in ruminal production of lactate in such quantities as to cause severe dehydration and cardiovascular failure from osmotic withdrawal of body fluids into the rumen. The study of these and similar problems involves the use of sophisticated knowledge and techniques from many fields.

2. Endocrinology. The endocrine control of growth, reproduction, protein synthesis, lactation, etc. in domesticated animals is of vast practical importance to the world supply of food.

Many examples of practical applications could be cited, but one of the most spectacular is the large scale treatment of beef cattle with steroids to promote meat production. Most of the beef cattle in the United States are now subjected to this treatment which adds about 15% to the usable weight of each animal without increasing food intake. The applied aspects of endocrinology are of such economic significance that research in this area has been liberally supported by the government. In general, however, this support has been given to the large agricultural research facilities rather than to relatively small departments of physiology in the Veterinary Schools.

The use of large animals for endocrine research has some unique

advantages. For example, the large size permits permanent implantation of catheters into arteries and veins supplying some of the endocrine glands. Several liters of venous blood draining a gland can be collected for fractionation and analysis without causing deleterious hemodynamic effects. Biosynthesis and release of hormones can be studied by these means on normal animals and under a variety of experimental conditions.

3. Cardiovascular and respiratory physiology. We may preface this paragraph with the reminder that the first measurements of blood pressure and of cardiac work were carried out on the horse by Stephen Hales in 1733. Some of the earliest studies of cardiac output and of salivary blood flow were also carried out on horses. In recent years there has been a revival of interest in the use of large animals for cardiovascular research. This interest has, in part, been stimulated by the discovery that the pulmonary blood vessels of cattle are remarkably sensitive to mild hypoxia. Pulmonary hypertension leading to the fatal edema of "Brisket" disease may be induced by exposure of cattle to altitudes of less than 10,000 ft. The mechanisms underlying this extraordinary response are of significance for both cardiovascular and respiratory physiology.

The comparative physiology of the cardiovascular system is only beginning to be studied. However, it may be expected that the size of the heart and major blood vessels in some of the larger animals will accentuate certain physical limitations inherent in all cardiovascular systems. From a technical point of view it is relatively easy to carry out circulatory studies in some of the larger animals, an obvious advantage being the large size of the blood vessels supplying internal organs.

Publications and Societies

The "American Journal of Veterinary Research" is the principal journal for publication of original articles in the veterinary sciences. Very few of these articles are ordinarily of interest to the physiologist; most are concerned with problems in pathology, microbiology or nutrition. This is perhaps a reflection of the relative strength and practical importance of these disciplines in the veterinary schools. Research publications from the physiology departments are scattered in a variety of journals, including the "American Journal of Veterinary Research," the "Journal of Dairy Science", "Endocrinology", "Journal of Animal Science" and "Poultry Science". Some excellent physiological papers are published in the form of agricultural bulletins. Relatively few articles appear in journals of the American Physiological Society. During the past five years the "American Journal of Physiology" and the "Journal of Applied Physiology" have published an average of seven papers per year from Veterinary Schools and an additional six papers annually from departments of animal husbandry in the agricultural colleges. Approximately 1 out of every 60 papers is derived from one of these sources. The corresponding average for the "British Journal of Physiology" and "Quarterly Journal of Experimental Physiology" is 1 out of every 20 papers. There is no separate society of veterinary physiologists. However, there is a small group primarily interested in physiology and pharmacology which meets in conjunction with the "American Veterinary Medical Association" to discuss mutual problems in teaching and research.

This meeting does not fulfill the need felt by many of its members for the discussion, communication and learning of new advances in physiology. Most staff members in the newly developing departments in physiology and pharmacology in the Veterinary Schools feel that the publications and meetings of the American Physiological Society are most closely identified with their interests.

Conclusions

Physiology in Veterinary Schools and associated agricultural colleges is undergoing an exciting period of development. Although the total number of physiologists working in these areas is small, and membership in our Society even smaller, their interests are clearly identified with the American Physiological Society. Publications and meetings of our Society embody the principal professional interests of physiologists working in the Veterinary Schools, both in terms of research and teaching. Conversely, many of the problems and opportunities for research in the Veterinary Schools will be of interest to membership at large. We ended our tour feeling that we were at the beginning rather than at the end of associations which can hardly fail to be stimulating and productive for all concerned.

APPEAL FOR TEACHING EQUIPMENT

One of the problems small colleges have is that of being able to afford laboratory equipment for teaching physiology. This has been brought to our attention on several occasions, especially from the reports of those scientists participating in our Visiting Scientist Program. Several college departments asked if it would be possible to set up some mechanism whereby small colleges could secure free (or at small cost) repairable, unused, obsolete equipment (obsolete for research) suitable for laboratory teaching purposes, from medical schools and research departments. Several such departments have store rooms crowded with unused equipment that would be suitable for teaching labs.

If departments that have excess, unused equipment would send a list of the equipment to the APS Central Office at 9650 Wisconsin Ave., Washington 14, D.C. the information could be relayed to small colleges. The interested small colleges could then contact the departments supplying the lists and make direct arrangements to secure the particular items they may need.

It is felt that both the larger research departments and the Society would be doing a worthwhile service if this were done.

NEW IDEAS ON THYROID FUNCTION

S. B. BARKER

Interest in thyroid function broadly speaking is being maintained at such a pace that a complete review of recent work would be impossible under the circumstances of these meetings. As the rather simple-minded title suggests, the writer has selected a few areas of current study for discussion. These are grouped under: Deiodination, New analogs of thyroxine, Membrane effects of thyroxine, Possible involvement of sympathetic nervous activity in T_4 action.

DEIODINATION

Non-enzymatic. Deiodination reactions, both those involving living processes as well as those not dependent upon enzymatic reactions, continue to receive attention. In the latter group, we have recently become interested in chemical deiodination of iodothyronines by ceric ion in acid (3). Bowden, Maclagan, and Wilkinson (7) originally noted that aromatic iodine ortho to a hydroxy or amino group was readily removed by cerium. They reported without special comment that the iodines of 3, 5-diiodothyronine (3, 5-T_2), next to the ether oxygen, were removed, although actually remote from the phenolic -OH (See Fig. 1). Our attention was aroused when we failed to find removal of the iodines in 4'-deoxy-3, 5-T_2. In an extended series of analogs studied, alteration of the alanine sidechain by acetylation, esterification or replacement by a fatty acid residue, made no difference in deiodination of 3, 5-T_2, nor did addition of various alkyl substitutions on the phenolic benzene. As shown in the figure, deiodination was prevented by removal of the 4'-oxygen or its blockade by formation of the O-methyl ether. Elimination of the diphenyl ether oxygen also stopped the reaction, although, as would be expected, iodine adjacent to the still remaining 4'-OH was reactive.

These results suggested the process shown in Fig. 2: that the ceric ion oxidatively ruptured the diphenyl ether, possibly through intermediate formation of a quinone, leaving a phenol or some other ionizable group at the 4-position so that removal of electrons was possible as part of deiodination. Of course, it is not possible even to hazard a guess concerning any possible relationship of this series of reactions to biological deiodination, but it may be useful as a prototype.

Another non-biological dehalogenation reaction is that occurring when electrolyte desalting of an iodothyronine solution is carried out (14). Since these circumstances result in the formation of sugar alcohols from aldoses, we assume that deiodination is here reductive rather than oxidative. In the length of time required for removal of salt in a physiological saline solution, 1 mg of thyroxine (T_4) was completely transformed to inorganic iodide, with only thyronine and tyrosine remaining as identifiable amino acids, plus an unknown non-phenolic, ninhydrin-positive material.

As the outgrowth of enzymatic deiodination studies, Galton and Ingbar (21) noted that heat-killed tissues carried out extensive deiodination of T_4 when supplemented with flavin compounds. They went on to delineate

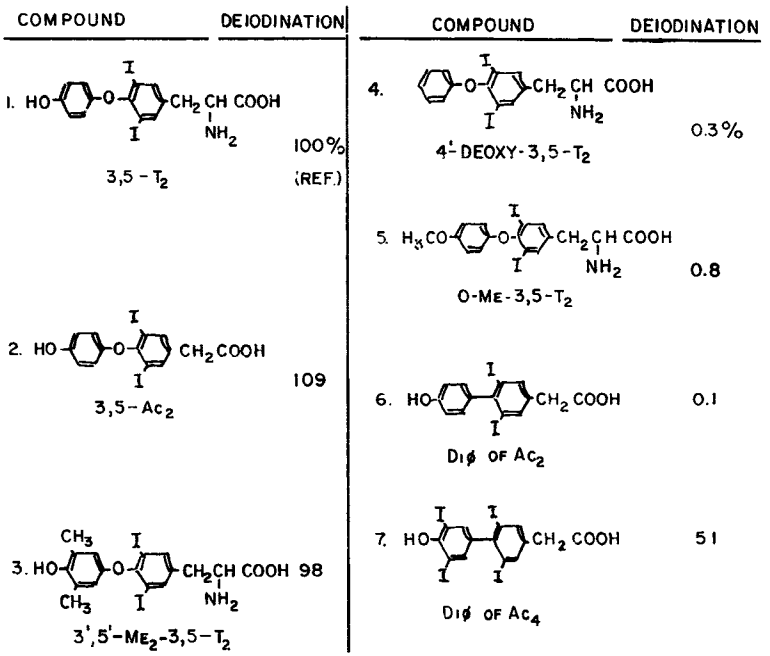

Fig. 1. Deiodination of 3, 5 diiodothyronine and a variety of structurally related compounds. The ceric sulfate-arsenious acid reaction was used on chromatography paper and deiodination evaluated by the diameter of the spot of decolorization produced after 15 minutes' incubation at room temperature. The compounds shown are: 1) 3, 5-diiodothyronine (3, 5-T_2); 2) 3, 5-diiodothyroacetic acid; 3) 3', 5'-dimethyl-3, 5-T_2; 4) 4'-deoxy-3, 5-T_2; 5) O-methyl ether of 3, 5-T_2; 6) diphenyl analog of 3, 5-diiodothyroacetic acid; 7) diphenyl analog of tetraiodothyroacetic acid.

