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Editor's Page

Right after receipt of abstracts for the Federation Meeting is a good time to discuss matters pertaining to abstracts of the 10-minute papers.

The Society at its meeting last April, voted to change the interpretation of the rules to make them more strict in an attempt possibly to reduce the number of 10-minute papers. The new interpretation was that a person's name (member or non-member) could appear only once. There seemed to be some confusion in the interpretation of this ruling. Simply explained it means that a person's name can appear on the author line, including (sponsored by -----) only once. Several abstracts had to be retyped eliminating some co-author whose name had appeared on another abstract. By so doing the abstract could be accepted. This chore was doubly burdensome since approximately 600 of the abstracts appeared in this office on January 14 and 15. The hurried preparation of abstracts was also evidenced by the fact that many did not accurately follow the typing instructions. It might be noted for next year that more attention can be given individual abstracts if they do not all arrive at once right at the deadline.

There were 934 abstracts received. In 1962 there were 847 so the attempt to reduce the number of 10-minute papers by the new interpretation of the rules did not work. Thirty-six per cent of the abstracts received were sponsored - that is, no member name appeared among the actual authors. If it is felt that the number of 10-minute papers is getting too large for a profitable meeting - and the number is increasing every year - members may wish to discuss some other mechanism for reducing the number of papers.

The new publication, Physiology for Physicians, seems to be receiving a warm welcome and acceptance. The January issue was distributed as an advertising copy to several thousand physicians, medical students, and members of the Society. The February issue is being distributed as advertising copy to more physicians and medical students. Copies of the March issue will be distributed to a large list of medical specialists. This means of advertising appears to be getting results. By the first of February we had about 1500 subscriptions. Members of the Society do not automatically receive Physiology for Physicians free as they do The Physiologist. The subscription rate for members is the same as for non-members, $3.00 per year. At this low subscription rate it is estimated that we will eventually have to have approximately 5000 subscribers to make the venture self-supporting.

WALTER BRADFORD CANNON
1871-1945

Walter Bradford Cannon was born October 19, 1871 in Prairie du Chien, Wisconsin. It was here that William Beaumont, in 1829-31, carried out some of his most significant studies of gastric digestion on Alexis St. Martin.

He received his A.B. degree from Harvard in 1896, A.M. in 1897, and M.D. in 1900. As an undergraduate he was influenced by the zoologists, Charles B. Davenport and George H. Parker; in medical school he was trained by Henry P. Bowditch. His official academic teaching career began with an instructorship in zoology at Harvard in 1899. He was instructor in physiology at Harvard Medical School in 1900, assistant professor in 1902, and succeeded Bowditch as George Higginson Professor of Physiology in 1906.

Stimulated by Bowditch he began his work on the movements of the alimentary canal in 1897 while still a first-year medical student. As a student he demonstrated the movement of a pellet through the gullet of a goose at an American Physiological Society meeting using the newly discovered Roentgen rays. His pioneering roentgenographic studies of movements of the digestive tract that attracted wide attention terminated in 1912. His facility for seeing different facets of a physiological problem led him to study the disturbance of digestive processes by emotional states. This led to the study of the sympathetic nervous system and the adrenal medulla and then to the discovery of sympathin. He studied the essential conditions for normal existence of the higher animals. The constancy of the conditions immediately surrounding the tissue cells led Cannon to call this steady state, homeostasis. His several presentations of the bodily organization for physiological homeostasis, particularly his book, "The Wisdom of the Body", have exerted widespread influence on the thinking of physiologists.

During World War I he was commissioned Lieutenant Colonel in the Medical Corps serving from 1917-1919. He devoted energy and skill to a study of the problems of traumatic shock, collaborating closely with Sir William Bayliss in the development of the gum-saline technique of replacing blood volume.

Dr. Cannon became a member of the American Physiological Society in 1900 and continued to be an active contributor to its scientific programs. He was treasurer of the Society from 1905-1912 and served as president from 1914 through 1916. He was chairman of the local committee for the Thirteenth International Physiological Congress held in Boston in 1929 and later became a member of the International Committee on Physiological Congresses. He took part in the establishment of the National Research Council in 1916 and served as a member of the Council of the National Academy of Science for several years. He was truly an international physiologist. He made extended visits as exchange professor to several foreign countries. In his 36 years as professor more than 50 students from 17 different countries came to his laboratory for advanced study. He held honorary degrees from many foreign universities and

was a member of many learned societies both abroad and at home. Though he received almost every public distinction for which a scientist is eligible he never thought highly of himself. He was acutely modest. He could, however, fight vigorously for ideas in scientific controversy and in the field of public affairs.

He had the faculty of finding profitable lines of inquiry. He was a master of technique. He had a genuine and keen interest in the problems on which his students were working, an interest entirely free from any attempt to dominate or modify their research programs. When appealed to for suggestions he was always ready to take as much time as necessary to consider the problems and would suggest ideas that were both stimulating and helpful.

Cannon always was ready and willing to go before groups of physicians, gastroenterologists, neurologists, endocrinologists, surgeons, army officers, psychiatrists, and other specialty groups to explain to them recent discoveries in physiology and to help them in applying these discoveries to the solutions of their practical problems. He taught medical students and physicians to think of disease as disturbed physiology and treatment as an effort to restore physiological function to normal.

At the celebration of the 25th anniversary of his professorship Dean Edsall spoke of his possession in abundance of those qualities of personality which produce what we call character. Walter Alverez, in reviewing the reasons which made Dr. Cannon such a good foster father of research, mentioned his open-mindedness to the ideas of others, his genuine interest in the problems of his students and his scrupulous fairness in apportioning credit. President Lowell spoke of a quality which impressed all who knew him - his very great modesty.

Arthur Redfield said of Cannon in 1931: "Dr. Cannon's great success is due to the fact that the search for truth, and particularly physiological truth, is akin to a religious issue which he pursues with an almost evangelical zeal. It is his faith in the importance, I might even say righteousness, of physiological investigation which seems to give him the tremendous energy which his work shows and which he manages to instill into the students who are working with him. This zeal is for the establishment of truth in general, but it is also very markedly for the establishment of physiological truth in particular."

Dr. Cannon was an outstanding exponent of the scientist's public responsibility. He saw that the freedom and beneficence of science could be guaranteed only within the framework of a just society, national and international. He was a citizen-scientist.

SPECIAL APS PROGRAMS AT THE SPRING MEETING

APRIL 16-20, 1962

SYMPOSIA

"Regulation of Secretion of Gonadotrophins" - S. M. McCann, Chairman

"Nervous Control of the Heart" - W. C. Randall, Chairman

"Respiratory Physiology in Space Craft" - A. B. DuBois, Chairman

Teaching Session

"Analog Computers in Physiology Teaching" - L. H. Peterson, Chairman
(Programming and use of an analog computer will be demonstrated with aid of closed circuit television)

Thirty-Minute Introductory Talks

Integration of Neural and Hormonal Control of Gastric Secretion - M. I. Grossman

Distribution of Blood Flow in the Kidney - A. C. Barger

Transport of Gases by the Blood - A. B. Otis

New Ideas on Thyroid Function - S. B. Barker

Current Trends in Circulation Research - L. H. Peterson

Spinal Mechanisms which Control Muscular Contraction - E. Henneman

Some Cellular Effects of Neurohypophyseal Hormones on Permeability and Transport - A. Leaf

Some Problems in the Study of Neurophysiological Mechanisms of Sensation - V. B. Mountcastle

SURVEY OF TRAINING FOR Ph.D. DEGREE IN PHYSIOLOGY

In order to obtain some information as to the present manner in which graduate students in physiology are being trained questionnaires were sent to departments in graduate schools offering the Ph.D. in physiology. Information was also obtained relative to the type of training it is desirable for a student to have upon entering the Ph.D. training program.

Replies were received from 68 departments of physiology in medical schools and 20 non-medical school departments now training Ph.D's in physiology. Several medical schools do not currently have training programs for Ph.D's in physiology.

The schools reported that they are now training students in the following areas of physiology.

Area of Physiology	Medical School Departments	Non-Medical School Departments	Total # Schools
General physiology	22	17	39
Comparative	2	14	16
Marine	0	1	1
Insect	0	6	6
Avian	0	3	3
Plant	0	2	2
Cellular	24	17	41
General mammalian	45	11	56
Neurophysiology	42	7	49
Psychophysiology	8	4	12
Cardiovascular	49	3	52
Respiratory	26	3	29
Muscle	23	3	26
Gastrointestinal	17	2	19
Renal	32	2	34
Endocrine	34	14	48
Environmental	14	7	21
Other	9	4	13

The 68 medical schools reported they had 457 students currently working for a Ph.D. in physiology while the non-medical schools reported 139. Since this represents most of the schools offering the Ph.D. degree in physiology there are probably less than 800 now in training. This means a yearly average output of about 200. The present demands are far greater particularly in some of the sub-specialties. Of course some of the demand for human physiologists can be met by MD's with

This report supplements Dr. Brown's summary of Program Directors' Comments on graduate training in physiology published in the November 1962 issue of The Physiologist, page 248.

experience in research. The demand for physiologists in some of the other sub-specialties far exceeds the supply.

These figures again point up the necessity for vigorous recruiting if our science is to continue and flourish. Only one-fourth of the schools indicated that they had more qualified applicants than they were equipped to handle and many of these barely qualified.

The following schools indicated that they had more qualified applicants that they were equipped to handle and that they would be willing to recommend them to another school that may be seeking graduate students.

Medical Schools	Non-Medical Schools
Baylor	Univ. of Illinois (Urbana)(Physiol. Dept.)
Harvard	Southern Illinois Univ. (Physiol. Dept.)
Johns Hopkins	Brown Univ. (Biol. Dept.)
Louisville	St. John's Univ. (Biol. Dept.)
Marquette	Catholic Univ. of America (Biol. Dept.)
Maryland	Columbia Univ. (Zool. Dept.)
Michigan	Univ. of Wyoming (Zool. Dept.)
New York Univ.	
State Univ. of N.Y.	
Pennsylvania	
Rochester	
Seton Hall	
South Dakota	
Temple	
Univ. of Washington	
Washington Univ. (St. Louis)	
Wayne State	
Vermont	

Should these schools increase their facilities or should more training centers be established?

Present Requirements for Ph. D.

Since there are many types of physiologists, students are trained for specific areas in physiology, thus the graduate course content varies with the specific needs of the student. Approximately 70% of the schools felt that a uniform core curriculum for all graduate students of physiology would be undesirable. Those that did feel some sort of standard core curriculum was desirable generally felt that the requirements should be limited to certain courses with a wide selection of electives. The non-medical school affiliated departments stressed cellular and general physiology courses whereas the medical school departments, in addition to general physiology, stressed instrumentation, electronics and advanced math. as possible requirements for all Ph. D. students.

Thesis: All schools require a written thesis. Twenty-two of the 88 require that the thesis be published and several others require that the

thesis be of acceptable quality for publication.

Qualifying Exams: Sixty-seven require qualifying exams. Of these, 51 require both written and oral exams; 9, oral only; and 7, written only. There are 21 schools that do not require qualifying exams.

Languages: All but 6 schools require a reading knowledge of two foreign languages. Five of the schools requiring two languages will permit some students to substitute an expert knowledge of statistics for one language.

Only 10 schools limit the foreign language choice to German and French. Most schools permit other modern languages. The most common recommendations are German, French, Russian and Spanish, in that order.

Seminars: Nearly all schools require graduate student participation in advanced seminars.

Teaching Experience: Ten schools require graduate students to participate in laboratory instruction and/or teaching.

In addition to advanced and specialty courses in physiology the course requirements in ancillary subjects vary with the needs of the student and his specialty. The most frequent ancillary course requirements are, biochemistry; gross, microscopic and neuroanatomy; pharmacology; and biophysics.

Many schools feel that one full-time staff member per graduate student is a minimum for good instruction.

Desired Requirements for Matriculation

The departments were asked what levels of undergraduate training they would like their students to have before embarking on graduate training in physiology. These indications should be helpful to those undergraduates contemplating graduate work in physiology.

Chemistry: 86% of the schools desire training in inorganic; qualitative and quanitative analysis; organic; and physical chemistry. The remainder feel that training through organic is sufficient.

Physics: 49% of the schools would be content with one year of college physics. Most of these feel that a good course in engineering type physics is essential, not a premedical generalized course. Another 28% would require one year of physics plus courses in electricity and electronics. The remaining 23% would require a minimum of 2 years of college physics.

Math: All schools feel that the student should have college math training through calculus. Most feel that advanced calculus,

including differential equations, is essential.

Biology: The desires here vary from a low of one year of general biology to a battery of biological courses. The courses most frequently mentioned (in order of frequency) were - comparative anatomy; embryology; genetics; cellular and/or general physiology.

Qualifications of Staff Personnel

The questionnaire requested information on what qualifications department chairmen looked for when appointing new staff personnel. The answers may give some guidance to those seeking staff positions.

The factors listed as most important were:

Potential as an investigator
Recommendations from former or present associates
Personal qualities
Ability to lecture and teach
Quality of bibliography
Graduate school record
Specialized graduate training in a particular area of physiology

Factors of less importance to most were:

Undergraduate record
Dissertation
Length of bibliography
Specialized training in math, chemistry, or physics

Of course specific training and background are considered when hiring a staff member for strength in a specific subdiscipline.

The analysis reveals that there is a wide diversity in training curricula for Ph.D's in physiology. This indicates the growing importance of the sub-specialties in physiology. The medical school departments are training physiologists primarily in the sub-specialties of mammalian physiology whereas the non-medical school departments concentrate for the most part on general, comparative and cellular physiology.

SEVENTH BOWDITCH LECTURE

Intestinal Absorption of Vitamin B_{12}

T. HASTINGS WILSON

The subject of my discussion is a problem in cell permeability. This general area in physiology has now reached a considerable degree of sophistication and a number of types of phenomena have been classified and characterized in some detail. Passive diffusion through water-filled channels or through lipid-rich areas of membrane is well established. One may even estimate with some degree of precision the quantitative aspects of these two routes of entry in certain cells. Carrier-mediated transport (both the active transport and the "facilitated diffusion" varieties) is currently the subject of intense investigation in many laboratories and extensive data are now available on cells of animals, plants and microorganisms. A third category of permeability phenomena is membrane vesiculation (phagocytosis and pinocytosis). These processes have been known for many years in a number of primitive cell types, and have recently been found in a wide variety of other cells. Elegant morphological studies with the electron microscope have stimulated renewed interest in this form of membrane transport.

With our present extensive fund of knowledge of membrane phenomena it should prove a simple matter to classify, at least tentatively, any given instance of cell permeability. This being the case, let us consider one specific example of translocation of a substance across a cell membrane: the intestinal absorption of vitamin B_{12}. After considering some of the features of this physiological process we should be able to arrive at a diagnosis as to classification.

Let us begin by looking at the structure of this substance (Fig. 1). One is immediately struck by its chemical complexity. This is the largest essential nutrient in the animal diet (a molecular weight of 1350). It is 2 or 3 times larger than any of the other water-soluble vitamins. In addition, it is quite insoluble in lipid. For these reasons B_{12} would seem to be a poor candidate for simple passive diffusion.

It should be mentioned that vitamin B_{12} probably does not exist, as such, in nature but like many other vitamins is present in living cells as a more complex molecule which possesses a coenzyme function. Barker (3) discovered several important coenzymes. One of these (5, 6-dimethylbenzimidazolylcobamide) differs from B_{12} in that is possesses an additional nucleoside, probably attached to the cobalt. These facts, however, do not alter our discussion, as the mechanism for the intestinal absorption of the vitamin and of Barker's coenzyme are apparently the same (15, 31).

What makes this story especially fascinating is the incredible fact that the large B_{12} molecule is not absorbed without the simultaneous presence of a much larger molecule, a specific mucoprotein, discovered by Castle (11) and named by him "gastric intrinsic factor". As far as we know B_{12} is the only substance in the diet which requires such a

specific substance for its absorption.

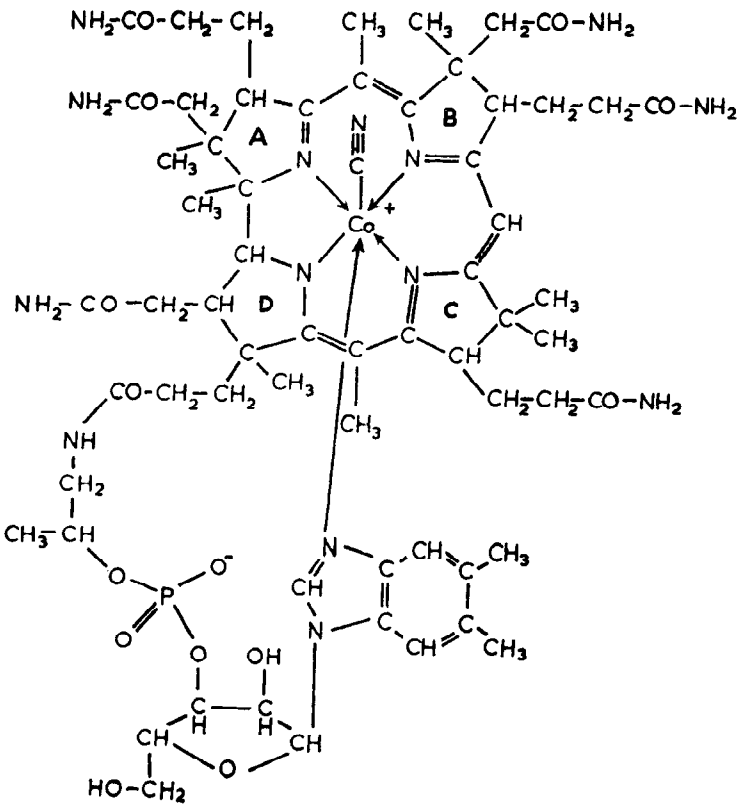

Fig. 1. Structure of vitamin B_{12} (34).