an entirely non-living system of phosphate-buffered flavins (riboflavin, flavin mononucleotide or flavin dinucleotide)capable of complete deiodination of 10^{-7} MT_4 in one hour at 37°C in the presence of oxygen and bright illumination (Fig. 3). The pH optimum was found to lie between 6.4 and 7.4. Activity disappeared in the absence of oxygen or light, and it was considered that light energy permitted flavin formation of a peroxide which was the actual deiodinating agent, although the effects of addition of H_2O_2 or of catalase were not conclusive.

These studies raise important questions concerning T_4 deiodination in the presence of tissues supplemented with flavins or "purified" deiodinase

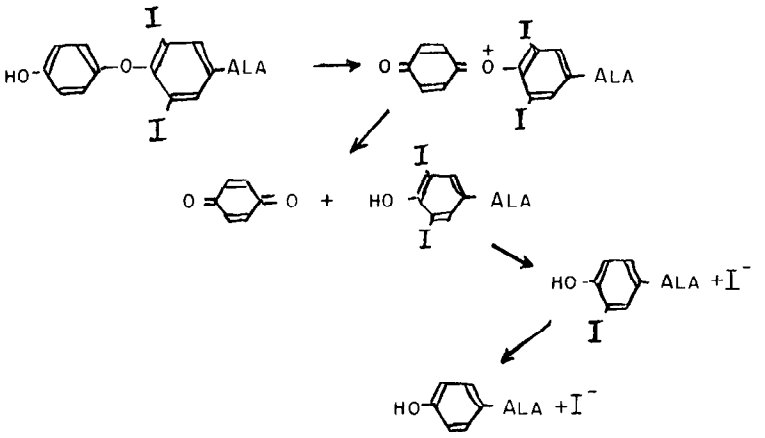

Fig. 2. Possible mechanism for ceric ion deiodination of 3, 5-diiodothyronine in the presence of oxygen.

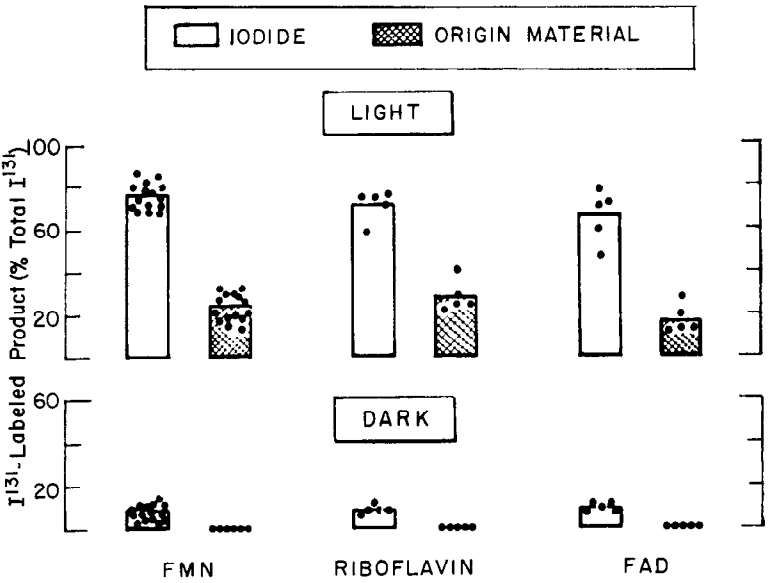

Fig. 3. I^{131}-labeled products of the photoactivated, flavin-induced degradation of T_4 in Ringer phosphate solution, pH 7.4 Flavin concentration was 5×10^{-5} M. (Galton and Ingbar, 21).

preparations requiring similar supplementation for significant activity (37, 56). In contrast to Lissitzky's report (37) that heating destroyed the deiodinating action of his enzyme, Galton and Ingbar found no difference between activity of unheated and of boiled "purified" mammalian deiodinase when flavin was added (Fig. 4) and the incubation carried out in the presence of bright light, although a small difference was detectable when the less intense ambient daylight was used. In the absence of quantitative measure of the amount of light present, any more exact differentiation is impossible. Even in tadpole liver homogenates, where flavin supplementation and light exposure were not necessary for full activity, the boiled homogenate was much more active than the unheated when flavin and light were present.

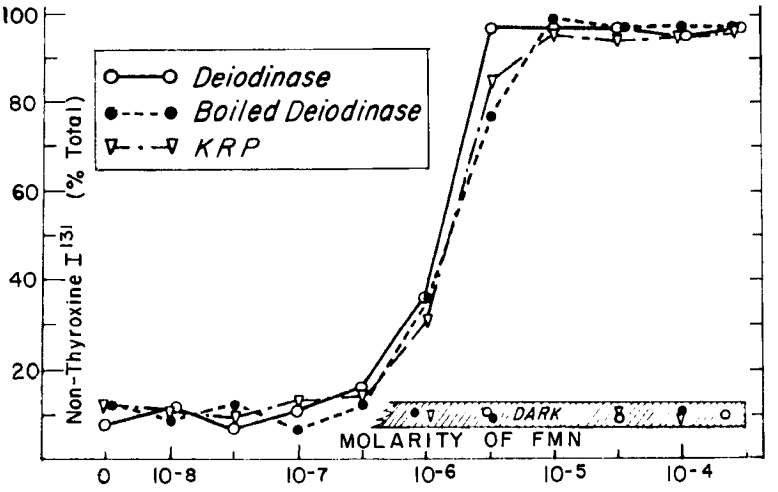

Fig. 4. Effect of flavin mononucleotide (FMN) concentration on the photo-activated flavin-induced degradation of T_4 by a purified mammalian deiodinase. Except where indicated, all reactions carried out in bright light. (Galton and Ingbar, 21).

There have been other, less thoroughly studied heat-stable tissue preparations capable of deiodination of T_4. In the Etling and Barker instance of boiled rat kidney cortex slices (15), these were transferred from the solution in which they had been heated for the incubation, so that flavin concentration must have been extremely low. Exposure to light was also slight during incubation. Sprott and Maclagan (51) and Lissitzky, et al. (38) reported rat liver homogenates capable of deiodinating T_4 after 2 hours of heating at 100°C, although other tissue preparations did lose activity after some heating (39). In contrast, a microsomal fraction of liver and kidney was considerably activated by 2 minutes of heating at 100°, followed by inactivation with more prolonged heating (52).

It is quite apparent that methods for the direct approach to studying deiodination of iodothyronines still deserve critical attention, especially in view of the possible biological importance of such a process, now to be discussed.

Biological implications of deiodination. Lissitzky has long argued that deiodination represented primarily a protective mechanism for disposal of excess T_4(37). The recent demonstration of 3, 3', 5'-triiodothyronine and 3, 3'-diiodothyronine from T_4 injected into normal and hepatectomized dogs (18) points out the diversity of deiodination processes which exist. Although at one time Tata (57) associated the level of T_4-deiodinating activity in skeletal muscle with thyroid function, he appears since to have abandoned such a relationship as bearing on hormonal action in favor of a more general one on intracellular enzyme alignments (58).

However, Galton and Ingbar (22) continue to adduce evidence paralleling various metabolic responses of the tadpole to T_4 (liver weight, hepatic ATPase) with the ability of homogenates of whole tadpole and of tadpole liver to deiodinate T_4. Although oxygen consumption was not measured by these authors, there are acceptable reports in the literature (cf 17) that exposure to T_4 increased metabolic rate as metamorphosis was produced. In contrast, the adult frog exhibited no change in any of these modalities when treated with T_4, nor were slices or homogenates of frog liver, kidney, heart or spleen able to deiodinate (Fig. 5).

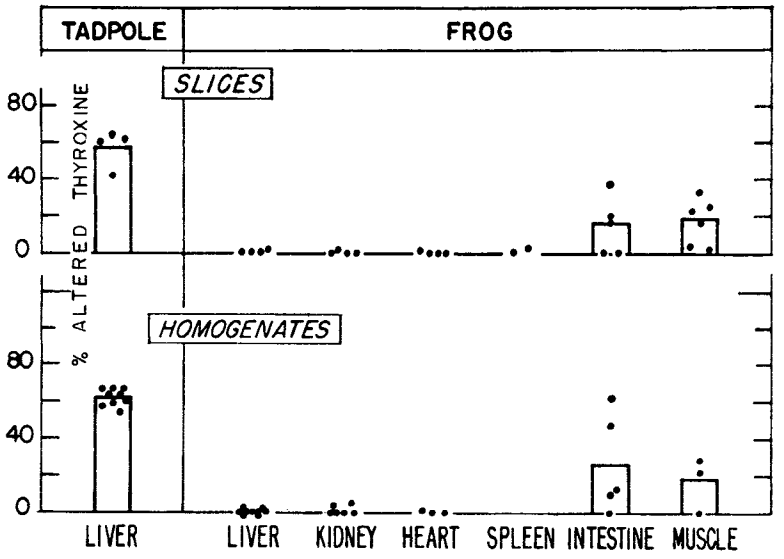

Fig. 5. Metabolism of I^{131}-labeled T_4 by homogenates and slices of tissues obtained from the tadpole and the frog. Values have been corrected for the degradation products produced by incubation of boiled controls. (Galton and Ingbar, 22).

Galton and Ingbar discounted the deiodination responses from intestine and skeletal muscle on the basis of variability, but even a small increase in activity on the part of the latter tissue could be a significant factor in view of its high proportion of the total body weight.

From quite a different point of view, Barker (4) suggested that 5'-deiodination of T_4 in a target organ such as skeletal muscle, heart, liver or kidney must be of specific importance to its effects on oxygen consumption. This conclusion can be supported on the basis of such metabolic responses and heart rate changes as those shown in Fig. 6, wherein thyroidectomized animals responded well to 3'-substituted but not to 5'-substituted 3, 5-iodothyronines, the 2'-substitution being used to obtain specific orientation of the 3'-or 5'-substitution. Jorgensen, who synthesized the compounds used in this study, obtained similar results (31).

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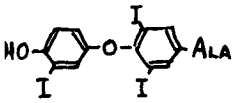
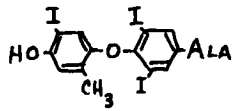
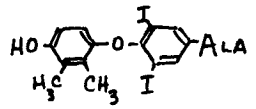
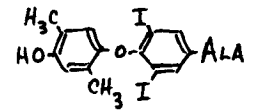
	459% T_4	438% T_4
	0.5	0.5
	23	18
	0.3	0.8

Fig. 6. Oxygen consumption and heart rate changes in thyroidectomized rats receiving specifically substituted iodothyronines. All results are calculated in terms of percent of thyroxine activity.

From still another direction, evidence has been accumulating that, in addition to a thyroid gland action, the thiouracils block some aspect of the extrathyroidal metabolism of T_4 probably involving deiodination (13, 29, 35, 53). There is interference with the usual effect of T_4 on the pituitary TSH production (29), possibly based on interrupting a specific deiodination reaction, as claimed by Grinberg, et al. (27). The elevated oxygen consumption resulting from tetraiodinated analogs was interfered with more severely than that from triiodinated (53). It is even possible that these extra-thyroidal deiodination effects of thiouracils are related to the blockade in deiodination of iodotyrosines in the thyroid gland, resulting in the slower turnover of iodine in this particular pool, as described by Halmi and Pitt-Rivers (28). The same deficiency may occur genetically (33).

On the basis of all this material, Fig. 7 advances the hypothesis relating T_4 biological action to a specific deiodination at target organ active sites. Roche and co-workers (46) have presented evidence supporting the initial step of binding and they and others have suggested its specificity (37, 47, 55). The reaction labeled 1A is in accord with Lissitzky (37) who emphasized the function of removal of any excess of T_4 present, whereas 1B is in line with the developing concept of a preliminary step necessary to further 'activation' of T_4. It should be emphasized that this is conceived as being quite different from the formation of 3, 5, 3'-triiodothyronine in a free form, easily extractible from any given tissue. In fact, there is every reason to expect that such a specific attachment of T_4 could represent an extremely small proportion of the total T_4

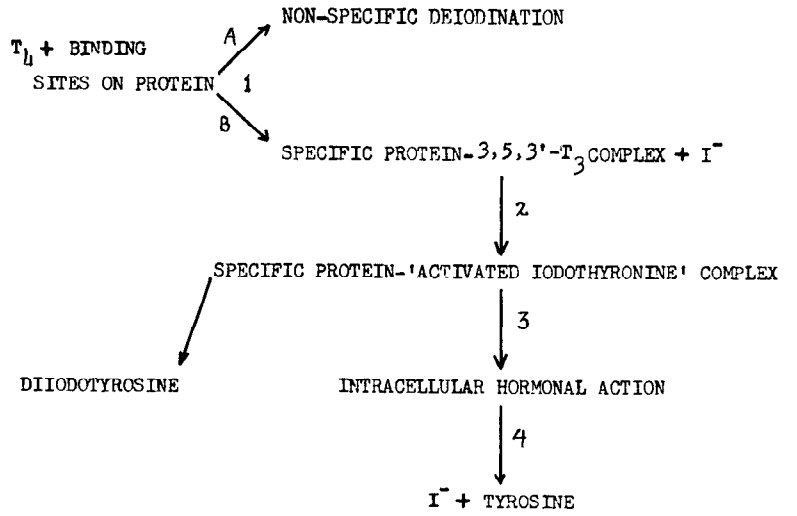


Fig. 7. Proposed relationship between thyroxine action at a target cell with its metabolism.

undergoing change in any particular tissue at any time. Step 2 implies that there may be a further change in the already complexed 3, 5, 3'-T_3 as it is entering its special phases of hormonal action. Plaskett's findings (45) suggest the formation of a bound form of a 5'-hydroxy-iodothyronine, capable of liberating diiodotyrosine upon treatment with alkali. For the most part, iodide is all that is identifiable after T_4 action in an animal, and even a more restricted system such as one undergoing in vitro incubation with the hormone may produce only iodothyroacetates as deaminated and decarboxylated products in addition to iodide (14a). The keen observer will have noted that this hypothesis approaches closely in steps 2 and 3 the heart of the problem of T_4 action, and then rapidly moves away. Perhaps this is the best we can do in an hypothesis of target organ action based on in vivo studies!

It has long seemed probable that SH groups of any deiodinase enzyme protein must be involved in deiodination reactions. Based on their concept that pyridoxal phosphate and vanadyl ions increased the activity of amino acid SH groups. Aubar and Inbar (2) injected both substances and were able to increase the deiodination of T_4 injected into mice, as judged from an increased ratio of serum I^{131}/ (PBI^{131} - I^{131}). They also obtained a marked fall in oxygen consumption, and concluded that a reciprocal relationship had been established, without discussing the possibility of inherent toxicity of vanadium salts.

Iodide (I^-) as the active thyroidal agent. A somewhat different approach to the possible significance of deiodination is offered by the surprising report by Evans, et al. (16) that milligram doses of iodide injected per day into thyroidectomized rats were able to restore a nearly normal growth rate, although there was no change in B.M.R. According to Asling and Evans (1), the growth effect, including general bone age, of 3.8 mg I^- (as KI) per day was about equivalent to 0.16 µg of T_4-iodine (Fig. 8). This might represent a conversion efficiency of 0.005%, but a series of extremely careful studies from the same laboratory (16, 59) persuaded these workers that organification to T_4 had not occurred. After dialysis to remove the excess iodide, no T_4 or diiodotyrosine was found in plasma (Fig. 9) or liver (Fig. 10), using techniques capable of revealing the minute amounts of labeled T_4 resulting from injection of I^{131} into hypophysectomized rats. An I^{131} - containing protein was found in both plasma and liver, but this yielded only monoiodotyrosine upon hydrolysis. The absence of diiodotyrosine was considered as additional evidence for the lack of progressive iodination with eventual condensation to thyroxine.

This situation is quite different from the excessive and nonspecific iodination resulting from in vivo injection of I_2 (5). In this instance, such a large amount of iodoprotein was formed that it was difficult to prove the specific presence of T_4 with the crude techniques in use when these experiments were done. It would be interesting to compare the lack of organification after iodide with a more adequate partitioning of the various types of iodinated material resulting from iodine.