Let us compare the molecular size of B_{12} and intrinsic factor (IF) with the pore size in the intestinal epithelial cell (Fig. 2). The value of 4 A^{o} for the average pore radius was taken from the recent study of Lindemann and Solomon (27). This is probably the order of magnitude of water-filled channels in membranes of most cell types. The size of gastric intrinsic factor was calculated (33) as the size of a sphere with the same diffusion coefficient (18) as hog IF. The value of 8 A^{o} for vitamin B_{12} was roughly estimated (33) from its molecular weight and an assumption as to its density. The large discrepancy between the 4 A^{o} pore radius of the epithelial cell and the B_{12}· IF complex is obvious. This cannot be the route of entry.

Further vital statistics about these two substances may be of interest.

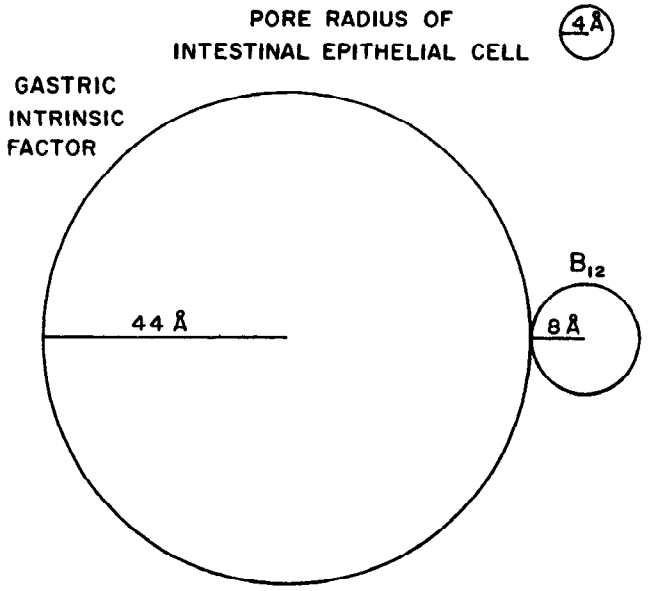

Fig. 2. Comparison between the pore size of the intestinal absorptive cell and molecular dimensions of B_{12}-intrinsic factor complex.

The quantities of B_{12} involved in our consideration are fantastically small. Table 1 shows some rough calculations of the absorptive capacity of the human small intestine. At one extreme is the capacity of

TABLE 1

Capacity of the Human Intestine to Absorb Nutrients

Substance	Absorptive Capacity (m Moles/day)	Ref.
Water	1,000,000	(37)
Glucose	20,000	
Triglycerides	900	
Iron	0.2	
Vitamin B_{12}	0.000001	

the intestine to absorb water while at the opposite extreme is the absorption of vitamin B_{12}. The capacity for absorption of B_{12} in 24 hours is about 1 millionth of a millimole (1-2 micrograms). There are 12 orders of magnitude difference between the value for water and that for

B_{12}. Furthermore, the value for B_{12} in the table is for a normal human subject. A patient with pernicious anemia absorbs 1/100th to 1/1000th this amount. We are dealing with incredibly small amounts.

Gastric intrinsic factor has many interesting properties. It is a carbohydrate-containing protein with a molecular weight between 50,000 and 100,000 made in the chief cells of the stomach (6, 26). With regard to assay, Castle's original method for estimation of IF was the hemopoetic response of pernicious anemia patients. With radioactive B_{12} it is now possible to assay IF by its stimulation of B_{12} absorption in vivo or in vitro. No IF activity has been found in any organ except the stomach and the lumen of the small intestine. One important feature of IF is that it strongly binds vitamin B_{12}, its binding capacity being much greater than most proteins. There is probably 1 molecule of B_{12} bound to each molecule of IF, although this is not known for certain.

Now let us consider some of the physiological interactions between B_{12}, intrinsic factor and the intestinal epithelium. Many studies have been carried out since the discovery of IF by Castle in 1929 (11) and no attempt will be made to give a historical survey of the subject. There are so many investigators working in this general area as to warrant two separate international symposia on vitamin B_{12} and intrinsic factor, one in 1956 (20) and another in 1961 (21). In the published proceedings of these meetings will be found excellent reviews on all aspects of this subject.

The most important single fact is that IF is essential for intestinal absorption of vitamin B_{12}. In man the complete absence of gastric intrinsic factor causes a severe deficiency in B_{12} absorption which results in an inability to produce a normal number of erythrocytes. This disease, which is called pernicious anemia may have a fatal outcome if untreated. Many experiments were carried out by Castle and others on patients with this disease. However, with the advent of radioactive vitamin B_{12}, absorption studies were extended to experimental animals. I should like to illustrate the effect of IF in an in vitro system. Let me digress for a moment to describe briefly this method which was developed in collaboration with Dr. Wiseman (40) at the University of Sheffield.

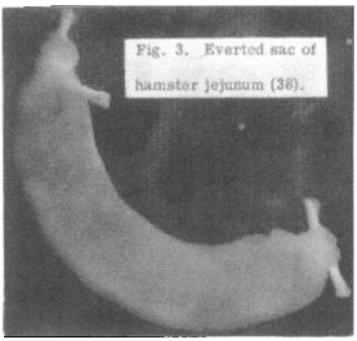

Fig. 3. Everted sac of hamster jejunum (38).

Fig. 3 shows an everted sac of hamster small intestine. The small intestine is stripped from its mesentery and turned inside out with a long stainless steel rod. A short segment of this everted intestine is tied at one end, a blunt needle attached to a tuberculin syringe is introduced into the open end and a thread tied loosely over the tissue. After introduction of fluid the needle is withdrawn and the thread tied. The sac in the figure

contained 1 ml of solution and represented about 200 mg of intestinal tissue. Such a sac is normally incubated in a 50 ml Erlenmeyer flask containing 5 or 10 ml of solution with 95% oxygen, 5% CO_2 as the gas phase. Incubation is usually for 1 hour at 37°, with shaking.

This invitro technique was utilized for studies of B_{12} absorption. In the experiment shown in Fig. 4 two everted sacs were prepared in the manner just described (35). One was incubated in 4 ml Krebs' solution containing radioactive vitamin B_{12} and the second was incubated in a similar solution plus hamster gastric mucosa. At the end of 1 hour incubation period the sac was removed and washed in three separate beakers of saline to remove radioactivity entrained between the villi, and that loosely bound to the tissue. The sac was opened, contents discarded and the tissue weighed and counted. In this experiment the IF stimulated B_{12} uptake by a factor of 20 fold.

Although considerable amounts of B_{12} were taken into or onto the epithelial cells none appeared in the serosal fluid during the 1 hour incubation. This brings us to another interesting feature of B_{12} absorption. Between 1 and 3 hours are required for the B_{12} molecule to traverse the 10-15 micron length of the epithelial cell. This is very much slower than the absorption time for other nutrients, such as ions, sugars and amino acids. Booth and Mollin (9) performed an experiment that

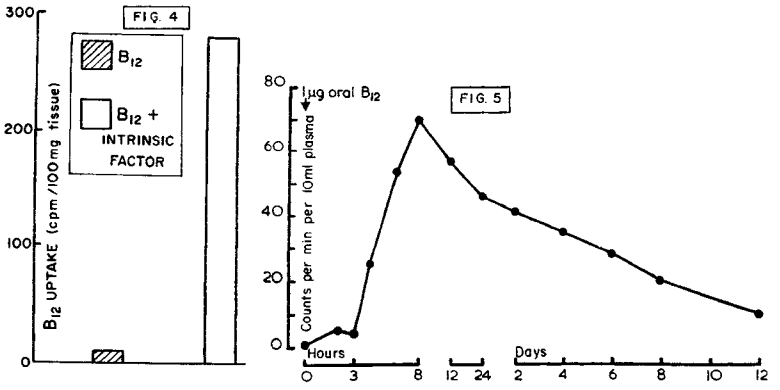

Fig. 4. Effect of intrinsic factor on B_{12} uptake by hamster ileum. Two sacs (about 200 mg tissue each) were prepared from consecutive segments of hamster ileum. Control flask contained 4 ml of Krebs bicarbonate-saline with Co^{60}-labeled vitamin B_{12}. The 2nd flask contained a similar solution with 0.1 ml of an extract of hamster gastric mucosa (35).

Fig. 5. Plasma radioactivity after an oral dose of 1 µg of Co^{56}-B_{12} given to a normal subject (9).

illustrates the delay in B_{12} absorption (Fig. 5). One microgram of radioactive vitamin B_{12} was fed to a normal human subject and the appearance of radioactivity in the blood was measured. Little or no vitamin appeared in the blood during the first 3 hours. Then considerable amounts appeared and reached a maximum at 8 hours. This same type of lag has been found in other animals.

The epithelial cells from different locations along the intestine behave very differently with regard to B_{12} absorption. In all animals thus far tested the cells from the upper jejunum were incapable of absorbing the vitamin with or without IF. The ileum was most active in B_{12} absorption with IF. This may be illustrated in an in vitro experiment carried out in collaboration with Dr. Strauss. In this experiment (Fig. 6) the entire jejunum and ileum of a hamster was everted, filled with about 4 ml of solution and incubated in a 250 ml Erlenmeyer flask containing 12 ml of Krebs' solution plus B_{12}. The gut of a second animal was similarly prepared and placed in a similar solution plus intrinsic factor (rat gastric juice). At the end of the hour's incubation each tissue was carefully washed and cut into 6 segments which were then counted. Fig. 6 shows that little or no uptake occurred in the upper section of the intestine with, or without, IF but IF had an increasing

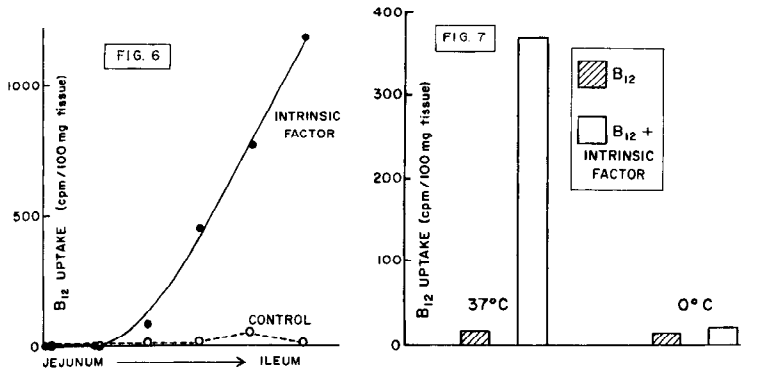

Fig. 6. Effect of location along hamster intestine on B_{12} uptake with or without intrinsic factor. The entire jejunum and ileum of 1 hamster was everted, filled with 4 ml saline and incubated in a 250-ml flask containing 12 ml solution (with 0.005 µg Co^{58}-labeled B_{12} and 3 ml pooled rat gastric juice). Incubation for 1 hr. at 37°C. The intestine of a 2nd animal was incubated in a similar solution without addition of gastric juice (35).

Fig. 7. Effect of low temperature on B_{12} uptake by guinea pig intestine with or without intrinsic factor. Four sacs of guinea pig ileum were each incubated in 6 ml Krebs bicarbonate-saline containing 0.005 µg $Co^{58}B_{12}$ with or without 10 ug purified hog IF. Incubation for 1 hr. at the temperature indicated (35).

effect as the ileocaecal valve was approached. In the lowest ileum in this particular experiment there was a 100 fold stimulation of absorption.

Incubation temperature has a profound effect on B_{12} absorption. In Fig. 7 the first pair of bars show the effect of IF on B_{12} uptake by guinea pig ileum at 37°. One interesting aspect of this experiment is that highly purified hog IF (kindly provided by the Eli Lilly Laboratories) was used, rather than the crude stomach homogenates used in much of this work. It is active at a concentration of less than 1 microgram per ml. The two bars on the right hand side of Fig. 7 represent a similar experiment performed at 0°. IF had little or no effect. Anaerobic conditions also completely blocked the stimulation due to IF. Presumably metabolic energy is required for the intrinsic factor effect.

There are some remarkable species differences with regard to IF stimulation of B_{12} uptake. Table 2 shows that the human intestine can use IF from the human, hog (36) and rat (1). The monkey is similar (6, 24). The rat is most fastidious; it will use only its own IF (12, 14, 29, 39), that from 5 other species being inactive. The guinea pig, on the other hand, is at the opposite extreme; it will use all IF preparations tested (39).

Let us turn to some of the events occurring at the subcellular level. Our knowledge of this aspect is extremely fragmentary. One fact, however, is clearly established. The binding of B_{12} to IF is an essential prerequisite to B_{12} uptake by epithelial cells. When B_{12}-IF complex

TABLE 2

Species Differences in IF Stimulation of B_{12} Uptake

Animal Used For Absorptive Study	Gastric Intrinsic Factor						
	Human	Hog	Rat	Hamster	Rabbit	Guinea Pig	Beaver
Human	+	+	+				
Monkey	+	+	+	+		0	
Rat	0	0	+	0	0	0	
Hamster	0	+*	+	+	+	+*	+*
Rabbit	0	+	+	0	+	0	
Guinea Pig	+	+	+	+	+	+	+
Beaver	+		+				+

+* = weak activity

and free B_{12} (labeled so that they can be distinguished from one another) are added to the intestine, it is the B_{12} added as the complex which enters the cell and not the free B_{12}. This was first demonstrated by Bishop, et al. (5) and later confirmed by Nieweg et al. (30). Furthermore, neither free B_{12} nor free IF appear to be bound to the epithelial cell; only B_{12}·IF complex can react with the cell membrane (35).

Does the B_{12}·IF complex enter the cell? This is an important question, but one which has been impossible to answer due to the difficulty in the assay procedures for IF and B_{12}·IF complex. Recently Miss Agna Boass has developed a very sensitive and reproducible assay with small rings of hamster ileum (7). The appearance of these small rings is shown in Figure 8. The individual villi are clearly visible at this magnification. About 100 rings are prepared and mixed in a beaker. Then alliquots of about 10 are placed into each flask. The assay for B_{12}·IF complex involves measuring the uptake of radioactivity by these tissue segments.

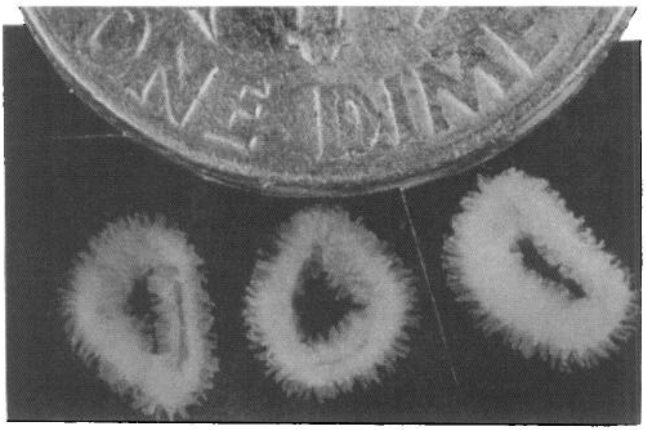

Fig. 8. Small rings 1 to 5 mm in width were cut from everted intestine of the hamster. Dime shown for comparison. Approximately x 7 (Wilson: Intestinal Absorption, 1962, p. 35).

In an attempt to detect the B_{12}·IF complex within the absorbing cell the following experiment was performed. A sac of hamster intestine was incubated in a solution containing B_{12}·IF and carefully washed. The mucosa scraped off and homogenized in 0.3M sucrose. B_{12} was found to be distributed throughout all of the particulate fractions and the supernatant fluid. These fractions were then assayed for B_{12}·IF complex with the ring assay system just described.

Table 3 shows an experiment illustrating the results in one experiment, with appropriate controls. Radioactive B_{12} was added to various protein solutions and then dialyzed exhaustively against Krebs solution. When B_{12}·IF was added to the ileal rings 11.7% of the B_{12} was taken up. When B_{12}·albumin complex was added, less than 0.1% was taken up. Similar low intake was observed with B_{12} rat muscle protein complex or B_{12}·rat intestinal mucus complex. The particulate fraction from the cells absorbing B_{12}·IF complex gave 0.5%. This indicates either that B_{12} was not attached to IF or that B_{12}·IF complex was tightly bound to the particle and unavailable. The supernatant fraction in this particular experiment gave 2.7% uptake or 5 times that of the particulate fraction. Six such experiments have been carried out and the average uptake was 3.8%. It is inferred from such data that some B_{12}·IF complex is present within the cell. The exact proportion cannot be determined from the present data.

TABLE 3

Presence of B_{12}·IF Complex in Epithelial Cells During B_{12} Absorption

Co^{57}-B_{12}·Protein Complex (dialyzed)	Uptake of Radioactivity (By Hamster Gut) (% of total counts)
B_{12}·IF	11.7
B_{12}·Albumin	0.05
B_{12}·Muscle Extract	0.5
B_{12}·Intestinal Mucus	0.4
B_{12}·Particulate Fraction of Epithelial Cells Absorbing B_{12}+IF	0.5
B_{12}·Supernatant Fraction of Epithelial Cells Absorbing B_{12}+IF	2.7

Cooper and Castle (17) have recently presented evidence that some factor in the epithelial cells--probably an enzyme--can split the bond which holds B_{12} to the IF. However, this "releasing factor" is not present in the ileum where B_{12} is absorbed but in the upper jejunum (22). The physiological significance of this releasing factor is, therefore, not clear. The extremely interesting question of whether IF is absorbed into the blood stream along with B_{12} has not yet received a definite answer. Blood plasma does not seem to contain IF although the sensitivity of the analytical methods may not be adequate. Various experiments indicate that small amounts are absorbed following very large doses of IF in man and in animals, but the physiological significance is uncertain.