As already discussed, Evans et al. prefer the explanation of iodide effect that the ion itself in high concentration can achieve a thyroxine-

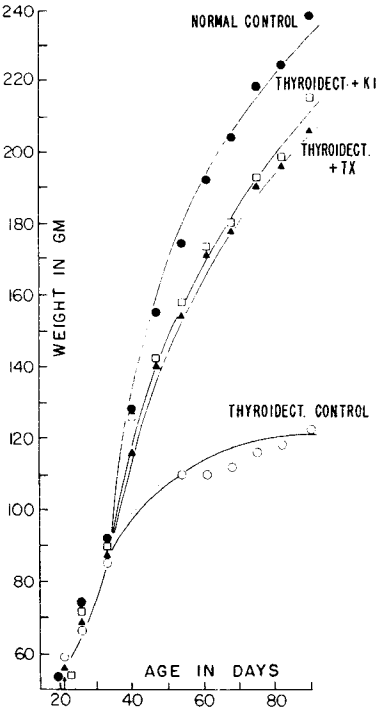


Fig. 8. Graph showing body weights of thyroidectomized rats, uninjected and injected with thyroxine (Tx) or potassium iodide (KI), and of normal rats during the same period. (Asling and Evans, 1).

like action (16). Galton and Ingbar (20), at one stage in developing their concept of a relationship between deiodination and T_4 action, pointed out that these growth findings, as well as the uncoupling produced by I^-(44), could implicate iodide as the active agent in T_4 effects rather than a deiodinated rest. Much of the work with T_4 analogs does not support this idea. There is clearly a difference between the presence of iodines at 3 and 5 (3, 5-diiodothyronine, with its very low order of activity) and substitutions at 3' and 5' (T_4, T_3, or, even more important, 3'-alkyl-3, 5-diiodothyronine, as will be discussed later). On such a basis, one would have to postulate that deiodination of T_3 somehow led to a more active form of I^- than deiodination of T_4. It is not entirely reasonable to rule out localized formation of organic iodine until an extremely careful search has been made of the tissues showing the most definite changes

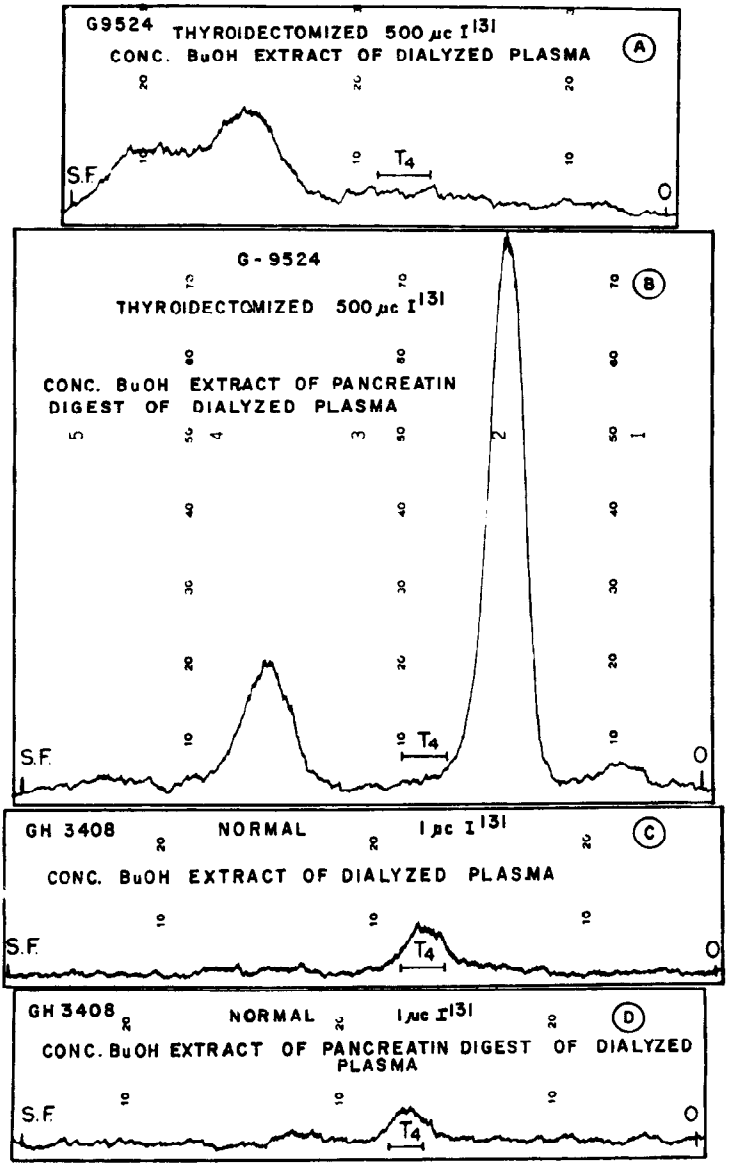


Fig. 9. Distribution of I^{131} on paper chromatograms of plasma obtained from thyroidectomized rat injected with 500 μc of I^{131} and from normal rat injected with 1 μc I^{131}, both as I^-. In A and C, 1.5 ml of dialyzed plasma were extracted. In B and D, 1.0 ml of the same respective plasma as A and C was digested and extracted. Symbols, solvent and peaks are the same as Fig. 8. (Taurog et al. 59).

in the iodide-treated rats, such as pituitaries (26) or active calcification centers (1). Possibly even the sites of injection of iodide should be examined.

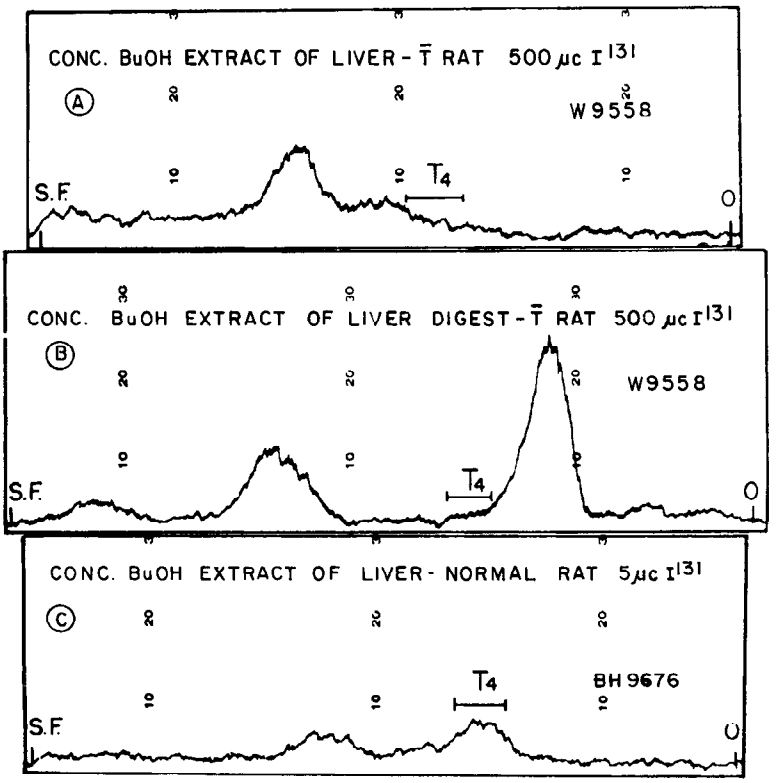


Fig. 10. Distribution of I^{131} on paper chromatograms of dialyzed liver homogenates prepared from liver of thyroidectomized rat ($\bar{T}$) and from liver of normal control rat. A. Concentrated butanol extract of liver A and C. Concentrated butanol extracts of livers of thyroidectomized and normal rats, respectively. B. Concentrated butanol extract of pancreatic digest of same liver as in A. Symbols: O, origin; T_4, position of added thyroxine carrier; S. F., solvent front. Chromatographing solvent: collidine-water-ammonia. The peaks of radioactivity to the left of the T_4 position are iodide; that to the right is monoiodotyrosine.

ANALOGS OF THYROXINE

Reference has already been made to some important implications of studies with analogs of T_4 having structural modifications on the phenolic benzene permitting differentiation between substitution at the 3'-and at the 5'-position. Further evidence suggests that, in addition to the desirable lack of substitution at 5', the necessary group at 3' is more effective if it approaches the size of the iodine atom normally present. As Fig. 11 shows, 2', 3'-dimethyl-3, 5-diiodothyronine displayed activity, but the 4-(4'-hydroxynaphthyl)-replacement of the outer benzene ring was even more effective, and 3'-isopropyl-3, 5-diiodothyronine is the most active T_4 analog yet studied. Greenberg, Blank, and Pfeiffer (25) are reporting calorigenic, blood cholesterol-lowering, antigoitrogenic and heart weight-increasing actions at these meetings, to which we (Shimada and Barker, unpublished) can add the heart rate and oxygen consumption data in the thyroidectomized animal shown in Fig. 11.

The isopropyl group is a more active potential electron donor than the methyl, but its electronic character is quite different from that of iodine, and it is possible that the main function of 3'-substitution is to lend some type of spatial stability to the phenolic benzene portion of the T_4 analogue. These are the most exciting structural modifications to

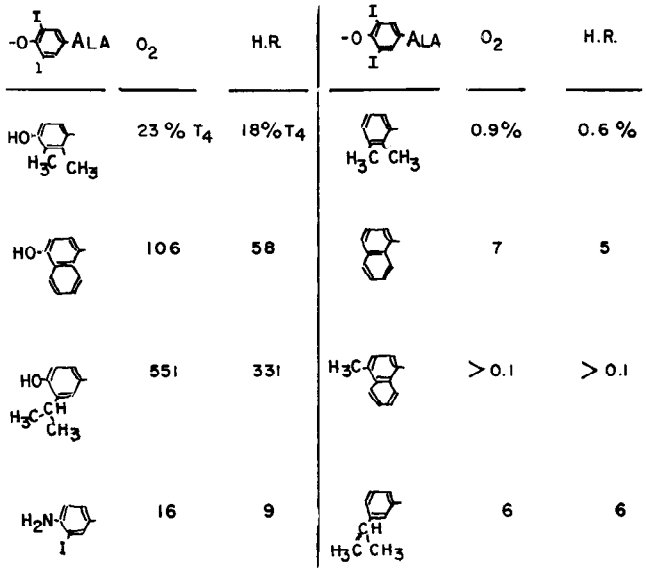


Fig. 11. Oxygen consumption and heart rate changes in thyroidectomized rats receiving thyroxine (T_4) analogs specifically altered in the outer, phenolic ring. All results are shown in terms of percent of T_4 activity.

emerge since the discovery of triiodothyronine in 1952, except perhaps the misguided enthusiasm once generated by the acetic acid derivatives. At the present time, all structural evidence points to some special importance of the lopsided portion of the molecule projecting from what is probably the anchoring amino acid and diiodophenyl 'head' end and reinforces the concept presented earlier of an important 5'-deiodination of T_4.

The analog study summarized in Fig. 11, again dependent upon the synthetic skill of Jorgensen's group (30), includes the demonstration of biological activity of 4'-amino-4'-deoxy-triiodothyronine and of several 4'-deoxy analogs. To match these results, Shimada has been able to detect the presence in bile of conjugates of several 4'-hydroxy analogs following administration of the corresponding 4'-deoxy compound, so it appears likely that this is the basis of any activity. In addition, when a 4'-methyl group prevented addition of oxygen, activity was absent. Of course, this procedure does not deny that there may be some inherent activity of the 4'-deoxy compound itself.

It will be interesting to see further developments of the new series of iodinated 5-hydroxybenzofurans reported by Siegel and co-workers (50) to be effective metamorphosing agents in Rana catesbiana.

MEMBRANE EFFECTS OF THYROXINE

In many ways, one of the most unusual in vitro tissue responses to T_4 has been reported by Matty and Green (40) using the isolated urinary bladder of the toad Bufo bufo. To induce water movement, the bladder was filled with five-fold diluted amphibian Ringer solution and immersed in undiluted Ringer. Thyroxine or triiodothyronine placed on either the serosal or mucosal side of the bladder increased water transfer, as shown in Fig. 12, at concentrations from 10^{-8}M to 10^{-5}M (8 mg/ml to 8 µg/ml). Since the control levels of fluid movement were about 12 µl/cm^2/hr, even the lowest concentration of T_4 produced a definite effect. Although T_4 concentration curves were not shown for oxygen consumption, comparable increases in both water transfer and metabolic rate were obtained at 10^{-6}M, as seen in Fig. 13. A supplemental publication (41) has presented direct measurement of the actual net sodium flux from mucosa to serosa under comparable conditions.

These are time plots, the most surprising feature of which is the continuing increase in both water movement and oxygen consumption over the entire 60-minute period, in the presence of T_4. When T_3 was used, both effects were seen in the first few periods, but fell off thereafter. Although many of us had hoped that the specter of Tetrac and Triac as uniquely rapidly-acting analogs had been laid to rest, Fig. 14 from Matty and Green shows an extremely rapid toad bladder response to these derivatives. It can be seen that the peak was reached within 2 to 4 minutes, and water movement fell off rapidly after that time. In contrast, the changes in T_4 did not return to control values until 150 minutes.

When these experiments were run in a sodium-free solution, choline

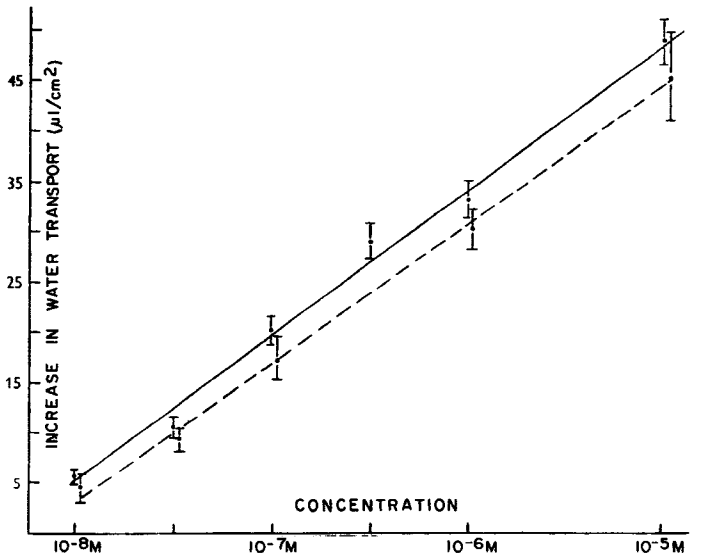


Fig. 12. Effect of varying concentrations of T_4 (solid) and T_3 (dash) on water movement across isolated toad bladder during one hour. (Matty and Green, 40).

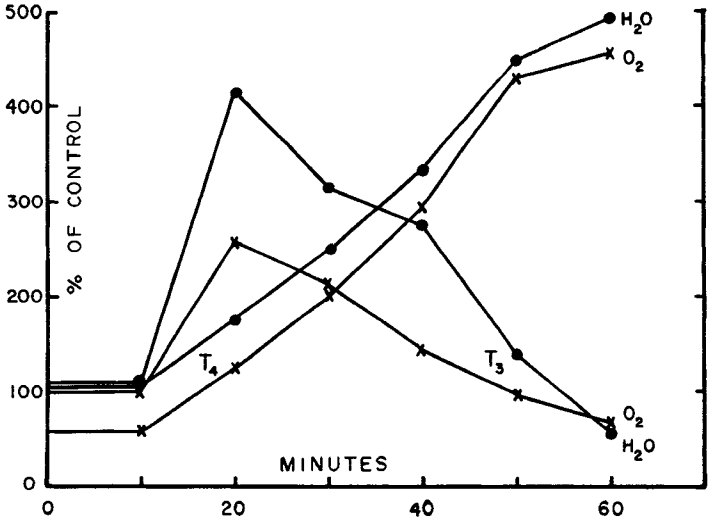


Fig. 13. Oxygen consumption and water transfer effects of addition of thyroxine (T_4) or triiodothyronine (T_3) to solution bathing toad bladder. The results are shown in 10 minute increments and are not cumulative. (Redrawn from Matty and Green, 40).

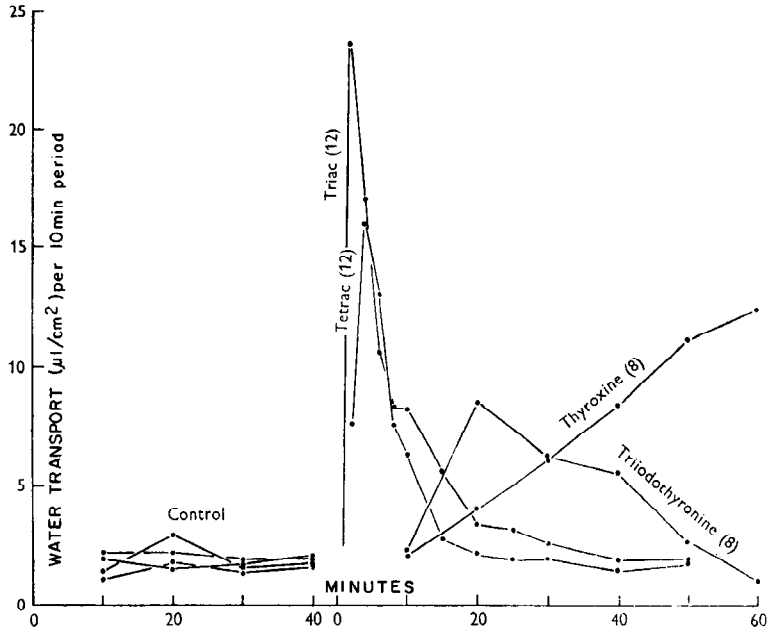


Fig. 14. Effect of Triac and Tetrac, plotted with T_3 and T_4 for comparison, on water movement ($\mu l/cm^2$ bladder/10 minute intervals) across the isolated bladder of the toad. (Matty and Green, 40).

chloride being substituted for sodium chloride, T_4 still produced increases in both oxygen consumption and water movement. In contrast, vasopressin was found by other workers not to be effective in the absence of sodium. The simplest interpretation is that T_4 increases metabolic processes, part of the energy of which is made available for water and electrolyte transfer, whereas vasopressin specifically increases the latter, with an energy increment being required.

With isotonic Ringer solution on both sides of the bladder, control water movement from mucosa to serosa was only 2 $\mu l/cm^2/hr$ (compared to 12 using 20% isotonic inside). This value was doubled upon application of 10^{-6}M T_4 to the mucosal side, and further increased to 14 $\mu l/cm^2/hr$ with serosal addition of the T_4. Under these conditions, the directional specificity was similar to that of vasopressin.

Just as one can accept an in vitro action of tetraiodothyroacetic and tetraiodothyrobutyric acids on yeast cells as demonstrating some sort

of fundamental biological responsiveness (6), it is not necessary to quibble about the general refractoriness of adult, differentiated anuran forms to thyroid hormones in any form as a contrast to the highly sensitive responses seen in the unmetamorphosed larvae (22). However, it would certainly be of great interest to know how such a highly sensitive response can be obtained from one tissue of the adult and whether any sort of comparable water and electrolyte actions of T_4 could be seen in tadpoles.