I should like to return to the question I posed at the beginning of our discussion. What is the physiological mechanism of B_{12} absorption? All of us have intuitive feelings about certain relationships which cannot be proven--usually they cannot be proven because they are incorrect. Occasionally, however, the idea is quite sound but there are insufficient

data available at that time to prove the point. What I should like to discuss now is mainly this type of speculation with only a very sparse sprinkling of experimental facts.

My first speculation is that the mechanism of B_{12} absorption is not unique but falls into one of the categories of membrane transport which are known to occur in other cells (that is, passive diffusion, carrier-mediated transport or membrane vesiculation). Passive diffusion can be excluded without much argument on the basis of size and lipid insolubility of the B_{12}-IF complex. Carrier-mediated transport cannot be dismissed so easily. The requirement for a specific protein molecule, however, would certainly be unusual for this type of permeability phenomenon. By a process of elimination, one mechanism remains--one which is currently in disfavor among many physiologists--namely, membrane vesiculation.

Let us consider some experiments. Fig. 9 shows data on B_{12} uptake by two different tissues of the rat. The yolk sac experiments were performed in collaboration with Dr. Helen Padykula of the department of anatomy of the Harvard Medical School (32). The experiments on the intestine were performed by Miss Agna Boass (8). What I propose to do is to indicate a correlation between morphological appearance of the tissue and the capacity to absorb B_{12} with IF.

The yolk sac is derived from the gut to which it remains attached until birth. In the rat the yolk sac completely surrounds the fetus and with the amnion makes up the fetal membranes. The villi of the yolk sac face the uterine lumen with which they freely communicate after about the 14th day of gestation. The visceral yolk sac possesses the intrinsic factor mechanism for B_{12} uptake. I will not, however, speculate as to a possible physiological significance of this mechanism, if any. IF stimulates B_{12} uptake 700% on the 13th day and 300% on the 21st day of gestation. The units on the ordinate in Fig. 9 are on a logrhythmic scale. Also, the total uptake with IF in the young animal is 10 times greater per milligram tissue than that in the older animal.

Dr. Padykula has studied the morphology of this tissue with the electron microscope (32). The endodermal cells lining the villi of the yolk sac on the 13th day of gestation possess abundant long slender microvilli. There are many small vessicles just below the membrane and a few probably communicate with the surface. There is considerable intercommunication between tubules. This morphological appearance is typical of pinocytosis. There is physiological as well as morphological evidence of pinocytosis. Luse (28) has shown that these cells are capable of absorbing colloidal gold as well as intact protein molecules. Passive immunity is obtained by the fetus in utero by the absorption of antibodies from the uterine lumen through the endodermal cells and into the fetal circulation (10).

Electron micrographs of cells at 21 days of gestation show that the microvilli are less frequent, much shorter and blunter. There are perhaps fewer small vesicles (32). The morphological interpretation is that there is less pinocytosis in this cell. There thus appears to be a

correlation between morphological evidence of pinocytosis and capacity to absorb vitamin B_{12}.

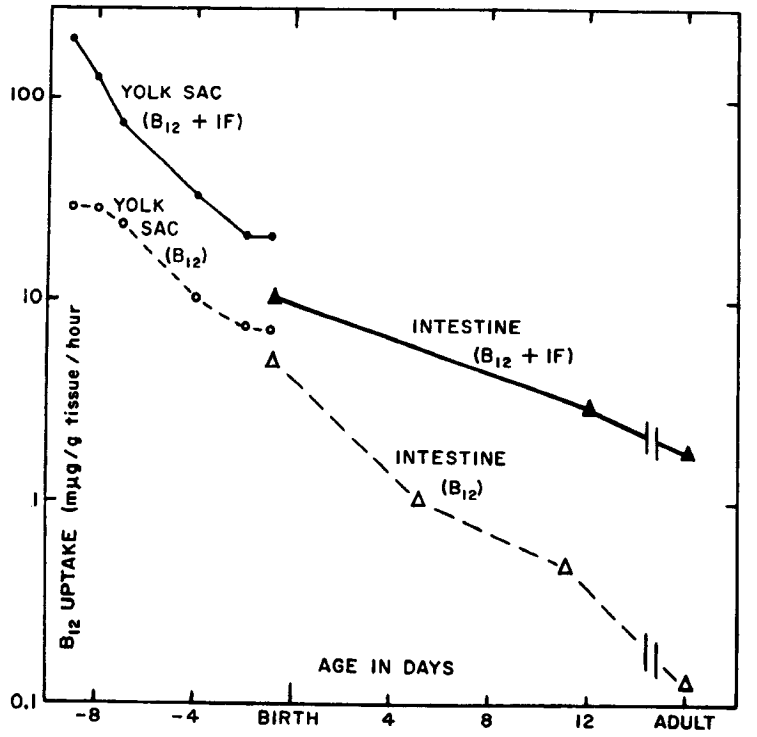

Fig. 9. Effect of intrinsic factor on B_{12} uptake by yolk sac and intestine of the rat. Tissue uptake of vitamin B_{12} with and without intrinsic factor. Tissue was incubated in an Erlenmeyer flask containing 5 ml of Krebs' bicarbonate-saline containing B_{12} (1 mμg/ml) with or without rat intrinsic factor. Gestation period in the rat is taken as 21 days.

Fig. 9 also shows striking changes in the capacity of the gut to absorb B_{12}. After birth there is a marked fall in B_{12} uptake both with and without IF. The curve with IF falls 5 to 10 fold during this period. Let us again look at the morphology of the tissue at these two times. Fig. 10 (B) shows the appearance of the apical portion of an absorptive cell under higher magnification (13). Just under the microvilli there are numerous small and large vesicles. One vesicle clearly communicates with the surface of the cell. This is one of the best examples of pinocytosis in animal cells. Clark (13) has shown that feeding proteins

stimulates this vesicle formation. Furthermore, certain specificity is observed. Thus, rat plasma globulin is absorbed 50 times faster than albumin; and rat globulin is absorbed in perference to globulin from other species (2). The capacity of the young rat to absorb intact protein molecules disappears at exactly the same time that this pinocytosis, seen morphologically, disappears--at the end of the 3rd week of life (19). The appearance of the epithelial cell at three weeks is shown in panel A. This is the same as the adult. There remains only a remnant of pinocytotic activity. The arrow in the upper left points to an invagination which appears to be the first step in the formation of a small pinocytotic vessicle. According to my hypothesis the marked fall in capacity for B_{12} absorption is related to the great reduction in pinocytosis from the newborn to the adult. My hypothesis is that in the adult this remnant of pinocytosis can be stimulated by B_{12}·IF complex to absorb the complex.

If this hypothesis were correct one would predict that an animal such as the guinea pig which does not absorb protein at birth (and presumably does not show pinocytosis) would not show the type of change in B_{12} absorption shown by the rat. Such an experiment was carried out on the

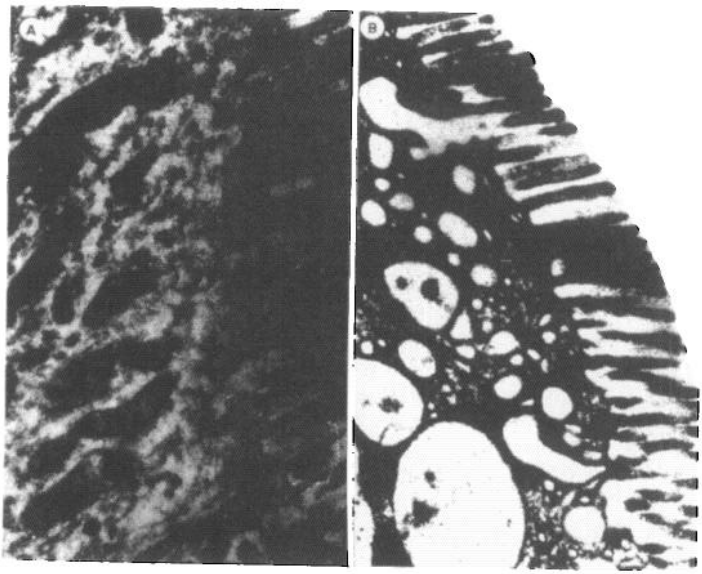

Fig. 10. Morphological changes associated with protein absorption in the suckling rat. Apical cytoplasm of the intestinal epithelium following ingestion of protein by a 23-day old rat (A) and an 8-day old rat (B). Approximately x 25,000 (13).

guinea pig and the results are shown in Fig. 11. The new-born guinea pig shows the adult mechanism and no change occurs with age.

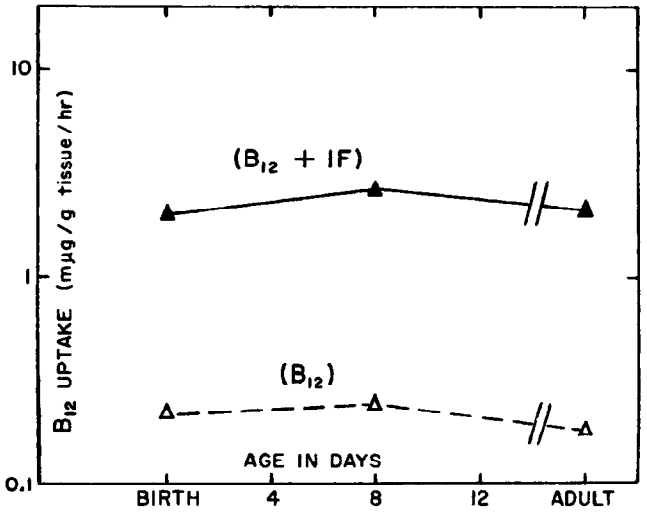

Fig. 11. Effect of age on B_{12} uptake by guinea pig intestine with and without intrinsic factor. Conditions similar to those in Fig. 9 (7).

There is certainly a remarkable parallelism between the morphological appearance of pinocytosis and IF-stimulated B_{12} uptake in two tissues of the rat. Perhaps this is mere coincidence--perhaps not. It must be admitted that conclusive evidence for the hypothesis must include an experiment showing that the addition of B_{12}-IF complex to tissue actually stimulates pinocytosis. This has not yet been shown.

There are a number of examples in other cells of proteins stimulating membrane vesiculation. Perhaps there is some similarity to the phenomenon of plasma factors which stimulate phagocytosis by blood leucocytes. Factors in serum (sometimes identical with antibodies) react with bacteria in some manner which permits phagocytosis (25). In the case of a certain strain of Staphlococcus aureus, bacteria plus leukocytes in normal serum result in no phagocytosis; bacteria plus immune serum plus leucocytes result in active phagocytosis (16). Membrane vesiculation has thus been stimulated by a specific protein.

Insulin stimulates pinocytosis in adipose tissue of the rat (4).

In still another case, pinocytosis in amoebae, Holter has shown that

the substance which produces the greatest stimulation of pinocytosis is protein (23).

Thus, there are a number of known examples of membrane vesiculation stimulated by protein--in some cases by a specific protein. In fact, membrane vesiculation is the only known mechanism capable of translocating large molecules. The conclusion that B_{12}·IF complex is absorbed by pinocytosis rests on extremely circumstantial evidence. On the other hand, the hypothesis has the merit of explaining many of the otherwise anamalous features of this process.

Summary. We have considered a most peculiar permeability phenomenon, the stimulation of absorption of a large molecule by an even larger molecule. In the gastrointestinal tract coenzymes related to B_{12} (bound to protein in the food) are liberated with the aid of digestive enzymes. The B_{12} coenzymes thus freed are then tightly bound to gastric intrinsic factor. This B_{12}·IF complex or coenzyme ·IF complex passes into the ileum where the B_{12} is absorbed by the epithelial cells. Perhaps the complex is absorbed intact. The fate of the intrinsic factor is, however, still in dispute and remains an important unsolved problem for future study. The mechanism by which the B_{12} molecule traverses the epithelial cell of the small intestine is not yet clear, but a speculation has been advanced that this mechanism is by pinocytosis of the B_{12}·IF complex.

It is a pleasure to acknowledge the generous research support by the U.S. Public Health Service and the National Science Foundation.

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PRESIDENT'S MESSAGE

H. S. MAYERSON

Who Speaks for Physiology?

The American Physiological Society has been operating for 75 years. It was formed on Friday, December 30, 1887 in the physiological laboratory of the College of Physicians and Surgeons, 437 West 59th Street, New York City. The invitations to attend the meeting and participate in the organization of the Society were sent out by a committee consisting of Drs. Silas Weir Mitchell, Henry Newell Martin and Henry Pickering Bowditch. The first constitution stated "This Society is instituted to promote the advance of Physiology and to facilitate personal intercourse between American Physiologists". At the Spring meeting of 1953, the objective was re-defined as "The purpose of the Society is to promote the increase in physiological knowledge and its utilization". The membership, in its usual wisdom, eliminated the secondary objective of facilitating "personal intercourse between American Physiologists".

It is not my purpose, at the present time, to review the history of the Society subsequent to its inception. This has already been recorded in written form for the first 50 years and Dr. Wallace Fenn will review the developments of the last 25 years at the Fall meeting in Miami. From a small and rather casual beginning with 28 members, the Society grew and prospered so that Dr. Walter J. Meek could write in the foreword to the history of the first 50 years: "The American Physiological Society from its foundation has been an important factor in the scientific life of our country. It has become a notable American institution. It is a forum in which are presented the current researches in the physiological sciences. It is the owner and manager of two great journals. It is the mother of other societies. It is a vital, growing organization. Not only has its past been honorable and productive, but at the present movement it is more prosperous in point of members and scientific activity than at any period of its history. There is every indication that its value and influence will continue to increase as the years go by."

Events in the subsequent 25 years have amply justified Dr. Meek's optimistic predictions. At the close of the 49th annual meeting in Memphis, the Society had 631 members. On April 1, 1962, there were 1996 active, 123 retired, 136 associate and 16 honorary members, a total of 2,271. In other words, we have added more than twice as many members in the last 25 years as were elected during the first 50 years of the Society's operation. The Society now publishes four "great" journals, an ambitious Handbook, a house organ and a new publication directed towards practicing physiologists. Our summer workshop and visiting scientist programs, development of laboratory experiments in general and human physiology and the institution of an associate membership classification are positive efforts to help our colleagues in colleges. The new publication "Physiology for Physicians" is an attempt to further fulfill our objective of "promoting the increase in physiological knowledge and its utilization."

Our founding fathers conceived of the Society as the instrument of physiology in this country for they named the Society, The American Physiological Society. But over the years we have seen the formation of other physiological societies, the Society of General Physiology and the Comparative Physiology Division of the American Society of Zoologists, each with reasonably large memberships and their own publications. The "good" reason which has so often been given for the formation of these separate groups is that our Society was dominated by "medical" physiologists. The "real" reasons are much more complicated. Splintering and formation of new groups and societies is inevitable as a natural consequence of the widening of horizons and growth in any field of endeavor. It will unquestionably continue in our Society and, to use Dr. Meek's expression, we shall "mother" other societies and groups as we did early in our history when the biochemists and pharmacologists decided to establish their own societies.

Our efforts are being expended, as they should be, not in attempts to entice these groups into our Society (there is already a reasonably large overlapping membership) but in strengthening our lines of communication so that we can work together for advancement of physiology. Thus the Society of General Physiology and the Comparative Physiology Division have representatives on our Education Committee and are contributing much to its effective operation. Representatives nominated by the Society of General Physiology are members of the Editorial Board of Physiological Reviews. We should add representatives of Comparative Physiology as well. The teaching session at the next Fall meeting in Miami will be concerned with comparative physiology and should be of unusual interest and profit. I am in communication with the responsible officers of both groups and we are exploring further means of cooperation and collaboration. We are discussing the possibilities of joint seminars at our respective meetings, of collaboration in planning symposia, of reciprocal visits of members to meetings of the Executive Councils of the three societies and the concept of occasional joint meetings is within the realm of possibility.

Our job of establishing and maintaining communication with physiologists should extend to other less well-known and organized groups. For example, Drs. Rahn and Pappenheimer on their recent tour were stimulated and very much impressed by their experiences in visiting a group of selected veterinary schools. They found a high level of teaching and research in physiology and an eagerness on the part of the groups concerned to be more closely identified by and with the Society. We shall explore the situation further and hope we can maintain the cordial relationships which Drs. Rahn and Pappenheimer have established.

In effecting these relationships, we shall need the cooperation and understanding of our membership. I hope it will feel free to make suggestions and bring to the attention of Council other areas to which our efforts should be directed. It is fitting that the American Physiological Society, as the oldest and largest group, should assume leadership and attempt to speak for physiology. To do so it must however, be eclectic and in a position to speak with the knowledge and conviction that it is representing opinions of physiologists of at least the majority of breeds and denominations.

TEMPERATURE REGULATION AND COLD ACCLIMATION*

LOREN D. CARLSON

The questions concerned with temperature regulation raise sufficient controversy in themselves so that little but valor or foolishness can be attributed to one who chooses to discuss this subject in the furor of a second controversy - acclimatization. However, I should like to introduce the papers of this session with a summary and a synthesis of the data with respect to control of metabolism and peripheral circulation on cold exposure. The term "acclimatization" as I use it might well be synonymous with acclimation, adaptation, or habituation. What is of concern is cold exposure.

Temperature regulation seems to be governed by thermodetectors of the hypothalamus, dependent on skin temperature receptors for its function, but not necessarily dependent on these receptors for elicitation of regulation. Whether there are thermoreceptive structures in the hypothalamus which generate impulses in response to temperature changes or whether temperature modulates a train of impulses is not of importance in our argument. The modification in performance attributable to skin receptors is responsible for the delicate regulation achieved. The regulation is achieved in two stages - the first, control over circulation, and the second, control over metabolism. The latter usually is achieved after the first has been used maximally. As a result of changes in circulation, heat is supplied from storage - cooling body tissues. The cutaneous thermoreceptors may be considered important for the control of heat debt as well as behavioral aid in thermoregulation.

Thermal regulation has been recently reviewed by James D. Hardy (17) and Curt von Euler (15). Benzinger, Pratt, and Kitzinger (4, 5) graphically present thermoregulatory heat production in a manner germane to this discussion (Fig. 1). These are results of experimentation with one healthy young man, cold stimulation being obtained in water baths. Internal temperature is tympanum temperature. Regulation, that is increased heat production, is a resultant of internal and skin temperature. The lower the skin temperature, the greater the response at any internal temperature.

What of regulation in men chronically or intermittantly exposed? The results of six different studies are assembled in Fig. 2. These studies include chamber and field studies with Caucasians, Eskimos, various Indian groups and Australian aborigines (7, 8, 9, 10, 11, 13, 18, 19, 30). A variety of experiments are represented. Exposures made at 10°C and 15°C, covered with blankets or sleeping bags, or clothed. The subjects were basal supine, sleeping, or standing. Internal controls were used as well as selected comparison groups. In Fig. 2, metabolism (as a ratio) is plotted against skin temperature since it is one of the body's signals for response to cold. This technique seemed imminently

*Aided by Air Force Contract AF 41(657)-335, administered by Arctic Aeromedical Laboratory, and NIH Grant RG-8429.

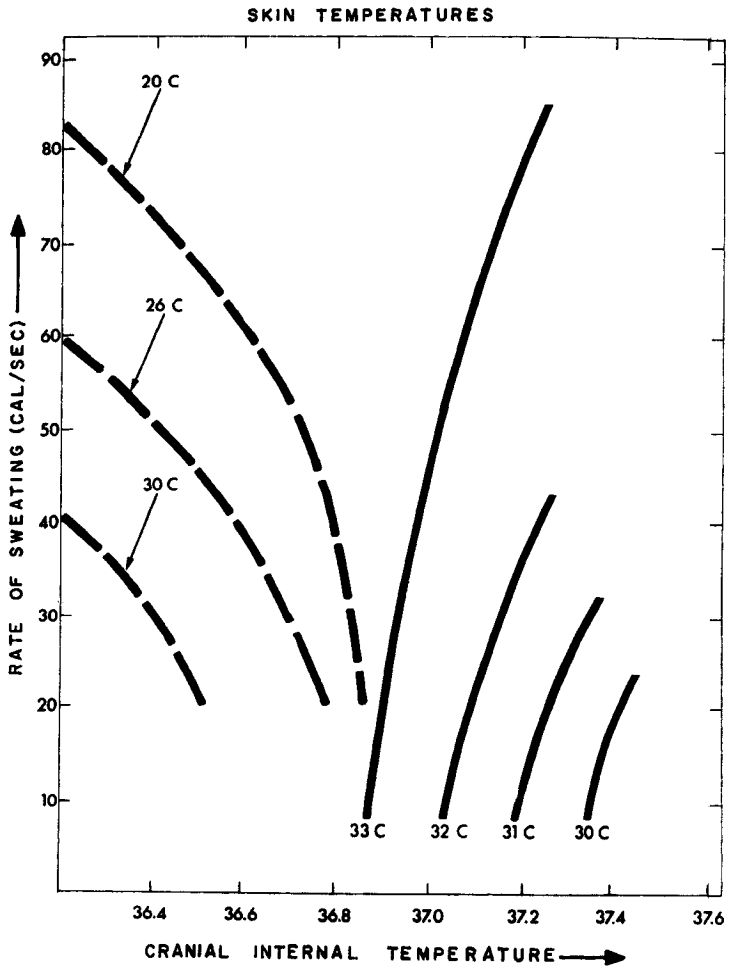

Fig. 1. Redrawn from Benzinger et al. (5) to illustrate the interdependence of skin temperature and internal temperature in regulation of heat production. If skin temperature is high, the internal temperature change must be greater in order for an increase in metabolism to occur. Conversely, a decrease in skin temperature may cause an increase in metabolism with little change in internal temperature.

logical to us (7) but has not appealed to the other investigators. Each of six studies is represented by a number which is encircled to denote the acclimatized group. Compared at the same average skin temperature, the acclimatized person tends to produce less metabolic heat as determined by oxygen consumption. This is not to say that there is less heat loss, which would follow from the Newtonian law of cooling, although it is possible if convection were changed. In the single instance where heat loss was measured (7) there was no difference noted. You may question the initial metabolism. I am uncomfortable in presenting the metabolic events as a ratio. The M_O level varied from 32 to 55 Kcal/M^2/Hr.

In Fig. 3 the metabolism (as a ratio) is plotted against rectal temperature - the only index of internal temperature available. There is some resemblance to the presentation by the Benzinger group and what seems apparent is that there is less metabolic response to lowered internal temperature in the acclimatized individual. Hammel attempted to relate metabolism to average body temperature with little success (18). The use of weighting factors for average body temperature during cooling or in cool environments is questionable (24).

What explanations can be offered for these trends? The first might be characterized as habituation - a lesser response to repeated exposure. This merely names what has been described. The reduction in shivering might allow a greater portion of the body to cool and reduce the convective loss to the surface as well as convection from the surface. In Fig. 3 one could argue that rectal temperature is not indicative of internal temperature. There are no ready answers. Since internal temperature

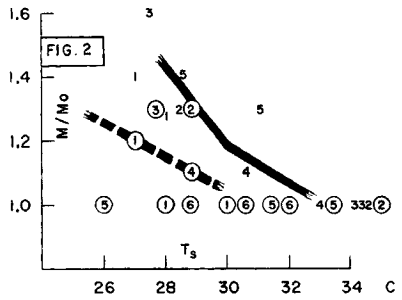

Fig. 2. Increase in metabolism plotted against average skin temperature. Enclosed numbers are acclimated, others non-acclimated. Numbers are authors 1 (7), 2 (30), 3 (10), 4 (13), 5 (18), 6 (19).

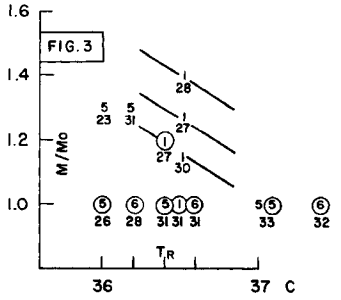

Fig. 3. Increase in metabolism plotted against rectal temperature. Enclosed numbers 1-6 are acclimated, others non-acclimated. Double digit below figure is average skin temperature. References are as given in Fig. 2.

and skin temperature are the signals for regulation, some cognizance must be given these concepts in future studies. Rather than propose these data as significant (though this is possible), I suggest this as a way of looking at our data and that it be considered in planning other experiments. I wonder, frankly, whether a complete balance study on one or two individuals would not provide useful data.

It is helpful to explore each of the possible explanations of the change I have indicated in more detail. Habituation is defined as a process of forming a habit, or accustoming. The implication is that the process depends on the mind and that it may mean diminution of normal responses or sensations. The physiological basis may be the same as that of learning or a conditioned response, but habituation differs in being a decrease in a response. The cold pressor response diminishes with cold exposure (29) and with repeated immersions of the hand(16). In the broad definition of habituation, the tendencies we observed in these data could be considered as a diminution of a response. I know of no physiological explanation of this effect, but it would be of interest to see the results of studies of the sensors and the reaction of the hypothalamus to temperature changes in acclimated animals. Glaser's (16) suggested alternative explanations are as follows: less production or increased destruction of some substances such as histamine, loss of nerve ending sensitivity, or a change in the way that CNS deals with stimuli, i.e. formation of new pathways.

A shift from shivering to nonshivering metabolism is now well documented in the rat and has been reported in man (10, 11). In the rat the nonshivering thermogenesis is mediated by the autonomic nervous system. There are two possibilities - either a shift in response of the regulating system to select the autonomic activation rather than the motor neurones to muscles or a change in response occurs to an existing neural input. There is a change in metabolic response to injected or infused epinephrine and norepinephrine. The circulating levels of these hormones are increased in the cold-exposed animals. There is also the possibility of a change in the rate of destruction of the catecholamines. It is important to determine where this increased heat production occurs. In the human, heat production varies greatly depending on the organ or tissue. An illustration provided by Aschoff (1, 2) will elucidate this. Note the high heat production in the brain; its circulation must function in cooling it. While muscle is only 18 percent of heat production at rest, it may increase markedly. But, a threefold increase in internal organ heat production would more than duplicate this with the advantage of the central source and its small surface to volume ratio. Indeed, if shivering is only 11 percent efficient in providing heat to the body, as Horvath et al. suggest (24), then the metabolic requirement is not large.

A subtle shift in circulation, dependent on the extent to which muscles are activated, might allow more of the body to participate in heat exchange. Figure 4 illustrates the extent to which this can occur and Fig. 5 illustrates a possible mechanism for an increase in contribution of stored heat during cooling. The deep temperature profiles published by several researchers (1, 3, 12, 23) should be a pattern for study on cold-acclimated animals. Aschoff's model of the exchanger system illustrates the feasibility of this speculation.

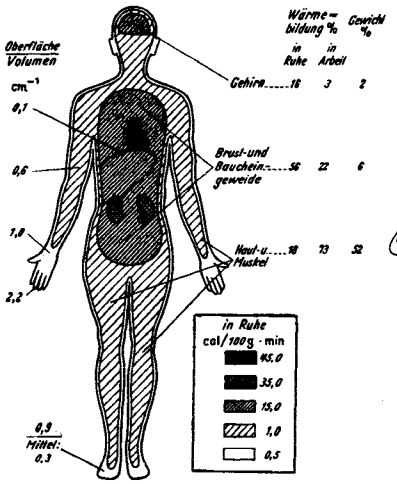

Fig. 4. Relative heat production in the various regions of the body at rest and in exercise. (From Aschoff and Wever (1)).

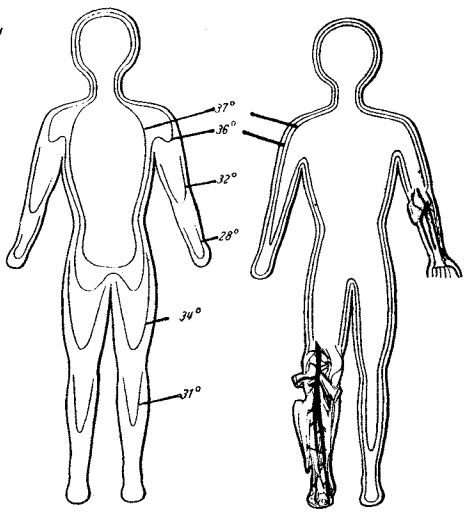

Fig. 5. Schematic of isotherms in the body at a warm temperature, right; and in a cool temperature, left. Superimposed are anatomical drawings of the circulatory system. (From Aschoff and Wever (1)).

At the cellular level the critical question is whether thermogenesis is achieved by exploiting inefficient processes. Shivering has zero mechanical efficiency - thus maximal heat, and it brings circulation near the surface as well as changes convection by motion. In non-shivering all possibilities suggested by Smith in his review (31) are shifts in response systems which may give a greater response for the same stimulus. The possibilities are: a) alternate pathways where little phosphorylation attends the transfer of electrons, b) disruption of ATP bonds or c) uncoupling.

Peripheral vasoconstriction and the response of peripheral blood vessels to catecholamines has been carefully studied by Mellander (28). Resistance and capacitance vessels are affected in a different manner by neural activity than by adrenal medullary secretions (Fig. 6). In the upper center are data indicating the relationship of blood flow to environmental temperature. Arm and leg are different from the hand or foot. Not only are resistance vessels affected by vasoconstrictor responses, but the capacitance vessels as well. This causes a shift in

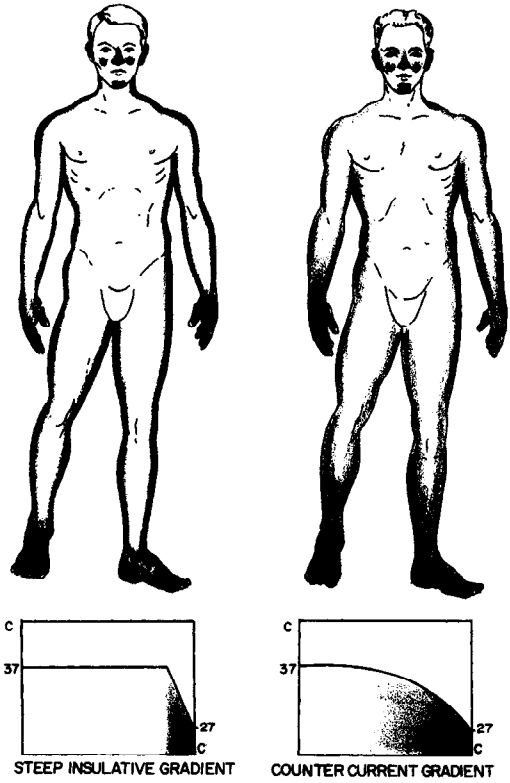

Fig. 6. Schematic illustration of manner in which heat exchange system may cause change in temperature gradient in the body.

blood volume. A detailed study of a skin-muscle tissue illustrates the difference in the effects of neural activity, adrenal medullary activation and injected epinephrine and norepinephrine (Fig. 7).

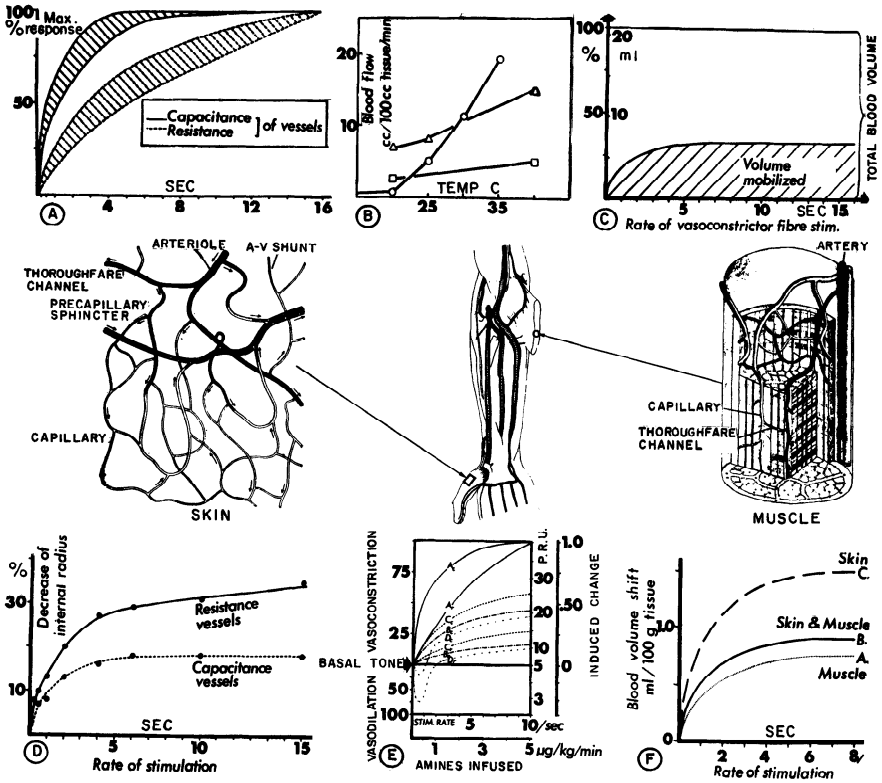

Fig. 7. A composite drawing illustrating properties of the circulatory system in skin and muscle. Upper center indicates the temperature dependence of hand or foot (O) flow in distinction to arm (△) and leg (▭). Surrounding figures illustrate the difference in response of resistance and capacitance vessels to site of stimulation of sympathetic nerves. Lower center figure summarizes the effect of stimulation of vasoconstrictor fibres, adrenal medullary nerves and infusion of catecholamines on capacitance and resistance vessels. Symp. Vasoconst. Fibres, A_r, A_c, Both Ad. Med. B_r, B_c, Upper Abscissa; 1 NA, C_r, C_c, 1 Ad., D_r, D_c, Lower Abscissa, (r, resistance; c, capacitance vessels). (After Mellander (28)).

In early studies there is an indication that hand temperature changes with chronic cold exposure, the extremity temperature being maintained after acclimatization (7, 8). Early studies on the Eskimo finger blood flows were consistent with this finding (6). Subsequent studies have not been entirely consistent. LeBlanc, Hildes, and Heroux (27) found higher finger temperatures, less pain, higher heat flow from hands of Gaspé fisherman when compared to a nonfishing group. Hellstrom and Lange-Andersen (21) found no difference in the heat output of Arctic fishermen contrary to findings on Arctic Indians (14). Krog et al. (25) studying Lapps and North Norwegian fishermen state that there are no differences in hand blood flow. Their typical temperature curves attained from controls, the Lapps and fishermen show rather striking differences in time course and temperature which are similar to those we suggested to be characteristic of acclimatization (25). Flow to the hand is dependent on body heat economy - a fact that is continually rediscovered. We (7) were able to demonstrate this effect in the experiments. The experiments are complicated due to the possibility of multiple mechanisms and lack of standard techniques.