From a different point of view, one is struck by the possible relationship to two other types of membrane study being pursued. Turkington (61) has prepared a cell membrane fraction from calf thyroid glands, exhibiting ATPase activity dependent upon Na, K, and, to a lesser extent, Mg. Addition of TSH doubled the ATPase and ouabain blocked it. On the other hand, Wolff and Halmi (63) have been concerned with the association of thyroidal iodide collection with Na- and K- activated, ouabain-sensitive ATPase activity. More and more it becomes evident that ATPase activity is linked with electrolyte transport although usually of cations. Tata and his associates (58) still prefer to emphasize oxygen consumption effects of T_4 as incidental to more fundamental enzyme changes, but the increasingly dominant position of ATP at the crossroads, as it were, of energy turnover and various biological processes makes it important to know more about any possible mutual involvement with T_4. It may even be possible that as important an action as the T_4-increased incorporation of amino acids into protein (43) is an expression of a greater availability of ATP.

POSSIBLE INVOLVEMENT OF SYMPATHETICS IN THYROXINE ACTION

A few remarks should be made in reference to the present revival of the old thesis that thyroxine operates via some sort of mediation of the sympatheticoadrenal system. The basic concept originated at the turn of century, when a triad of adrenal, thyroid and pancreas was popular. The results were undoubtedly severely influenced by the effects of operative trauma and more elegant studies showed that complete denervation did not measurably alter the metabolic response of the heart to desiccated thyroid. However, Knight's demonstration that the sympathetic component in thyroid storm could be controlled by sympathetic blocking agents led Brewster et al. (8) to study total preganglionic blockade produced by epidural injection of procaine. This procedure was found to abolish the greater hemodynamic effects of catecholamines infused into hyperthyroid animals and to lower the hyperthyroid metabolic rates.

With the advent of powerful sympathetic blockading drugs, reports appeared that dibenzyline would prevent the usual rise in BMR of rats following T_4, although Schwartz et al. (48) were able to obtain a still further increased metabolic rate when dibenzyline was administered to animals which were clearly hyperthyroid. Reserpine and guanethidine produce both sympathetic neuroeffector blockade and discharge of stored catecholamines (32, 49). There is no good agreement concerning interrelationship of these events, since bretylium produces equally good

sympathetic blockade but without any catecholamine discharge (11). Reserpine has been claimed to lower the elevated BMR of clinical (9, 10) and experimental (12, 34) hyperthyroidism, although this has been far from consistent (23, 24, 62). Guanethidine has also been reported to return elevated BMR's and heart rates partially (36) or completely (19) to normal. These studies do not truly differentiate between a possible depression of thyroid gland function and of peripheral hormonal effects. Taylor and Fregly (60), in the course of body temperature research in cold-exposed rats, concluded that reserpine clearly interfered with the thyroid gland stimulation by TSH but did not alter the animal's metabolic response to T_4.

Our own experience with experimental animals has yielded a variety of complications. A single large dose of guanethidine injected into euthyroid rats produced only slight effects, but a prolonged tachycardia resulted in hyperthyroid animals and marked bradycardia in thyroidectomized. These are similar to the effects of epinephrine injection correlated by Swanson (54) with the circulating level of T_4 and probably represent an expression of the discharged catecholamines mentioned earlier. In addition, Maxwell et al. (42) and Bartlet (6a) have demonstrated hypersensitivity to injected norepinephrine in guanethidine-treated animals, a response which may conceivably be conditioned by the T_4 level. When guanethidine was injected for several days at a much lower dose level, the animals became debilitated and many fatalities resulted. Injection was necessary because orally ingested guanethidine was very poorly absorbed.

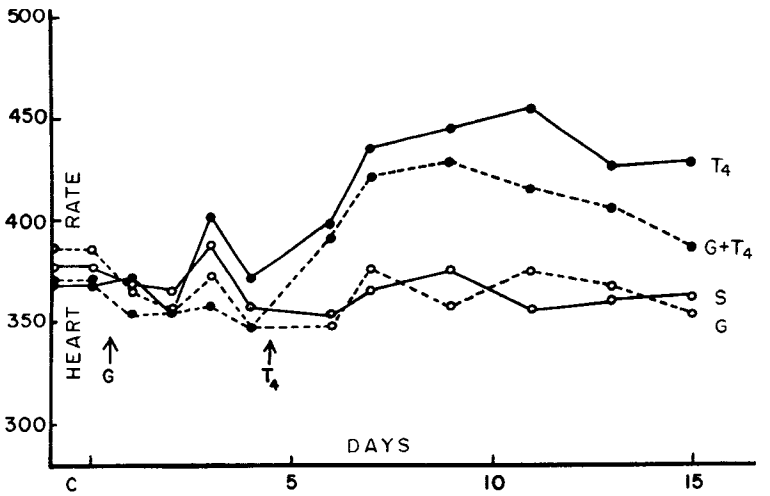


Fig. 15. Heart rates of normal rats injected with saline (S), guanethidine (G, 15 mg/kg/day), thyroxine (T_4, 100 μg/kg/day) and guanethidine plus thyroxine (G + T_4). The control period (C) represents the average of 5 sets of multiple determinations over 10-14 days. Guanethidine or saline injections were started at G, on day O, and T_4 injections superimposed on day 4, following determination of heart rates.

Results charted in Fig. 15, obtained by Makiuchi, illustrate another complication of a chronic experiment when T_4 was superimposed on a sympatholytic compound. After 4 days of preliminary treatment with guanethidine, additional injection of T_4 led to a rise in heart rate for a few days, but a return nearly to untreated rates at the end of 11 days. Bretylium, a sympathetic blocking compound which does not discharge endogenous norepinephrine (11), produced a similar effect. Neither drug exerted any consistent influence upon the heart rate maintenance of endogenous T_4, and the possibility must be considered that there was some change in sensitivity to, or increased destruction of, the exogenous T_4. Obviously, this important field requires much more extensive exploration.

L'ENVOI

It is quite apparent that I have selected a few aspects of the target organ actions of thyroid hormones for discussion in depth, to the neglect of others which are important not only to those working in such areas. Such a slight is the more regretted because it is deliberate, but necessary.

ACKNOWLEDGMENT

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CURRENT TRENDS IN CARDIOVASCULAR PHYSIOLOGY

LYSLE H. PETERSON

Physiologists and physicians have traditionally gone to great lengths to divide the bodies' organs and functions into such systems as the cardiovascular, nervous, endocrine, renal, etc. Furthermore, these traditional systems divisions have tended to isolate each from the other in thought and in research. Medical students are taught to systematize patient history taking and physical examinations along such separate lines. Medical text books separate disease considerations into such systems. Students in physiology are taught such systems as separate entities and, in some schools, the separation is exaggerated by "horizontal" instruction. Faculties tend to be separated and/or organized by the systems they represent; the research they perform has tended to be compartmented along such lines. Recent surveys of physiology Ph.D. programs suggests a trend to further subsystems specialization (1, 2). The computer programming which determines this Federation's annual meeting recognizes these segregations and the meeting itself is an excellent representation of these rather distinct divisions.

There are many good reasons for such divisions which have aided research and clinical thinking and, for many considerations, it is desirable to continue to observe the unique properties and behavior of these traditional dissections of the body. There is, however, growing awareness that nature does not recognize these same divisions and that to better understand normal and abnormal physiology we must reorient our thought and research processes. It is, for example, impossible to consider cardiovascular responses to most stresses without heeding the interaction of the nervous, endocrine, renal, etc., functions with the cardiovascular system.

A second practice, which has tended to limit the development of man's understanding of the nature of biological systems, is the usual experimental practice in which single independent and dependent variables are observed while assuming that all other influential factors remain constant or in a "steady state." This custom has not been due so much to our naivete as to the practical constraints of our experimental methods and of our mental abilities to contemplate more than a limited number of simultaneous variables. Of course, few of the properties and behaviors of biological systems are determined by such limited numbers of variables. Indeed, the many interacting functions of the many interacting systems noted above frequently involve feed-back loops which require that, to ascertain the behavior of even one function, there must be simultaneous awareness of the state of a multiplicity of other functions even though they may not be undergoing marked change at the time of the investigation.

There are many examples which might be chosen to illustrate the thesis that we should break down the traditional barriers of our subspecialties and also that we should learn to deal with multiple simultaneous variables. For example, a complete understanding of the physiology of exercise, the responses to hostile environments and to most disease

processes will await such an evolution of our thought and research processes. The disease hypertension is one germain example. This condition (s) is a good example because it apparently involves most of the traditionally separated body systems and the multiple feed-back functions which exist between and within these systems. Also, it is an example involving a consideration of "abnormal" physiology. The chronicle of research in this disease is resplendent with once promising leads which seem to become lost in the intact hypertensive person. Thus, when isolated functions or systems are examined separately they seem to exhibit properties which are not evident when they are part of the intact body. There are many other diseases which are analogous to hypertension in these respects.

Figure 1 is an admittedly over-simplified diagram representing some of the factors which have been implicated in the disease and/or which are known to affect the tone or stiffness of the blood vessel wall. The elevated blood pressure characterizing hypertension is, of course, thought by most to be associated primarily with an increased "peripheral resistance" thus, the "final common path" is the vessel wall and an increased tone or stiffness. A more detailed discussion of the known characteristics of each of the "black boxes" and of their interaction is published elsewhere (2). Figure 1 does illustrate, however, the kind of problem with which investigators must deal in attempting to illucidate the character of hypertension.

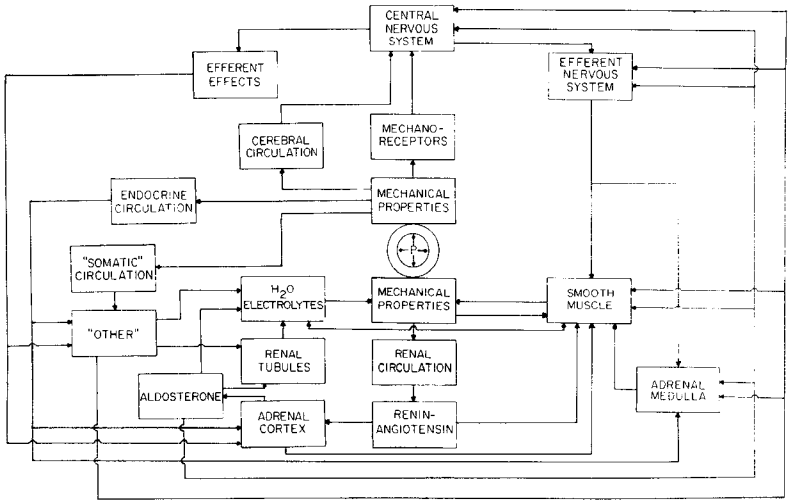

Fig. 1. Simplified model of functions relating to the stiffness or tone (mechanical properties) of the arterial walls as seen by the investigator interested in the disease arterial hypertension. See text and reference (2) for further discussion. (Reprinted from Circulation Research 12 Suppl. 1963 courtesy of American Heart Association.)

The multiple feed-back nature and interactions of many traditional systems is evident.

Figure 2 will serve to emphasize the problems in investigating the properties and functions of systems which contain feed-back elements. Often, if not most frequently, we assess the properties and behavior of a system, organ, tissue or function thereof by relating inputs and outputs e.g., inputs such as stimulus concentration or force or energy and related outputs such as response, concentration, force or energy etc. Consider that the function being sought in Fig. 2 is A which may be any biological function relating output and input or dependent to independent variables e.g., flow to pressure, response to stimulus etc. If the output or dependent variable is, in some way, fed back to the input or dependent variable through some other functional relationship it is evident that a measurement of the output/input relationship will not directly give a measure of A. It is also necessary to evaluate B at the same time. Not only are such feed-back relationships operating in the control and regulatory systems of the body but are also, as illustrated in Fig. 1, common to most biological functions. The functions A, B, C, etc. may be represented by anything from simple algebraic functions to complex non-linear differential equations.

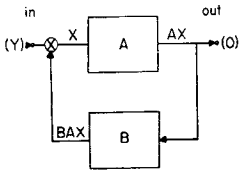

Fig. 2. Represents a single feed-back loop in which the output (O) of the system is AX and the transfer function or operation of the upper "black box" is A. Thus A operates upon its input to produce AX which then is the input to another black box with transfer function B such that its output is BAX which is then fed back to A. Thus, BAX is subtracted (negative feed back) from the input (Y) to the system to produce X. Thus the transfer function for the entire system is $\frac{O}{Y} = \frac{A}{1+AB}$. (Reprinted from Circulation Research 12 Suppl. 1963 courtesy of American Heart Association.)

Without going further into the subject of feed-back systems, it may be noted that (i) if functions, such as represented by the black box containing A, are investigated in isolation the function itself may be evaluated but, the manner in which the input-output variables will behave within the intact animal may not be evaluated. Conversally, if the relationships within the intact body are observed the behavior may not provide adequate knowledge of the individual functions. Better understanding of the behavior and properties of biological system, therefore, requires not only that physiologists extend their considerations beyond the limits of their traditional systems but also that the interactions of biological functions be studied in manners such that individual transfer functions and also their interactions within the whole body can be evaluated.

The trend of physiology is, of course, in those directions and there are many examples of this trend. There is also increasing recognition of constraints upon physiologists which must be corrected in order to facilitate this trend.

It is evident that there is a need for analytical thinking and methodology in contrast to descriptive processes. It is also evident that this analytical accumen and the necessity for dealing with multiple simultaneous variables requires the application of analytical tools such as mathematics and computers. Such tools are considered essential in the physical sciences and engineering as well as in modern management where the systems dealt with are certainly not more complex than biological systems.

The educational background for those preparing for the biological sciences has been characterized by a greater emphasis on descriptive than on analytical techniques. Recent surveys (1, 2) of training for Ph. D. degree in physiology indicated that all schools would like to have their students entering the doctoral program "have college math training through calculus. Most feel that advanced calculus, including differential equations, is essential." Having studied many applications for the Ph. D. program at the University of Pennsylvania it is evident to me that most candidates have not had such preparation although there is a trend toward greater emphasis on mathematics in high school and college. Unfortunately, courses in mathematics do not necessarily prepare students to use mathematics for such purposes as deriving and solving equations representing the properties and behavior of systems. The usual premedical curricula are also characteristically devoid of training in analytical approaches. Premedical physics and chemistry courses are usually taught without a prerequisite of calculus. Most medical schools do not require more than college algebra. Again, however, there is evidence that an increasing number of students applying to medical schools have had more advanced mathematics and analytically based programs in the natural sciences.

It must be said that at least part of the raison d'etre for the growth of interest in bioengineering, biophysics, biomathematics, bio- etc., programs is the slowness of the biologist himself to acquire the analytical skills and to apply the methods long used by the physical sciences and engineering. The engineer, physicist and mathematician have seen the opportunity to apply these skills to approach biological problems and have been making significant contributions.

Figure 1 further illustrates the kinds of challenges we face in expanding our interests in the directions noted above. All would agree that traditional and proper cardiovascular interests are concerned with the functions which determine the flow and distribution of blood. Thus, the cardiovascular physiologist seeks to define the relationships between the force delivered by the heart muscle tending to produce flow and the forces tending to impede flow due to the properties of the blood and blood vessels. For any single segment of artery the relationships are represented by rather complicated, probably non-linear, differential equations since the wall itself is visco-elastic and since the blood has non-linear viscous properties, inertia and develops complex flow profiles. Next, the vascular system is a vast, highly complex distributed array of vessels with changing mechanical and geometric properties and with varying surround. Thus, our model becomes a complex, transmission line with multiple and diffuse reflections, harmonic dispersions and distortions of

the pressure and flow pulses. Next, alterations of impedance and blood flow are the result of changes in vascular smooth muscle and in water and electrolyte shifts within the vascular wall. Little is known about vascular smooth muscle but certainly there are many dynamic influences affecting the muscle's behavior. These influences are chemical, mechanical, and electrical. Not only must the properties and behavior of the muscle itself be assessed in its environment within the wall but also in such manners that the effects of each of these many influences can be evaluated. Again, such studies require elaborate multifactor analysis. Although it is known that the water and certain electrolytes within the vessel wall undergo changes in amount and concentration, it is not known within what compartments the changes occur, nor are the course(s) of the changes, nor the effects of the changes on the wall known. One popular loop related to vessel water and electrolyte change is that involving the kidneys and hypertension. It is thought by many that renal circulation disturbances, the nature of which is undefined in some also undefined way causes the juxtaglomerular cells to release increased amounts of renin which then alters certain blood polypeptides, or angiotensin substrate, to form angiotensin which then acts upon the adrenal cortex to release aldosterone. While aldosterone causes sodium retention by the kidneys this does not, however, explain the increased concentration of sodium within the vessel wall i.e., most measurements indicate the interstitial sodium concentration to be normal in appropriate hypertensive subjects. Thus, some unknown somatic "other" factor tends to concentrate the sodium if, indeed it is concentrated. Unfortunately, the methods currently available for evaluating "spaces" and compartments within tissues are primitive and unreliable. New techniques will require sophisticated analytical techniques.

These few examples from the model represented in Fig. 1 are but samples to illustrate the requirements and challenges to "cardiovascular physiology." Few of the properties and behavior of the cardiovascular system are understood and a thoughtful student can soon penetrate the superficial layer of information the teacher can provide.

SUMMARY

Current trends in cardiovascular physiology include the tendency for cardiovascular physiologists to extend their interests beyond the cardiovascular system. Few, if any, cardiovascular functions are confined to or determined by the anatomical limits of the cardiovascular system. Also, there is a tendency for physiologists to deal with the fact that it is necessary to study multiple simultaneous variables which characterize and determine the properties and behavior of biological systems. Such considerations require the utilization of analytical techniques for formulating complex models, to perform simulation studies in order to compare conceptual models with reality. These efforts require skills for deriving and solving a variety of mathematical formats such as differential equations, statistical approaches, etc. They also require the use of computers and other instrumental arrays. These trends are reflected in the changing educational programs at all levels. Physiology graduate programs are requiring more background in mathematics and analytical tools, it is becoming more difficult to inform

medical students of what physiologists are doing in their laboratories because the usual premedical curricula are lacking in mathematics and analytical training. The biophysicist, bioengineer, and biomathematician are "filling in" for the practicing physiologists who have not yet acquired these skills. In spite of the constraints resulting from the traditional descriptive rather than the analytical educational background, the trend is evident and accelerating. This is a very good thing.

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ANIMAL CARE PANEL

The Animal Care Panel will meet in Los Angeles, Ambassador Hotel, October 1-4, 1963. Over 40 papers on the care, management, procurement and production of animals used in biomedical research will be presented. There will be two special sessions on the management of animal laboratory facilities and on laboratory animal diseases. For further information write Mr. Joseph J. Garvey, 4 E. Clinton Street, Joliet, Ill.