A novel approach to acclimation has been proposed by Laties and Weiss (26). Rats were trained to bar press for heat. Acclimatized rats generally waited longer than control rats before starting to work at a steady rate for heat. The authors suggest the difference is due to the fact that subcutaneous temperature drop is less rapid in the acclimatized rats.

Conclusions from experiments on man and animals seem paradoxical. After chronic cold exposure less heat is produced at a given skin temperature and at a given rectal temperature (not necessarily less heat loss). At the same time the possibility exists for more heat to be produced from nonshivering thermogenesis. There may be differences in peripheral blood flow, though quantitatively this does not give a large increase in heat loss. There are in time significant shifts in the effector system - metabolism. Altered responses are possible via pathways which have an apparent change in sensitivities. These pathways are summarized in Fig. 8.

The hypothalamus has separate regions for those mechanisms regulating heat loss and heat conservation. The preoptic region is most thermoreceptive per se. In addition to possible reciprocal action between the two hypothalamic units, control in cold is primarily via the sympathetic pathways (vasoconstriction and nonshivering thermogenesis) and via motor pathways (shivering).

The shivering pathway is complex (22). The hypothalamic stimulus site is medial between the mamillothalamic nucleus and formix; the pathways lie lateral to the red nucleus in the lateral reticular in the pons and medulla and in the lateral white columns. The Field of Forel has a coordination influence. Sympathetic pathways related to vasoconstriction have intimate relations with the medullary vasomotor centers. Sympathetic pathways involved in metabolic heat production are not definitely described. The influence of this system is over a metabolic system that is markedly changed in several aspects.

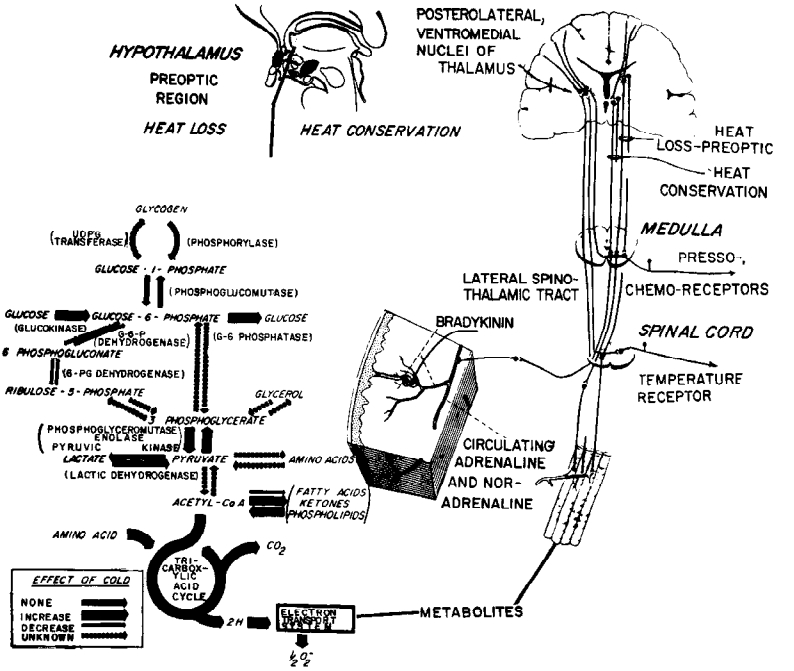

Fig. 8. CORTICAL REPRESENTATION OF SYMPATHETIC VASOCONSTRICTOR FIBERS

Motor and Premotor Cortex — Cingulate Gyrus
Orbital Cortex — Temporal Lobes — Insula

Shivering Pathway (Hemingway)
Field of Forel — Coordination
Hypothalamus - medial between mammillothalamic nucleus and fornix
Lateral to red nucleus - lateral reticular in pons and medulla
Lateral white columns

Pathways of control. Sensory inputs of cold and heat travel mainly in the lateral spinothalamic tract reaching the ventromedial nuclei of the thalamus and projecting to the sensory cortex. Some projection to the medullary reticular area and to the hypothalamus must be conjectured. The heat loss area is in the preoptic area, heat conservation in the posterior hypothalamus. The main effector system is vasoconstrictor and this must be influenced or modulated by input from presso-receptors, and from cortical projections. The exact nature of the autonomic effect on metabolism is not known. Shivering can be initiated in the hypothalamus but the pattern is influenced by inputs from the Field of Forel. The pathway is lateral to the red nucleus and in the lateral reticular in the pons and medulla and thence to the white columns (20). Biochemical systems are shown in the lower left. Changes related to the effect of prolonged cold exposure on the intermediary metabolism of rat tissue. In general, the changes apply to both liver and skeletal muscle. From Hannon (20).

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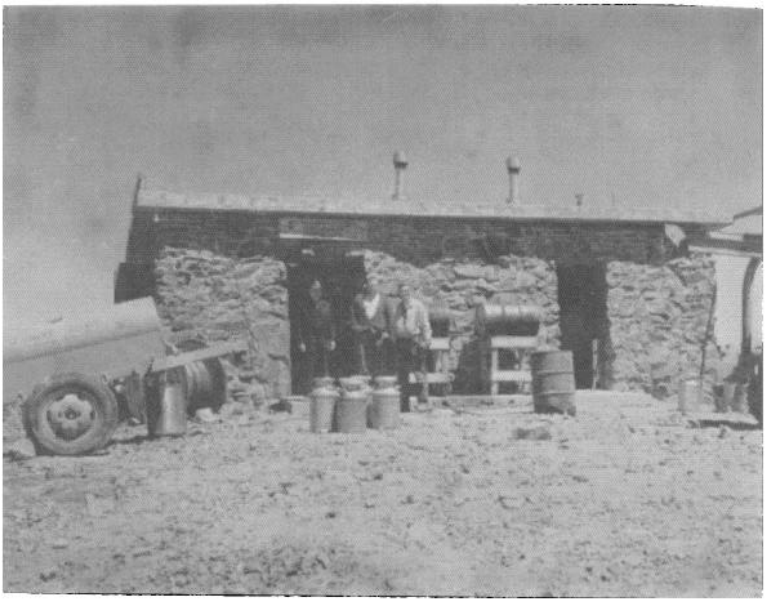
REUNION AT HIGH ALTITUDE

D. B. DILL

Last summer six of the eight surviving members of the International High Altitude Expedition of 1935 took part in a follow-up study. They were D. B. Dill, W. H. Forbes, F. G. Hall, A. Keys, R. A. McFarland, and J. H. Talbott. E. H. Christensen of Stockholm who is spending a year in India and Bryan Matthews of Cambridge were unable to join us. H. T. Edwards died in 1937 and E. S. G. Barron in 1957.

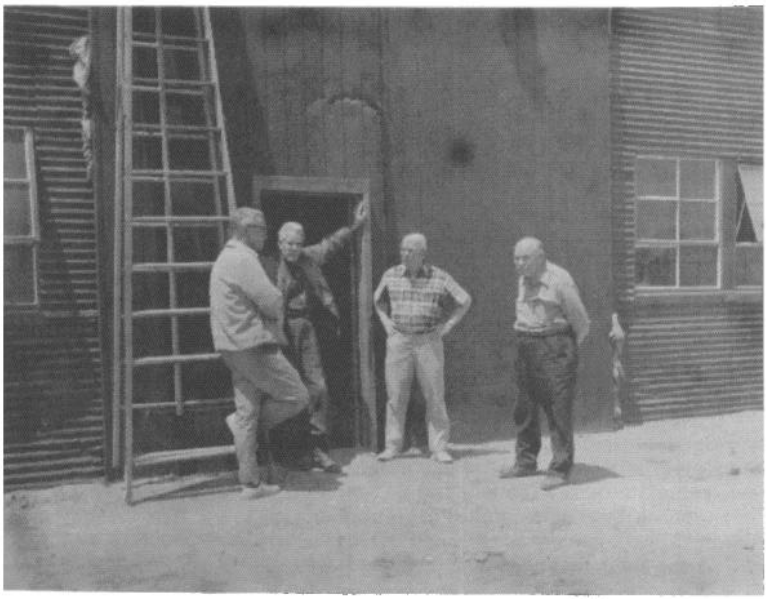
The locale was the White Mountain Research Station, California. Its mail address is Big Pine, California, altitude 1220 m, where its base laboratory is located. This is in Owens Valley which lies between the Sierra Nevada to the west and the White Mountain chain to the northeast. The Crooked Creek laboratory, 3093 m, is 33 miles northeast of Big Pine, in a sheltered valley. The upper stretches of the road to it and the slopes above it are the habitat of the bristlecone pine - the world's oldest living trees. The major laboratory, Barcroft, 11 miles north, is at 3800 m on the slope of Mt. Barcroft and above the tree-line. It is in year-around operation. The Summit laboratory 4343 m, is a substantial stone building, 15 X 30 ft., with adequate heating and insulation. It is accessible by 4-wheel-drive vehicles in the summer and fall.



Sid Robinson, Jerry L. Newton, and James W. Terman standing before the Summit laboratory.

Our major goal was to learn how successfully we would acclimatize as compared with when we were 27 years younger. Our plan for the first week of acclimatization was to make daily measurements of respiratory function, metabolic rate, pulse rate, blood pressure and body temperature, all in the basal state. To accomplish this, two graduate students from Indiana, Jerry L. Newton and James W. Terman, arrived a few days in advance and had the equipment assembled and ready for action when Forbes and I arrived on June 28. We were subjects as well as observers at Crooked Creek for two days, at Barcroft for three days and the summit for two days. Forbes remained for two more weeks and helped with similar observations on Hall and McFarland when they arrived on July 9. Hall remained until August and helped complete the series on Keys and Talbott after they arrived on July 21.

Arterial blood was obtained at least once on each subject in the basal state at each station and several times on the three of us who were there three weeks or longer. Analyses included pH at body temperature using the Beckman GS meter, hemoglobin colorimetrically, oxygen combining capacity and content, CO_2 content and combining capacity at pCO_2 = 40 mm Hg using the Van Slyke apparatus and Hall's equilibration system (2). From these analyses pO_2 and pCO_2 were calculated.



R. J. Hoch, D. B. Dill, J. H. Talbott, and F. G. Hall standing before Barcroft laboratory.

Besides observations in the basal state, performance on the bicycle ergometer was evaluated on most of us. In these studies Bruno Balke and two assistants, all of the Civil Aeromedical Research Institute of the Federal Aviation Agency, collaborated. When they left in late July, Sid Robinson arrived and continued these studies until early August.

Support for the summer's study was provided by the Federal Aviation Agency under Contract FA-2049 with Indiana University. We are indebted to Nello Pace, Director, Raymond J. Hock, Resident Physiologist, and the members of the Station staff. The latter men are characterized by versatility, enthusiasm, effectiveness, and good humor. An attractive feature of the Station is the wide range of stimulating post-prandial conversations. With physicists, geophysicists, astronomers, and a broad range of biologists the topics of conversation ranged up from the mohole to the treadmill running of Ray Hock's native deermouse and on to hot spots on the moon. One week John Severinghaus, Robert Mitchell and four associates were across the hall from us at the Barcroft laboratory. This gave us an opportunity to compare the technique we were using for pH and arterial pCO_2. The results shown in the table were gratifying.

Comparative pH_S and pCO_2 values in arterial blood at 3093 m

Subject		Hall	Terman	Newton
Date		7-19	7-18	7-18
pH_S	S	7.522	7.471	7.454
pH_S	I	7.53	7.47	7.46
Art pCO_2	S	22.4	29.1	31.2
Art pCO_2	I	20.9	28.0	29.3
Alv pCO_2	I	19.9	28.5	31.9

Note:

"S" values were obtained by John W. Severinghaus and five associates from the University of California Medical Center, San Francisco. They used the Radiometer pH meter and glass electrode and determined the arterial pCO_2 directly. Our values, labeled "I", for arterial pCO_2 were calculated from the arterial CO_2 content and pH_S. The latter was determined with a Beckman GS pH meter and glass electrode. End expiratory alveolar air was obtained during the arterial puncture and analyzed on the Haldane apparatus.

Details of our observations are being prepared for publication. In general both the objective evidence and subjective impressions pointed to a slower rate of acclimatization than in 1935. Headaches, dyspnea on exertion and night-time Cheyne-Stokes breathing with associated

loss of sleep were experienced by all of us in varying degree but to a more severe and prolonged extent than before. On the average the respiratory minute volume in rest averaged the same as has been reported by Chiodi (1) for men 30 years younger. This phase of our studies was reported to the Gerontology Society November 9, 1962, and will be published in the Society's Journal. The basal metabolic rate and the per cent of hemoglobin in the blood responded differently than in younger men. These results are still under study: related observations by others are being reviewed.

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PHYSIOLOGICAL REVIEWS TOPICS

The Editorial Board for Physiological Reviews invites members to suggest topics and authors for reviews. The Board feels that a wide range of physiological reviews by experienced authors will continue to maintain the high standards and the broad utility of the journal. Authors are invited by the Board to write reviews. A large list of topics and authors to choose from enables the Board to do a more effective job. Suggestions may be sent to Dr. C. F. Code, Chairman of the Editorial Board.

INTERNATIONAL UNION OF PHYSIOLOGICAL SCIENCES

WALLACE O. FENN
Secretary General of IUPS

This Union was formally organized in 1953 when the International Congress of Physiology met in Montreal, largely at the instigation of American physiologists, notably, M. B. Visscher, R. W. Gerard, and H. C. Bazett. Preliminary arrangements had been made three years previously at the Copenhagen Congress. Thereafter, the Union took the place of a "Permanent Committee" for the International Congresses of Physiology which in prior years had undertaken to decide where each succeeding Congress was to be held. By means of this Committee, and its less formal predecessors, International Physiological Congresses have been held every three years since 1889 with some interruptions due to two World Wars. The Twenty-Third Congress will be held in Tokyo in 1965 and the Twenty-Fourth Congress in Washington or New York in 1968.

The "Permanent Committee" was an informal, self-perpetuating committee, but the Union is composed of delegates appointed by member countries. The Union (IUPS) was accepted as a member Union of the International Council of Scientific Unions (ICSU) in 1953. ICSU served as a coordinating body for all the scientific unions and it is composed of national members representing the different member countries and Union representatives from 13 member unions. This includes the unions of Biological Sciences (IUBS), Biochemistry (IUB), Pure and Applied Chemistry (IUPAC), Pure and Applied Physics (IUPAP), and many others. ICSU is supported by grants from UNESCO which are divided among the various Unions and by dues from the Unions and member countries.

The Presidents of IUPS have been C. H. Best (1953-1956), C. Heymans (1956-1959), B. A. Houssay (1959-1962) and Sir Lindor Brown (1962-1965). Maurice B. Visscher served with distinction as the first Secretary-General from 1953-1959.

IUPS is governed by a General Assembly composed of delegates from thirty-seven member countries. The number of delegates from each country depends upon the number of physiological scientists (including pharmacology, physiology, etc.) in that country. For the first 200 members or less, there is one delegate and another delegate for each 200 additional members, up to the limit of five delegates. The Assembly elects a Council as well as the officers who, together, make up the Executive Committee. In addition to the President, presently Sir Lindor Brown of England, the officers are B. A. Houssay of Argentina, Past-President; W. O. Fenn of USA, Secretary; J. W. Duyff of Netherlands, Vice-President; H. C. MacIntosh of Canada, Treasurer; as well as an ex-officio Vice-President, C. F. Schmidt of USA, who is President of the Pharmacology Section of IUPS, known as SEPHAR. SEPHAR was organized in 1959 after much discussion. It has its own officers and Council, and functions actually as an independent Union with representation on ICSU through IUPS. The first International Pharmacological Meeting of SEPHAR was held in Stockholm in 1961 and the next one will

be in Prague in 1963. Since pharmacologists continue to participate in IUPS, they have, in effect, two international congresses every three years.

The publications of IUPS include the lectures, symposia and abstracts of papers which constitute the Proceedings of the International Congresses. The Union also prints an IUPS Personnel Directory containing the names of all delegates and the officers and addresses of the adhering societies. There is also a pamphlet containing the Statutes of IUPS. In addition, an IUPS Newsletter has just been started which will include the news of the business of IUPS and notes concerning the activities of physiologists and physiological societies in all the member countries. For this purpose, each country has a Corresponding Editor who submits news items to the Secretary. The Corresponding Editor for the USA is Dr. Verner Wulff, who is also Secretary of the National Committee for IUPS. Copies of the Newsletter are distributed to each member country with as many copies as may be needed. Some countries translate it into the language of that country for distribution and others take it as it comes, in English.

The Adhering Body for ICSU Unions is usually the National Academy of Sciences or its counterpart in each country. "Supporting Societies" are the societies of Physiology or Pharmacology or Experimental Biology, which may send representatives to some national committee. In the USA, the National Academy of Sciences is the officially adhering body and appoints members of the National Committee for IUPS from nominees submitted by the supporting societies. According to the charter, there are three members from the American Physiological Society, three from the American Society for Pharmacology and Experimental Therapeutics and two from the Society of General Physiologists in addition to a representative of the National Research Council and any officers of IUPS from the USA. The committee elects its own chairman, the present Chairman being Ralph W. Gerard. For appointment by the National Academy of Sciences, the National Committee nominates the official delegates to the General Assembly of IUPS and advises them on matters of international concern. It also arranges for travel grants for American physiologists going to the various Congresses and will be responsible for organizing the 1968 Congress which will be held in the USA on invitation from the National Academy of Sciences.