RESPIRATION SUITE

A recording of this composition dedicated to Dr. Wallace O. Fenn, (see The Physiologist, February 1963) may be obtained by sending $1.65 (including shipping charges) by check or money-order to Dr. A. Bouhuys, Dept. of Medicine, Emory University School of Medicine, 69 Butler St., S. E., Atlanta 3, Georgia.

HUMANE VIVISECTION*

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'Which first perchance she'll prove on cats and dogs,
Then afterward up higher'. - Cymbeline, 1.5.8-9.

In the present context the title of this article is a startling incongruity. It was chosen by the Editor, and accepted without demur by the author. As the late Richard Fort said in his Stephen Paget Memorial Lecture (1959): 'Whoever first thought of applying the word "vivisection" to animal experiments and the agitation against them certainly struck on one of the most effective of all "witch words" from the point of view of arousing emotions which would lead to action'.

To add the epithet 'humane' would seem to create an insoluble contradiction. If animal experimentation is synonymous with vivisection, and vivisection is by definition cruel (as 'Roget's Thesaurus' would suggest), then animal experimentation cannot be humane. But any schoolboy can spot the fallacy residing in the word vivisection, which is quite the wrong term for the justifiable use of animals in the prosecution of medical and biological research.

Many of the other articles in this series demonstrate eloquently the need for the experimental use of animals, and indicate that from animal experiments have come, and will come, advances in medical knowledge of inestimable value to human and animal well-being; advances that could have been brought about in no other way. If the reader should doubt this, let him read 'Achievement: Some Contributions of Animal Experiment to the Conquest of Disease', by G. Lapage (1960). It is, however, a fair question to ask whether the conditions in which animal experiments are carried out are compatible with the greater humanity that motivates and inspires the most humane of all professions, the practice of medicine.

FALSE CONCEPTS

In discussing the possible intrusion of pain into the conduct of an animal experiment, Adrian (1951) has drawn attention to the false concepts that are commonly entertained. Severe pain will 'almost inevitably make the experiment valueless'; but various degrees of discomfort, which might be distressing in man, are tolerated without protest by animals that are well cared for. This, in fact, is the key to humaneness in our conduct of animal experiments. Veterinarians and paediatricians, whose patients normally possess uncomplicated mentalities, are familiar with their ability to tolerate without distress lesions and manipulations that most human adults would find insupportable; but they also know that this tolerance can only be evoked if there is a satisfactory relationship between patient and clinician.

*Reprinted from "The Practitioner" Symposium on the Development of New Drugs, Jan. 1963, Vol. 190, pp. 81-84.

The same is true of the experimental animal. There are two main sources of inhumanity in the laboratory: the badly designed experiment that inflicts severe pain on the animal and is for that reason less likely to produce reliable results; and the incompetent care of the animals before, during and after experiment. Suffering, far from being inseparable from animal experimentation, should in fact be regarded as a confusing variable whose elimination demands great effort on the part of the experimenter; the painful experiment is a measure of the failure of this effort.

This may perhaps be thought unrealistic. Some animal experiments are painful, but hastily to condemn those responsible for them as scientifically incompetent or morally base is neither reasonable nor conducive to the cause of animal welfare. It merely lets in the intemperate opponents of all animal experimentation who, for the sake of curing an imagined or fantastically exaggerated evil, would inflict an infinitely greater penalty on suffering humanity: namely a full stop to medical research. Medical scientists, being human, are not perfect. If they aspire to the ideal of animal experiments without offence, then occasional failures must be accepted as signs of human frailty, calling for humility on their part, the sympathy of their colleagues, and charity from their critics. In this way - and not by bandying witch words or accusing of cruelty those whose calling is inherently humane - will the advance of medical knowledge keep in step with the decent treatment of those creatures whose use makes that advance possible.

'STANDARD GUINEA-PIGS'

Twenty years ago the "British Medical Journal", in an annotation entitled 'Wanted - Standard Guinea-Pigs' (Annotation, 1942), drew attention to the desperate need for some sort of order in the supply and use of laboratory animals. Fifteen years ago the Medical Research Council set up the first unit ever to come into being devoted to the study of laboratory animal problems: the Laboratory Animals Centre (or Bureau as it was originally called). In 1950 the Animal Technicians Association in Great Britain, and the Animal Care Panel in the United States were formed. The next six years saw the foundation of the Centre de Sélection des Animaux de Laboratoire (France), the Institute of Laboratory Animal Resources (U. S. A.) and the Japan Experimental Animals Association (formerly Committee). In 1956 the International Committee on Laboratory Animals, sponsored by UNESCO and a number of international scientific unions, was formed. In the last six years laboratory animal organizations have grown up in at least a dozen other countries throughout the world. If we do not yet have the 'standard guinea-pig', there is certainly a widespread effort being made to improve the quality of laboratory animals everywhere, and to make standards by which they may be judged.

Drug testing alone - that is, bioassay, toxicity testing and the screening of new compounds of possible therapeutic value - consumes by far the largest number of laboratory animals. Yet the occasional bad drug, or bad batch, still gets through to clinical use. For this reason, as well as in the interests of more fundamental research, the investigator

is becoming much more exacting in his demands. He requires animals that are genetically defined, known to be free of a wide range of specified pathogens that are commonly present in conventional animals, and in many cases capable of specific pharmacological responses of a recondite nature. The laboratory animal is no longer the machina ex deo - or ex diabolo, it often seemed - but a biological analogue of increasing precision; even a respectable subject of study in its own right.

HUMANE TRADITION

In Great Britain, since 1876, when the few hundred animal experiments conducted each year were mostly acute, severe and connected with physiological studies, every person carrying out animal experiments has had to possess a license and observe certain conditions, which are rigorously enforced by the Home Office. The Act of 1876 was passed, not because abuse of animals existed - a Royal Commission specifically found that it did not in this country - but because the possibility of abuse existed. Despite its serious shortcomings, the Act, an account of which may be found elsewhere (Lane-Petter, 1962), has worked to the advantage of the animals and of the scientists, because the scientists have in the main made it work, and the administration has been strict and wise. The only people who do not support it are the antivivisectionists, who regard it as the vivisector's charter - a fine soap-box term.

By a series of historical accidents we have, indeed, arrived at a situation in which a law that was invented over eighty years ago, and has never been amended, is achieving its intended aim in the quite different and constantly changing world of today. Moreover, those who are controlled by it regard it as mainly beneficial, although certain explicit provisions, and certain administrative interpretations, are undoubtedly irksome and even damaging without benefit to the animals the law is intended to protect. It is questionable whether legal control, at least such as we know it, is the best method of regulating such a pleomorphic activity as medical research. Most thinking people, however, would agree that some sort of control is desirable, in deference to public opinion and to protect the good name of science.

In fact, of course, it is not the law that exercises the control, but the humane tradition that governs the work of most medical scientists. The law and the Home Office inspectors are today part of that tradition, and British traditions are notoriously persistent. But if we did not have the Act of 1876, emotively entitled the Cruelty to Animals Act, it is difficult to believe that today Parliament would wish to introduce anything like it de novo. If legislation were thought desirable, it would almost certainly define general principles only, and charge the administration with devising means for seeing that those principles were generally observed.

REGULATION WITHOUT LEGISLATION

In recent years scientists themselves have paid great attention to the improvement of laboratory animal conditions, and have themselves emphasized that the best results are more likely to come from docile

dogs, contented cats and relaxed rodents. The British were the pioneers in this awakening, but the veterinary profession in the United States has taken up the tale with enthusiasm, and laboratory animal medicine is a major branch of that profession's interest. Many American universities are evolving a new pattern of laboratory animal care and use, by the integration of the animal facilities serving all departments, under the control of a veterinarian who has the status of a departmental head. Such a person is responsible for providing all the animals needed for research, and their care throughout, according to the standards which his special training has taught him are necessary for good work. He also helps the investigators with problems in animal medication, anaesthesia and surgery, trains the technical staff of his department, and instructs young research graduates in the proper use of animals.

This system is still in its infancy in most places, and its success depends heavily on the character of the head of the animal department. Nevertheless, it is a system of regulation without legislation, and it holds promise of development in ways which are bound to be beneficial to science and animal welfare alike. For there is no-one who will be more readily listened to when he talks about the proper care and use of animals than the professional man on whom the investigator depends for all his animal requirements.

In short, animal experimentation is a part of the process of advancing medical knowledge. It is not inherently distressing to the animal or demoralizing to the experimenter - these are avoidable aberrations. British science has never been convicted of irresponsibility towards experimental animals, and the Act of 1876 is largely a safeguard against a theoretical evil. But abuses are possible, through ignorance or thoughtlessness, although deliberate cruelty is unknown in the laboratory; and the avoidance of abuses is a duty laid implicitly on every scientist when he uses an animal. He can be helped to discharge this obligation by those whose profession it is to study laboratory animals and their care.

CONCLUSION

The best, and in the long run the only, defence the scientist has against the attacks of those whose love of animals leads them into a hatred of science and even of humanity, is to ensure that in the conduct of his animal experiments there is nothing that would offend a reasonable person. Anything less than this is an abuse of science itself.

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