The activities of the IUPS include: 1) organization of the Congresses; 2) international symposia; 3) lecture tours to different countries and 4) participation in various international scientific projects through its representatives. The next international symposium of IUPS is being organized through cooperation with IUB (biochemistry) and will be held in London in August 1963 on the subject of Oxygen in the Animal Organism. Lecture Tours have been sent to Latin America in 1958, Japan in 1960, India in 1962, and a fourth will be sent to Yugoslavia and Rumania in 1963.

IUPS has representatives on the ICSU Committee on Space Research (COSPAR), the ICSU International Biological Project (IBP), the Council for International Organizations for Medical Sciences (CIOMS), the International Brain Research Organization (IBRO) of CIOMS, the International Cell Research Organization (ICRO) of CIOMS, the Joint Commission on

Applied Radioactivity of ICSU, the International Committee on Antarctic Research (SCAR) of ICSU, and the International Council of Laboratory Animals (ICLA). IUPS also has a joint committee with the Biophysics Union and is appointing a Commission on Nomenclature to point out areas where some international agreement on nomenclature would be helpful and a Commission on Physiological Anthropometry under the chairmanship of Prof. J. W. Weiner, of Oxford, to implement IUPS participation in the IBP (International Biological Project).

Perhaps the most important of all the functions of IUPS is the improvement of communications between physiologists of different countries and every international committee or effort contributes to this valuable objective. IUPS now includes members from 37 different countries and it is no small task for a Secretary to keep track of so many people and activities. All the officers and committee members, however, share the responsibility for making IUPS an important agency for the advancement of physiology throughout the world. IUPS has certainly great potentialities for this purpose but they are not yet being thoroughly exploited. The chief need is for more initiative, ideas and collaboration from individual physiologists from different countries. There are no paid officers of IUPS and the activities are voluntary.

ENGINEERING IN MEDICINE AND BIOLOGY

The 16th annual Conference on Engineering in Medicine and Biology will be held in Baltimore, at the Lord Baltimore Hotel, November 18-20, 1963. The Conference is sponsored jointly by the Institute of Electrical and Electronics Engineers and the Instrument Society of America. Four simultaneous tutorial courses, each having an hour on each of the three days, are planned. Subjects of these courses are Signal Theory, Analog-to-Digital Conversion, Muscle Physiology, and Receptor Physiology. Technical and commercial exhibits are planned. Further information can be obtained from George N. Webb, Johns Hopkins Univ., Baltimore.

RESPIRATION SUITE

As the Rhine courses through the Netherlands it passes the little town of Alphen. It is here that the "Respiration Suite" was born and dedicated to Wallace O. Fenn on the evening of September 12, 1962. Although it went largely unnoticed by the busy world, for those who were there it will long be cherished as an historical event and a sentimental occasion. On this evening two professional disciplines, physiology and musicology, met and celebrated. On the one hand there were several hundred physiologists from all corners of the earth, interested in the function of the lung; and on the other hand there were the finest Dutch wind instrument artists, interested in the lung as a functional device for the creation of harmonious sounds. The climax of this occasion was the World Premier of the Respiration Suite, composed for this occasion by Jurriaan Andriessen and performed by the Dutch Wind Ensemble under the baton of Thom de Klerk. However, the event which made this historical occasion particularly dear to respiratory physiologists was the dedication of the surprise Respiration Suite to Wallace O. Fenn.

But let us go back to view the events which preceded the dedication. After several days of regimented sessions, symposia, and lectures of the XXII International Congress of Physiological Sciences at Leiden, the respiratory physiologists were looking forward to Wednesday afternoon. This was the time that had been set aside for all sections to engage in informal talks, merriment and dinner.

That afternoon the respiratory physiologists assembled at a little

inn at Warmond, to the tunes of a Dutch band organ, and embarked upon two large glass-enclosed boats and sailed for several hours through a series of lakes surrounded by the picturesque Dutch countryside. The free flow of "young" and "old" genevre on board, provided by our host, J. G. Godart of N. V. Godart, contributed to the conversational mood and merriment but hardly prepared us for the welcome at the town of Alphen aan den Rijn, where as we docked band music greeted our ears. Not only were the children there to meet this strange group of international scientists but also a 35-man brass band in bright red uniforms, waving a 20-foot banner, "Welcome Respiratory Physiologists." We heard someone remark, "It looks as if respiration physiology has finally become a respectable science." With this touching and resounding welcome we disembarked, to stroll through the Avifauna Bird Reserve, beautifully landscaped and containing a magnificent collection of exotic birds, and assembled for dinner in its spacious restaurant.

Relaxing in armchairs after an excellent dinner flavored by a Riesling and a Beaujolais, we were now to be entertained by the Dutch Wind Ensemble with a concert sponsored by the Musicians Foundation "Eduard van Beinum." First we were officially welcomed by Dr. Arend Bouhuys and his Committee of the University of Leiden, who not only had organized this magnificant affair but had secretly planned with the composer, Jurriaan Andriessen, for the composition and dedication of this surprise Respiration Suite to Wallace O. Fenn. As Dr. Bouhuys reminded us and as it can now be read on the jacket of the recording of "Respiration Suite", "An understanding of the musical performance of these (wind instrument) artists, in a physiological sense, rests to a large extent on the work of Dr. Wallace O. Fenn and his associates on pressure-volume relationships of the lungs and chest, on the composition of alveolar air during breath holding, and on physiological effects of pressure breathing. In honour of his outstanding contributions to respiratory physiology, this Respiration Suite has been dedicated by its composer to Dr. Fenn.

"In the four movements of the Suite, the composer has given a musical impression of various aspects of respiratory physiology. The first movement deals with the most fundamental function of the lungs: the exchange of gas through the alveolar-capillary membrane. Movements 2 and 3 indicate the wide field of action of respiratory physiologists, working and enjoying themselves anywhere from the depth of the oceans to outer space. The suite ends with a dynamic impression of air flow into and from the lungs, the very breath of life."

The "Respiration Suite" was written for double wind quintet: (2 flutes, 2 oboes, 2 clarinets, 2 bassoons and 2 French horns.) Jurriaan Andriessen entitled the four movements: Blood-Air Dialogue, Deep Sea Saraband, Minuet at High Altitude, and Flowing Air. These descriptions are most fitting and will always remind us of Wallace Fenn's wide and varied interests and contribution to respiratory physiology.

Note: A few recordings of the Respiration Suite are still available (Produced by Riker Laboratories Ltd., Loughborough, England.) Anyone who is interested in obtaining one should write to Dr. Arend Bouhuys, Department of Physiology, Emory University, Atlanta, Georgia.

R. W. GERARD HONORED BY UNIVERSITY OF LEIDEN

In a picturesque academic ceremony in the historic St. Peter's church, held at the close of the XXII International Congress of Physiological Sciences on 17 September 1962, a signal honor was bestowed on Dr. Ralph W. Gerard. Dr. Gerard was made an honorary Doctor of Medicine of Leiden. The presentation was made by Professor J. W. Duyff, Professor of Physiology at the University of Leiden and organizer of the XXII International Congress. In his presentation he made clear the special significance of this award. He said in part:

"Our university is jealous of its honorary degrees. To be considered for such a degree, it is not sufficient for a man to have done beautiful and valuable work; it is necessary that he has broken fresh ground; that he has opened fresh and fertile fields, thereby enabling others to continue what he began. And above all it is necessary that, in the eyes of our Senate, he has, so far, been insufficiently honored.

"The fact that the Faculty of Medicine was unanimous in proposing to elevate you, Ralph Gerard, to the rank of a Leiden Doctor, and that the proposal was carried unanimously by the Senate is sufficient evidence of the fact that, in our eyes, you fulfill all three conditions. There are at least two important branches of modern neurophysiology which owe their very existence at least in part to your work; I refer to your work, with Libet, on dendritic potentials, and on that, with Ling, on the measurement of cellular resting and action potentials with the aid of micro-capillary electrodes. In addition, I would refer to your synthetic vision, thanks to which your chapter in the new Handbook is already a classic. It is this same vision which led you to propose, for the present Congress, a symposium on the processing of information in the nervous system, intended as a meeting ground for neurophysiologists, computer experts, communications engineers, information theorists, cyberneticians, in order that they get to understand each others languages; in order that these branches of science may cross-fertilize each other. This Symposium, in our opinion, again marks the opening of a new era in neurophysiology. This, then, is a fitting occasion for our University to award you one of its few and jealously guarded honorary degrees. And it is fitting that the ceremony should take place in this selfsame church where the thanksgiving service was held when Leiden was relieved, where our University was conceived, and which has, ever since, been the scene of its great celebrations.

"I now ask you to stand up to receive the honorary degree of Doctor of Medicine.

"Having acquitted myself of my appointed task, it is now my privilege to congratulate you on your newly acquired rank. You are now an honorary Doctor of Medicine of Leiden, which brings the total to two, and the grand total of Leiden honorary doctors to thirteen. You are now a member or, as we say, a civis, a citizen, of our University and, as such, bound by its rules and its traditions. In honoring you, our University has honored itself; by counting you among its citizens, it adds to its own luster."

EINTHOVEN LECTURE

Dr. Louis N. Katz, Director of the Cardiovascular Institute of Michael Reese Hospital and Medical Center, presented the Third Einthoven Lecture of the University of Leiden on the subject of "Recent Concepts on the Performance of the Heart." The lecture was also a principal address of the XXII International Congress of Physiological Sciences. The previous Einthoven Lectures were given by Dr. Paul D. White in 1956 on "The Evolution of Cardiovascular Surgery," and by Dr. Andre Cournand in 1958 on "The Pulmonary Circulation."

Dr. Katz reviewed the development of concepts in his laboratory on the inter-relations among myocardial oxygen concumption, coronary blood flow, and cardiac performance. He noted that the product of arterial pressure and heart rate serves as a first approximation to the oxygen and coronary flow requirements of the heart. Oxygen availability is ordinarily attuned to myocardial energetics over a wide range of effort and in conditions of hypoxemia. Coronary insufficiency, however, can limit oxygen consumption and lead to increased dependence of the heart on anaerobic metabolic pathways. The complete report will be published in the Proceedings of the Congress of Physiological Sciences.

At the close of the lecture, the President of the University of Leiden presented Dr. Katz with the Silver Medal of the University. This well-deserved honor signals forty years of intensive work by Dr. Katz in the physiology of the heart and the coronary circulation.

PERSONS WHO RECEIVED TRAVEL GRANTS FOR THE XXII INTERNATIONAL CONGRESS

The U. S. National Committee received funds from various national organizations and the Federation. They also received funds for the special Symposium on Information Processing. Below are listed the names of all those who received travel grants.

Alpert, N. R.
Barker, June N.
Beurle, R. L.
Bigelow, Julian
Bluemle, L. W., Jr.
Bonnycastle, D. D.
Brady, A. J.
Brauer, R. W.
Brazier, Mary A. B.
Brinley, F. J., Jr.
Broadbent, D. E.
Brooks, V. B.
Buchwald, N. A.
Bullock, T. H.
Carrasquer, Gaspar
Chapman, L. F.
Clarkson, T. W.
Clements, J. A.
Cole, L. J.
Connelly, C. M.
Cornwell, Anne C.
Corson, S. A.
Cowan, J. D.
Dagirmanjian, Rose
Danhof, I. E.
De Bon, F. L.
De Haan, R. L.
Derksen, H. E.
Dodge, F. A.
Dresel, P. E.
Du Bois, A. B.
Eccles, J. C.
Eiler, J. J.
Eisenman, George
Epstein, A. N.
Essman, W. B.
Estes, W. K.
Farhi, L. E.
Farooq, Ahmad
Featherstone, R. M.
Fenn, W. O.
Fitts, P. M.
Fleming, D. G.
Flynn, J. P.
Fregly, M. J.
Galambos, Robert
Galletti, P. M.
Gasteiger, E. L.
Glaviano, V. V.
Gordon, M. S.
Grimm, A. F.
Haddy, F. J.
Hansen, Eder
Hansen, J. T.
Harris, J. B.
Hastings, J. S.
Hill, R. B.
Hill, R. M.
Hock, R. J.
Holland, J. H.
Holz, G. G., Jr.
Huang, K-c.
Hubel, D. H.
Ichikawa, Santa
Ingraham, R. C.
Jacobs, H. L.
James, T. W.
Janowitz, H. D.
Jasper, Herbert
John, E. R.
Julian, F. J.
Kahn, A. J.
Katsuki, Yasuji
Katz, R. L.
Kellogg, R. W.
Kolff, W. J.
Krayer, Otto
Krivoy, W. A.
Lang, Stanley
Lark, K. G.
Le Brie, S. J.
Lessler, M. A.
Levine, Ruth R.
Libet, Benjamin
Luce, R. D.
MacKay, D. M.
Malvin, R. L.
Martin, A. R.

Maturana, Humberto
Maynard, D. M., Jr.
Mead, Jere
Michaelson, I. A.
Miller, N. E.
Milner, P. M.
Morgane, P. J.
Mountcastle, V. B.
Muehlbaecher, Clara
Mullins, L.
Nahas, G. G.
Neff, W. D.
Newell, Allen
O'Dell, Roberta M.
Ogden, Eric
Omachi, Akira
Oppelt, W. W.
Paganelli, C. V.
Pask, A. G. S.
Payne, L. C.
Pieper, H. P.
Pittinger, C. B.
Poggio, G. F.
Potter, G. D.
Premachandra, B. N.
Pressman, David
Radford, E. P., Jr.
Rapoport, Anatol
Robertson, J. D.
Rosenblith, W. A.
Roslamsky, J. D.
Rubini, M. E.
Said, S. I.
Salisbury, P. F.
Sanborn, R. C.
Sayre, F. W.
Scher, A. M.
Schottelius, B. A.
Schueler, F. W.
Sears, D. F.
Shanzer, Stefan
Shapiro, William
Shepherd, J. T.
Spaet, T. H.
Stamm, J. S.
Staub, N. C.
Stevens, S. S.
Stickney, J. C.
Strumwasser, Felix
Takemori, A. E.
Tanford, Charles
Teitelbaum, Philip
Tipton, S. R.
Towbin, E. J.
Visek, W. J.
Visscher, M. B.
Von Foerster, H.
Wagman, I. H.
Wiersma, C. A. G.
Wilson, Louise P.
Wong, H. Y. C.
Woodbury, J. W.
Woolley, Dorothy E.
Young, Ho Lee
Zotterman, Yngve

THE ANIMAL EXPERIMENTATION CONTROL BILLS IN THE UNITED STATES CONGRESS

MAURICE B. VISSCHER

Every physiological scientist must be concerned about the possible ultimate passage of the bills in the 87th Congress which will almost certainly be reintroduced in the 1963 session, which are aimed at regulating the conduct of all animal experimentation supported by Federal funds. These bills appear under the seemingly innocuous identical titles "A Bill... To provide for the humane treatment of animals used in experiments and tests by recipients of grants from the United States and by agencies and instrumentalities of the United States Government and for other purposes." Actually, scientists should look carefully at the fine print and the details to ascertain exactly what these bills would do if enacted into law. The texts of H.R. 1937 and S 3088 are appended to this report. It should be noted that these are companion bills in the House and Senate respectively.

The Moulder Bill (H.R. 3556), which has little chance of passage because it does not have the high-powered political support it would need, would be of little importance except for the fact that the proponents of the Griffiths-Clark Bill (H.R. 1937 and S 3088) use it as evidence that their bill is a compromise between what they call the "extreme regulators" (the Moulder bill proponents) and the "extreme opposition" (the animal experimenters, i.e., ourselves).

The Griffiths-Clark bill is a document which is said to have been prepared by Mrs. Roger (Christine Gesell) Stevens and/or her associates in the so-called Animal Welfare Institute. Physiologists will be interested in recalling that in 1952, Dr. Robert Gesell (Mrs. Stevens' father) addressed the business meeting of the American Physiological Society on the subject of alleged improper and unjustified use of animals in biological and medical research. He had previously suffered from a long period of illness and this was his last appearance at a Society meeting. At that time he accused cancer investigators of needless waste of mice in the screening of chemotherapeutic agents and other drugs, which he asserted could just as well be tested in tissue cultures or in invertebrate animals. He asserted that millions of mice were made to die unnecessarily of cancer in screening, nutrition and genetic studies. He also alleged that many other types of experiments were either unnecessary or improper, especially certain experiments on shock and on central nervous system function. In connection with his criticism of the shock experiments it is of interest that Dr. Gesell himself published a paper in the American Journal of Physiology, 1922, Vol. 51, p. 311, entitled "On the Relation Between Blood Volume and Tissue Nutrition" which was a study of hemorrhage, hypoxia and asphyxia in unanesthetized dogs and rabbits. Dr. Gesell called upon members of the Society to join him in sponsoring Federal regulation of animal experimentation patterned after British Act of 1876. His proposal was turned down.

Dr. Gesell was unquestionably a very sensitive person and believed that what he was saying was true. It happened that with two other former

presidents of the American Physiological Society the present author was asked to discuss with Dr. Gesell the details of his charges of improper and unnecessary use of animals. We spent several hours with him without obtaining any information as to specific instances of improper use of animals. Dr. Gesell was certain in his own mind that there was great waste of animal life in the execution of poorly conceived and poorly planned experiments and he thought that "regulation" would cure this evil. I have recently, in order to write this statement, read many of Dr. Gesell's earlier scientific papers. He himself used large numbers of experimental animals and it is extremely difficult to understand how he could reconcile his criticism late in his life of such a practice with his own earlier work patterns.

Mrs. Stevens is the president of the Animal Welfare League, which is a non-profit corporation which has concerned itself largely with two matters-legislation dealing with methods of slaughter of meat animals and with animal experimentation problems. Mrs. Stevens was successful in promoting the Humane Slaughter Act which was recently passed by Congress. Although some experts are dubious about the superiority of "electric stunning" as compared with other methods of humane slaughter, Mrs. Stevens gained widespread approval for her effort on behalf of humane treatment of animals by her promulgation of this Act. It must be recognized that this background is of considerable importance to her position of influence in connection with the Griffiths-Clark Bill. Both in the Congress and in press circles her standing is that of a rather sensible woman. She maintains stoutly that she is not an anti-vivisectionist and that all she wants to do is to make sure that no animal suffers unnecessarily. In this latter connection every responsible scientist would certainly agree with her stated objective, however much he might disagree with the methods she proposed to employ to achieve the objective. It is not unimportant to note that Mr. Roger Stevens, besides being an important financier, is a political figure of some influence, having been chairman of the National Finance Committee for one of the major political parties. These items of personal background information are essential to an understanding of the forces behind the Griffiths-Clark Bill. It would be unwise to underestimate the influence which Mrs. Stevens may have in promoting this bill.

Hearings on H.R. 1937 and H.R. 3556 were held on September 28 and 29, 1952 before the Subcommittee on Health and Safety of the Committee on Interstate and Foreign Commerce of the House of Representatives under the chairmanship of Congressman Kenneth A. Roberts. A 375-page report of these Hearings is available for $1 from the Superintendent of Documents, U.S. Government Printing Office, Washington 25, D.C. The majority of time at these Hearings was given over to proponents of the proposed legislation who had asked to be heard. Oral or written testimony in favor of one or both of the bills was presented by nearly 100 persons including Senator Maurine Neuberger, Mrs. Robert Gesell, Mrs. Stevens, and Dr. Leon Bernstein, a clinical physiologist attached to the V.A. Hospital and the University of California in San Francisco and a member of the American Physiological Society. The latter testified on the basis of his earlier experience in Great Britain that the British law did not impede scientific research in Britain. Two physicians from the Washington area and several from other cities testified in favor of H.R. 1937.

Mention is made of the testimony of these medical people because it is obvious that the Animal Welfare League has the support of at least a few persons with some scientific experience. There will not, in other words, be an entirely united front of medical and biological scientists against the Griffiths-Clark bill. There are obviously some few scientists who would prefer external policing to self-policing, although the number may be very small. Nevertheless, the existence of this minority must be taken into account in considering how the Congress will react to testimony on proposed legislation.

One of the highlights of the Hearings was the appearance, presumably at the invitation of Mrs. Stevens, of Major C. W. Hume (retired, Signal Corps), Secretary General of the Universities Federation for Animal Welfare (Great Britain). It has become obvious that the strategy of the proponents of H.R. 1937 is to point to the British Act of 1876 as a model which has not prevented British scientists from doing research and teaching, and which now has been accepted by them as having some virtues, along with many vices. The Major quoted numerous British scientists who supported his position. For example, Professor H. H. Krebs was quoted: "I am very glad indeed to support a move to introduce in the United States legislation on animal welfare similar to that operating in Great Britain."

Major Hume did not refrain from describing some American experiments as "so cruel that (they) shocked the moral conscience." He referred to some American scientists as "hysterically hostile" to regulatory legislation.

It is obvious that the question of whether the British law does or does not impede scientific research and teaching has become a question of some importance in connection with Congressional opinion and action. Solid evidence in this connection will be needed. We can, of course, point to the general backwardness of British surgery, for example in modern work on the open heart, on the chest, and in other fields. But equally important will be an analysis of H.R. 1937 in comparison with the British Act of 1876 to point out that the former is much more restrictive than the latter. Major Hume himself referred to some such items.

Testimony in opposition to the bills was presented on behalf of the U.S. Department of Agriculture; the Army; Health, Education, and Welfare; the Bureau of the Budget; the Veterans Administration; and NASA. The American Medical Association; the American Heart Association; the American Dental Association; the American Institute of Biological Sciences; the American Hospital Association; the Federated Societies for Experimental Biology; the American Public Health Association; the National Tuberculosis Association; and the National Society for Medical Research presented evidence against the bills either in writing or by testimony of representatives. In addition, representatives of the Animal Care Panel and of the Committee on Animal Facilities in Medical Research of the National Research Council made especially effective presentations. The opposition was alerted to the fact that Hearings would be held by the National Society for Medical Research and a number of individuals appeared before the Subcommittee on short notice. The opposition presentation

was impressive in quality and suffered in the Hearings only by virtue of the short time available for witnesses to speak.

An interesting facet of the Hearings is the fact that the out-and-out antivivisectionist societies strongly opposed the Griffiths-Clark bill. They maintained that the bill simply sanctions crimes against animals. On a slightly different key, the Humane Society of the United States strongly supported the Moulder bill as a practical measure to reduce the use of animals to the greatest degree possible.

The Washington press gave sympathetic treatment to the testimony of the proponents of the bills, and scarcely mentioned the fact that there was any opposition. The press in the country generally has given the Griffiths-Clark bill sympathetic editorial treatment. The biomedical scientific community has definitely not faced up to the fact that many people in the United States sincerely believe that present-day animal experimentation procedures are generally careless and sometimes improper. We may believe, equally sincerely, that improprieties are rare, but the fact is that we have not convinced important people that our position is correct.

It seems almost certain that Hearings on one or both of these bills will be resumed when they are re-introduced under different numbers, as they are expected to be in 1963. It is obvious to those who attended the 1962 Hearings that there is a very strong possibility that some crippling form of regulatory legislation might be recommended by the Subcommittee unless a major effort is made to mobilize public opinion against these bills.

In opposing the Griffiths-Clark bill, scientists have four major grounds for objection: The first major objection to the bill lies in its basic philosophy. It states, "That it is declared to be the policy of the United States that living vertebrate animals used for scientific experiments..... shall be used only when no other feasible and satisfactory methods can be used to ascertain biological and scientific information." By strict interpretation of this provision, virtually all animal experimentation could be stopped for years because it would take years to prove that no other method was feasible. This provision smells strangely like Dr. Robert Gesell's complaint that mice rather than tissue cultures were used for cancer chemotherapy screening. It is an unsound statement of policy. (Section 1).

The second major objection to the bill lies in the fact that a veto power over any type of animal experiment would be given to the Secretary of Health, Education, and Welfare. No mechanism is provided for appeal to any other authority. This would really be an intolerable situation. Even if one grants that he would be unlikely ever to use such dictatorial powers, the off chance remains that some future Secretary might be a "crank" or under the influence of antivivisectionists. A grant of such power is certainly unwise.(Section 9).

The third objection is the fact that, if passed, it would create a whole new set of impediments to undertaking scientific studies. It would require that a detailed plan of every experiment be on file in Washington before

one could legally begin work. Changes in experimental design could not be implemented without amendments being added to the file. Reports would have to be filed in Washington on every animal used. The expense in time and money would be very great. (Section 4 d, e, g, h, i).

The fourth major objection to the bill lies in its restrictions on the use of animals in teaching. The American people would surely not be well-served by a law which forbade a surgeon-in-training to learn whether his surgical technique on animals was compatible with survival, as this bill does. As to other uses of animals in teaching, the bill, if enacted into law, would require that every laboratory instructor obtain a license from the Secretary of HEW in order to supervise students. This bill further would require that project-plans for teaching laboratory experiments would have to be submitted to the Secretary for his approval. (Section 4 f and g).

No solid estimates as to the monetary cost of administering such a law have been made. However, it is easy to see that a large sum of money would be necessary. Many thousands of individual laboratories would have to be inspected. Tens of thousands of research and teaching personnel would need to be licensed. Tens of thousands of project-plans would have to be evaluated annually. Millions of individual animal experiments would have to be reported. Copies of every scientific paper based upon work done would have to be filed in Washington. Obviously, mountains of paper would have to be stored, hundreds of additional secretaries and clerks would have to be employed (each investigator and teacher would need additional secretarial and clerical help and the Secretary of HEW would require much of this type of help), many inspectors would have to be employed if surveillance were to be anything more than perfunctory, and scores of scientists would have to be diverted from productive work in order to evaluate project-plans, if that were to be done conscientiously.

Many millions of dollars would be required for this police work. But the obvious monetary cost would be only a trifle compared with the real total cost. The loss in time on the part of productive scientists who would have these mountains of additional paper work to produce would be great. But even more serious would be the discouragement to innovation. To quote from a letter from a distinguished British physiologist, a Nobel Laureate in neurophysiology: "When there is some doubt whether a particular kind of research or class experiment needs special certificates, etc. my own tendency has been to give up the idea and stick to what I know to be allowable. We certainly have been a good deal behind other countries in work on the central nervous system in the past 30 years." He also said, "State regulation, based on an act which dates from the last century, has made us rather unenterprising."

The greatest damage that the Griffiths-Clark bill would do might easily be to the creativeness of scientists. The stultification which such restrictive legislation would produce is hard to measure, but certain to occur. Our society has been one in which men and women have been encouraged to choose to be kind and generous and thoughtful of the rights and privileges of others. We punish criminal acts when they are perpetrated. We do not harass law-abiding citizens to prevent them from committing crimes.

I know of only one case in United States history in which a medical person was convicted of cruelty to animals. This was in the case of a surgeon in a small, non-teaching private hospital, who employed a farmer to care for dogs which he had used in surgical practice. He and the farmer were charged with cruelty in connection with their care on the farm. He pleaded guilty and paid a fine. The farmer pleaded not guilty and upon trial was acquitted. Consequently, it may be said that in no case has a charge of cruelty involving a scientist been finally upheld in a court of law.

There is no possibility of legislating kindness. Kindness is a sentiment that must be cultivated by education and example. Scientists themselves through their societies and through such agencies as the Animal Care Panel, have probably done more to improve the realities of animal care standards than a licensing and policing law could accomplish. Police systems under the force of law may satisfy laymen outside the scientific enterprise that all is well, but they will not promote attitudes of gentleness and kindness. It is imperative that the public, and especially that the members of Congress, be convinced that the standards of kindness in the care and use of laboratory animals can be improved most effectively by granting permission to relevant Federal Departments to support research and training in animal care, and by appropriating funds for the improvement of animal care facilities. As matters stand today, enactment of the Griffiths-Clark type of bill would only decrease the productivity of American science. What we need from the Congress is positive action to promote the humane treatment of laboratory animals. In obtaining such legislation, the members of the American Physiological Society and other scientific societies must take leading roles. They must educate others in the large voting public and they must provide objective information to their Representatives and Senators in Congress concerning the realities in this entire matter. Biological research, especially in medicine and agriculture is no longer a small private enterprise. It is now a big public venture involving all told more than a billion dollars a year. It is not surprising that the public should ask questions. It is our responsibility to see to it that the public is not misguided by persons like Mrs. Stevens who wrote, "It is in experimental work that the most terrible suffering is inflicted. At present, there is nothing to keep suffering within the bounds of decency and reason. Federal law is necessary to accomplish this aim." She (and unfortunately a few of our colleagues) would shackle a hundred thousand scientists to prevent one or two from committing what is already a crime. Let them first prove their charges of widespread cruelty in a court of law.

Our problem has several facets. We must on the one hand work for better conditions for animal experimentation. We must also continue our educational activities relating to humane animal care. On the other hand, we must not stand idly by while the Congress is being induced to pass legislation which would cripple biological science teaching and research in the United States. Many members of the Congress are quite well informed and will not be misled by the sentimentalists. Others, however, are far from being informed. Our task is clear.

(Copy of H. R. 1937 follows)

H.R. 1937
87th CONGRESS
1st Session

IN THE HOUSE OF REPRESENTATIVES

January 6, 1961

Mrs. Griffiths introduced the following bill; which was referred to the Committee on Interstate and Foreign Commerce

A BILL

To provide for the humane treatment of animals used in experiments and tests by recipients of grants from the United States and by agencies and instrumentalities of the United States Government and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That it is declared to be the policy of the United States that living vertebrate animals used for scientific experiments and tests shall be spared unnecessary pain and fear; that they shall be used only when no other feasible and satisfactory methods can be used to ascertain biological and scientific information for the cure of disease, alleviation of suffering, prolongation of life, the advancement of physiological knowledge, or for military requirements; and that all such animals shall be comfortably housed, well fed, and humanely handled.

SEC. 2. From and after January 1, 1962, no grant for scientific research, experimentation, testing or training, and no advance or payment under any such grant, shall be made by or through any agency or instrumentality of the United States Government, or by or through any person or agency pursuant to contract or authorization of the United States Government, to any person who uses live animals in research, experiments, tests or training unless the person applying for or receiving the grant has a certificate of compliance with this Act, issued by the Secretary of Health, Education, and Welfare.

SEC. 3. The Secretary shall, pursuant to such rules and regulations as he may prescribe, issue certificates of compliance to persons applying therefor upon proof satisfactory to him -

(a) that the applicant's proposed methods and procedures involving the use of live animals are in accordance with the requirements of this Act and the policy of the Congress:

(b) that the applicant's personnel and facilities are adequate and appropriate to enable it to comply with the requirements of this Act and the policy of the Congress stated herein; and

(c) that the applicant has complied or is equipped to comply with the requirements of section 4 of this Act.

SEC. 4. Each person to whom a certificate of compliance has been

issued, and each agency or instrumentality of the United States which uses live animals for research, experiments, tests or training shall comply with the following requirements:

(a) All premises where animals are kept shall provide a comfortable resting place, adequate space and facilities for normal exercise, and adequate sanitation, lighting, temperature control and ventilation;

(b) Animals shall receive adequate food and water and shall not be caused to suffer unnecessary or avoidable pain through neglect or mishandling;

(c) Animals used in any experiment which would result in pain shall be anesthetized so as to prevent the animals feeling the pain during and after the experiment except to the extent that the use of anesthetics would frustrate the object of the experiment, and in any event, animals which are suffering severe and prolonged pain shall be painlessly killed. Unless the project plan on file with the Secretary specifies a longer period during which animals must be kept alive for essential purposes of the experiment or test, consistent with this Act and the rules and regulations here-under, animals which are seriously injured as a result of the experiment shall be painlessly killed immediately upon the conclusion of the operation inflicting the injury;

(d) An accurate record shall be maintained of all experiments and tests performed. Procedures shall be employed to make possible the identification of animals subjected to specified experiments and tests, and a record shall be kept of the disposition of such animals;

(e) All cages or enclosures containing animals shall be identified by cards stating the nature of the experiment or test, or numbers which correspond to such a description in a record book;

(f) Painful experiments or tests on living animals shall be conducted only by persons licensed under section 5 of this Act or by students in an established training institution who are under the direct supervision of a licensee and all animals used by the students in practice surgery or other painful procedures shall be under complete anesthesia and shall be killed without being allowed to recover consciousness;

(g) No experiment or test on living animals shall be undertaken or performed unless a project-plan is on file in such form as the Secretary may prescribe, describing the nature and purposes of the project and the procedures to be employed with respect to living animals;

(h) An annual report and such additional reports or information as the Secretary may require by regulation or individual request shall be submitted to the Secretary. The annual report shall specify the number of animals used, the procedures employed, and such other matters as the Secretary may prescribe, and shall include a copy of any published work prepared or sponsored by the reporting person or agency, involving the use of live animals; and

(i) Authorized representatives of the Secretary shall be given access to the animals and to the premises and books and records of the agency or person for the purpose of obtaining information relating to the administration of this Act, and such representatives shall be authorized to destroy or require the destruction of animals in accordance with rules, regulations, or instructions issued by the Secretary, in conformance of this Act.

SEC. 5. For purpose of this Act the Secretary shall license individuals to engage in experiments or tests upon their submitting an application in such form as the Secretary shall prescribe, if the Secretary is satisfied that such individuals are qualified for such purposes.

SEC. 6. If the Secretary shall at any time determine that any agency or instrumentality of the United States has not complied with the requirements of this Act, he shall forthwith notify the head of said agency or instrumentality, and if such noncompliance is not corrected to his satisfaction within thrity days after notice is served, he shall give public notice of such noncompliance.

SEC. 7. The Secretary is authorized and directed to adopt and issue rules, regulations, procedures, and orders to carry out the provisions and purposes of this Act.

SEC. 8. The Secretary shall, subject to such terms and conditions as he may specify, suspend or revoke any certificate of compliance issued pursuant to section 3 of this Act, or any license issued pursuant to section 5 thereof, for failure to comply with any provision of this Act or the policy of the Congress stated herein, upon notice by registered mail to the holder thereof. Such notice shall set a time within which the holder may apply for reinstatement pursuant to such procedures as the Secretary may prescribe. A copy of any notice of suspension or revocation of a certificate of compliance shall be sent to all agencies which are considering or have made a grant to the holder of the certificate, and no grant or payment under a grant shall be made to any person whose certificate is suspended or revoked to the extent that the Secretary's order shall provide for the purpose of obtaining compliance with this Act.

SEC. 9. The Secretary shall refuse to accept any project-plan for filing under the provisions of subsection (g) of section 4 of this Act, or may strike any project-plan from filing if he determines that it does not conform with any provision of this Act or of the rules, regulations, procedures, and orders issued pursuant to this Act, or any of the purposes stated herein. The Secretary shall notify the person filing the project-plan of his refusal to accept it for filing or of his action in striking the plan from filing, and his action shall be effective upon notification: Provided, That the Secretary shall provide a reasonable opportunity for the person filing such project-plan to submit its justification thereof pursuant to such procedures as the Secretary may prescribe.

SEC. 10. The term "person" as used in this Act includes individuals, institutions, organizations, corporations, and partnerships.

S. 3088
87th CONGRESS
2nd Session

IN THE SENATE OF THE UNITED STATES
March 28, 1962
Mr. Clark introduced the following bill; which was read twice and

referred to the Committee on Labor and Public Welfare.

A BILL

This BILL (S 3088) introduced by Senator Joseph Clark of Pennsylvania is identical with HR 1937 introduced in the House of Representatives on January 6, 1961, by Mrs. Martha Griffiths of Michigan.

TRAINEESHIPS IN BIOMEDICAL COMMUNICATION

The Institute for Advancement of Medical Communication is reviewing candidates for its program to train workers for research and development in the field of biomedical communication. Applicants for traineeships should have a substantive educational background in the biological, physical, or social sciences, or extensive experience with information services for scientists or physicians. A Ph.D. or M.D. degree and research experience are desirable but not essential. Training stipends are flexible. Inquiries should be addressed to Dr. Richard H. Orr, Director, IAMC, 9650 Wisconsin Ave., Bethesda 14, Maryland.

ALEXIS ST. MARTIN COMMEMORATED

Following its twenty-sixth annual meeting at Laval University in Quebec, the Canadian Physiological Society on the ninth of June 1962 unveiled a tablet to the memory of Alexis Bidagan dit St. Martin, Dr. William Beaumont's patient. The Society thus brought to fruition a project which had begun in 1957 when, at the suggestion of Dr. Charles A. Mitchell, professor of bacteriology at the University of Ottawa, a committee was formed to locate the grave of Alexis St. Martin and mark it with a commemorative stone or plaque. The members of the committee were Drs. E. H. Bensley, Chairman, Roméo Boucher, Guy E. Joron, Charles A. Mitchell, Eugène Robillard, James A. F. Stevenson, and Lloyd G. Stevenson. The committee has remained unchanged from 1957 to the present except that Dr. Robillard replaced Dr. Bensley as chairman in 1960.

The first task was to determine the exact site of the grave. It was known that Alexis St. Martin had died on June 24, 1880 at St. Thomas de Joliette, a small village in the Province of Quebec adjoining Joliette about 40 miles northeast of Montreal. In the record of burial his age at death was stated to be 83 years.

Committee members visited the priests of the Parish of St. Thomas and were able to verify in the parish registers that Alexis St. Martin had indeed been buried in the cemetery there on June 28, 1880. However, the churchyard contained no tombstone bearing the name of an Alexis St. Martin dying in 1880. The parish records were of no further help. There was no record of sale of a burial plot since it was not the custom at that time to sell plots, the churchyard cemetery being available to all families in the parish.

The oldest parishioners of St. Thomas remembered Alexis but did not know where he was buried. Finally descendants were traced and in particular two granddaughters, Madame Angélina Thibault and Madame Adéline Duval. The elder of the two, Madame Angélina Thibault was seven years old when her grandfather died. She now lives in Montreal, but kindly consented to come to St. Thomas to identify the site of Alexis' grave. She stated that there was common agreement within the family on the site of the grave and pointed out a spot in the churchyard near the west end of the south wall of the church. This dear old lady, who had very discreetly whispered this secret, later confided that she had only done so after much hesitation. On the wall of the church facing this spot the Canadian Physiological Society has erected a bronze tablet.

It is interesting to note in passing that the committee succeeded in adding three years to St. Martin's life. Thanks to the help of the Institut Généalogique Drouin of Montreal, a copy of Alexis' birth certificate was obtained. This states that Alexis Bideguin (a variant of Bidagan) was born at Berthier the 18th of April 1794 and not in 1797 as was previously concluded from the record of his death. When he died Alexis was therefore 86 and not 83 as has been thought. He was the son of Joseph Pierre Bidagan (or Bideguin) and Marie Des Anges Angélique Guibeau, both of whom were born in Canada. Alexis' grandfather,

Près d'ici repose
Alexis Bidagan dit St-Martin
né à Berthier le 18 avril 1794
décédé à St-Thomas le 24 juin 1880

Patient du Dr. William Beaumont à la suite d'un accident dont il fut victim à Michillimackinac le 6 juin 1822, il consentit à se soumettre aux expériences scientifiques de son célèbre médecin.

Vous qui lirez cette inscription, offres, en souvenir de reconnaissance, une prière fervente pour Alexis St-Martin et tous les malades qui, en se prêtant aux exigences de la recherche scientifique, contribuèrent au soulagement de leurs frères et à l'avancement de la Science.

Société Canadienne de Physiologie,

juin 1962.

In Memory of
Alexis Bidagan dit St. Martin
Born April 18, 1794 at Berthier
Died June 24, 1880 at St. Thomas
Buried June 28, 1880 in an unmarked grave close by this tablet
Grievously injured by the accidental discharge of a shotgun on June 6, 1822 at Michillimackinac, Michigan, he made a miraculous recovery under the care of Dr. William Beaumont, Surgeon in the United States Army. After his wounds had healed, he was left with an opening into the stomach and became the subject of Dr. Beaumont's pioneering work on the physiology of digestion.
Through his affliction he served all humanity.
Erected by The Canadian Physiological Society,

June 1962.

Pierre Martin Bidagan was the first of the Bidagans to arrive in Canada. The surname St. Martin most probably comes from his middle name, Martin. The grandfather had come from Masparraute, a small community in the southwest corner of France which at that time was part of the diocese of Bayonne in the former province of Navarre.

The ceremony of unveiling the tablet took place on the afternoon of June 9, 1962 and brought together members of the Canadian Physiological Society, many parishioners of St. Thomas and a large number of the St. Martin family - all descendants of Alexis, several of whom had come from the United States for the occasion. Having signed the Golden Book of the parish the members were welcomed by Mr. Isadore St. Martin, great grandson of Alexis who represented the mayor of St. Thomas. Dr. Edouard Pagé, recent past president of the Canadian Physiological Society, reminded the gathering that the Society and in particular Dr. Charles A. Mitchell, deserved credit for having initiated this undertaking. Dr. Pagé drew attention to the presence of distinguished guests in the audience: Colonel Joseph R. Blair, representing the Surgeon General of the United States Army; Mr. Frederick G. Kilgour, curator of the medical library of Yale University; Dr. Cecil Pace, representing the Canada Department of Health and Welfare; Dr. Louis Poirier, representing l'Association Canadienne-Française pour l'Avancement des Sciences; Dr. Camille Roussin, Mayor of Joliette; Dr. Jacques Lussier, dean of the Faculty of Medicine of the University of Ottawa; Dr. Eugène Robillard, representing the Medical Research Council of Canada; Dr. Albert Geoffroy and Monseigneur Omer Valois of the Société Historique de Joliette, and M. l'Abbé Zotique Beauchamp, pastor of St. Thomas. Dr. Eugène Robillard then recalled the memory of Alexis Bidagan dit St. Martin. Following this Dr. Alan C. Burton, president of the Canadian Physiological Society, unveiled the tablet and delivered a short address in French. Finally the tablet was blessed by Monseigneur Omer Valois and the Reverend Father Beauchamp made a few appropriate remarks and invited the audience to enter the church for a short religious service which was enhanced by the singing of the Sisters of the Parish.

After the ceremony the members of the Society mingled with the members of the St. Martin family for numerous photographs and were guests at a civic reception in the Town Hall of Joliette. This was followed by a congenial family gathering in the home of Mr. Isadore St. Martin in St. Thomas.

In recalling the memory of Alexis St. Martin the Canadian Physiological Society wished to encompass in its tribute all the passive collaborators of science, all the patients who without prospect of immediate benefit contribute nonetheless to the growth and development of science. But most of all the society wishes to pay homage to Alexis, this uneducated man who consented to make the long trips of several months duration in the great canoes, to be separated from his family for years on end, and to endure who knows how many other forgotten discomforts, in order to be of service to that pioneer of physiology William Beaumont.

The Committee of Commemoration of
Alexis Bidagan dit St. Martin of the
Canadian Physiological Society

DR. FRANK C. MANN

Dr. Frank C. Mann, director of experimental medicine, Mayo Foundation, from 1914 to 1948 and a recognized authority on traumatic shock, the physiology of the liver, gastrointestinal surgery and surgery of the kidneys and blood vessels, died on September 30, 1962, at the age of 75 years, after an illness of several months. Throughout his mature life he had been singularly free of the petty ill-health annoyances that afflict so many people. The blessing of a robust constitution was his throughout all except the last few months of his relatively long life.

He was an experimentalist to the last, looking objectively at his own symptoms arising from a malignant tumor of the pancreas revealed by an exploratory operation. He was keenly aware of his prospects but advised his doctors he was willing to be a guinea pig for any new methods of treatment they considered worthy of trial - "If it doesn't help me it might benefit someone else." Socrates did not meet his final hours with greater fortitude and composure than did Dr. Mann. The end was precipitated by a massive gastrointestinal hemorrhage which occurred during the night. His extensive studies of the problem of shock enabled him to direct the nurses in charge just how to meet the emergency.

Dr. Mann was born on September 11, 1887, in Adams County, Indiana, the son of Louisa Kiess Mann and Joseph E. Mann. His boyhood and youth were spent on an Indiana farm. An abiding love of living things was revealed in his lifelong devotion to flower and vegetable gardening and to the breeding of chickens and Holstein cattle. To these pursuits he gave much of his time following his retirement. Success came to him in whatever area of endeavor he took an interest. His peonies, dahlias and other flowers won many prizes in local exhibits and his registered dairy cattle were worthy contenders for honors in the cattle shows of the state.

His early life on the farm was an ideal environment for a future experimental biologist, and the unusually inquiring mind with which he was endowed found much stimulation and wonderment which characterized his youth and later career.

He attended the Marion Normal College in Marion, Indiana, in 1907 and then Indiana University from which he received the degree of Bachelor of Arts in 1911, Doctor of Medicine in 1913 and Master of Arts in 1914.

In 1908 and 1909 Dr. Mann was an assistant in the department of physiology of Indiana University; from 1909 to 1912 he was a teaching fellow, then a teaching associate, in the department, and in 1913 he became an assistant in the department of clinical medicine. In 1913 and 1914 he was instructor in experimental surgery in the university.

Dr. Mann came to Rochester April 10, 1914, to serve as director of experimental medicine at the Mayo Clinic and to take charge of the pathologic anatomy service. After two years he devoted all of his attention to experimental medicine and surgery. When the Mayo Foundation

was created in 1915 as a part of the Graduate School of the University of Minnesota, he was appointed assistant professor of experimental surgery and pathology. He became associate professor in 1918 and professor in 1921. In 1933 he was appointed to the Board of Governors of the Mayo Clinic, a post he occupied until 1948 when he became senior consultant. He retired from the Mayo Clinic and Mayo Foundation on October 1, 1952.

On February 1, 1924, Dr. Mann and his laboratory staff moved into a group of new buildings located about four miles south of Rochester on land donated by Dr. Charles H. Mayo. This new institution was called the Institute of Experimental Medicine but to the people in the area it was usually referred to as the "dog farm." Dr. Mann was the director, a title that he said meant "errand boy for the laboratories." His philosophy of research would not permit him to direct his colleagues in their research efforts. He believed in a scientist following his own curiosity and light; that "an investigator worth his salt" didn't have to be told what he should do. He conceived of the Institute of Experimental Medicine as a place where biologists worked on their own "pet problems" but also brought their special training to bear on broader problems that required a cooperative effort. The exchange of ideas and the mutual assistance freely given made the spirit of the "Institute" like that of a big family. Those who were fortunate enough to participate in its research activities will remember the weekly seminars and will recall that "lift" that a word of praise from the director evoked. Dr. Mann was referred to by a number of titles that reflected his endearment to his colleagues, such as the "skipper," the "chief," and the "boss."

Dr. Mann used surgery as a tool in physiologic investigations. By postoperative study of animals after various organs or parts of organs had been removed, much insight into function resulted.

Being the pioneer in the first successful removal of the mammalian liver, he was asked just what had initiated his efforts in this area. The following is a transcript of a portion of a tape recording of an interview on his early work on the liver: "One morning in a break between our experimental work I was reading in our library... and I ran across an account of a case entitled something like this, "A Man Without a Liver," in which the pathologist had reported autopsy of a case in which he had noted a small hunk of liver made up mainly of blood vessels and bile ducts. This again fell into my old line of reasoning that probably the liver wasn't of as much importance as had been believed or as you would think in relation to its size so we started to think of some method by which we could take it out of the mammal and see how long it would live or what would happen.

"There were two problems involved in removing the liver, at least two that we could recognize. One was taking care of the portal circulation and the other was to take care of the circulation coming from the lower extremities through the vena cava. In the mammal it is very difficult and usually impossible to take the liver away from the vena cava and thus we devised an operative procedure in which we were going to make a stoma between the portal vein and the vena cava, ligate the portal

vein and have blood from the intestinal tract and other viscera flow into the vena cava and later ligate the vena cava. We found that didn't work so then we reversed the process, ligated the vena cava first and then later the portal vein, giving us a liver in which the only blood that was reaching it was coming from the hepatic artery and we could take it out as a block and have the circulation from the extremities and from the viscera maintained and thus take out the whole liver."

"Dr. Mann, do you remember anything about the first successful hepatectomy on the dog?" Answer: "The first successful one was the second one that I did. The first animal died while we were taking the liver out or shortly afterwards. It seemed to me that the reason why it died was as follows: In taking out the liver we did not use artificial respiration and the diaphragm just flopped back and forth and we could not get good respiration started again. So from then on we have always used forced ventilation for animals on which we have done hepatectomies. Now, I don't know whether that's necessary and I don't know whether my judgment in regard to the loss of the first animal was correct or not but that's what did occur. Now in the second animal we got the liver out very nicely, the animal recovered in a very short period of time and we put it in its cage and kept watching it, and I remember I went to lunch with Dr. Boothby (the late Dr. Walter Boothby) and I told him that we had a dog with the liver out and I didn't know whether the liver was a very valuable organ or not because the animal looked perfectly fine when we left for lunch. It still looked that way when we came back but in a short time later it developed characteristic symptoms which we now know are due to the low blood sugar and it went ahead and died, of course."

The foregoing quotations reveal a number of characteristics of Dr. Mann's personality. Although he was self-assured, yet he possessed a charming humility concerning what he knew. In the short paragraphs quoted above, the words "I don't know" repeatedly occur. When urged by one of his colleagues to write a book on the liver his reply was, "I don't know enough about the liver to write a book on it." He labored under the delusion that what he knew was common knowledge. One of his former teachers said to me in reference to Dr. Mann, "He was the most honest man I ever knew."

In World War I he received a commission as a second lieutenant in the Medical Corps, U.S.A., but was never called to active service. He gave courses in surgical technic to the medical officers assigned for study to the Mayo Clinic, and courses in anesthesia to the enlisted men assigned to the Mayo Clinic. He was appointed as a research worker on surgical shock by the National Research Council.

In World War II he was appointed a member of the Sub-Committee on Surgical Shock under the National Research Council. As a member of this committee from 1940 to 1943 he was given the responsibility of inspecting and reporting on the progress of work being done in all the laboratories (a total of 19) working on surgical shock which were being supported by grants under the National Research Council. He was also chairman of a committee appointed to write criteria on surgical shock for a guide to the investigators in war research on this condition.

Honors were accorded to Dr. Mann by learned societies and institutions all over the country. In 1932 he received the William Wood Gerhard gold medal of the Philadelphia Pathological Society, and in 1937 Georgetown College conferred the honorary degree of Doctor of Science on him. A year later Indiana University honored him with the degree of Doctor of Laws.

He was elected vice-president of the Western Surgical Association in 1946, and in the same year he was named an honorary foreign member of the Royal Flemish Academy of Medicine of Belgium. In 1950 he was elected to membership in the National Academy of Sciences. In 1953 he was elected an honorary fellow of the American College of Surgeons, and in 1955 he received the Julius Friedenwald medal of the American Gastroenterological Association for his contributions to the field of medicine indicated. The Phi Beta Pi professional medical fraternity established the Frank C. Mann Lectureship at Indiana University in 1942.

Dr. Mann was secretary of the American Physiological Society from 1933 to 1935 and president in 1936 and 1937. He was chairman of the Section on Pathology and Physiology of the American Medical Association in 1944, and he was appointed to the editorial board of the Annual Review of Physiology when the board was established in 1939; he also had served as chairman of this board. When the Hormel Institute was founded at Austin, Minnesota in 1941 as a part of the University of Minnesota, Dr. Mann was appointed to the board of the Institute, a post which he occupied until 1952. He was a member of the Physiology Study Section of the National Institutes of Health from 1948 to 1952, and a member of the Gastrointestinal Cancer Committee of the National Advisory Cancer Council from 1951 to 1953.

Dr. Mann alone or in association with colleagues and students contributed more than 400 papers and other writings to the medical and surgical literature. He was a member of the Western Surgical Association, the Society for Experimental Biology and Medicine, the American Gastroenterological Association, the Association of American Physicians, the American Physiological Society, the American Medical Association, the American Society for Pharmacology and Experimental Therapeutics, the American Society for Experimental Pathology, the American Society for Thoracic Surgery, the Harvey Society, the American Association for the Advancement of Science, the National Academy of Sciences, the Minnesota Academy of Science, the Alumni Association of the Mayo Foundation, the Society of the Sigma Xi, the Alpha Omega Alpha medical honor society, the Royal Flemish Academy of Medicine of Brussels and the Argentina Society of Biology. He was also an honorary member of the Indianapolis Medical Society, and associate member of the Minnesota State Medical Association and an honorary fellow of the American College of Surgeons.

Dr. Mann was married to Miss Velma J. Daniels, of Decatur, Indiana on July 21, 1914. Dr. and Mrs. Mann have three children: Dr. Frank D. Mann, of Phoenix, Arizona; Miss Ruth Mann, a member of the staff of the Mayo Clinic Library; and Dr. Joseph D. Mann of Grand Rapids, Michigan. ---(Hiram E. Essex).