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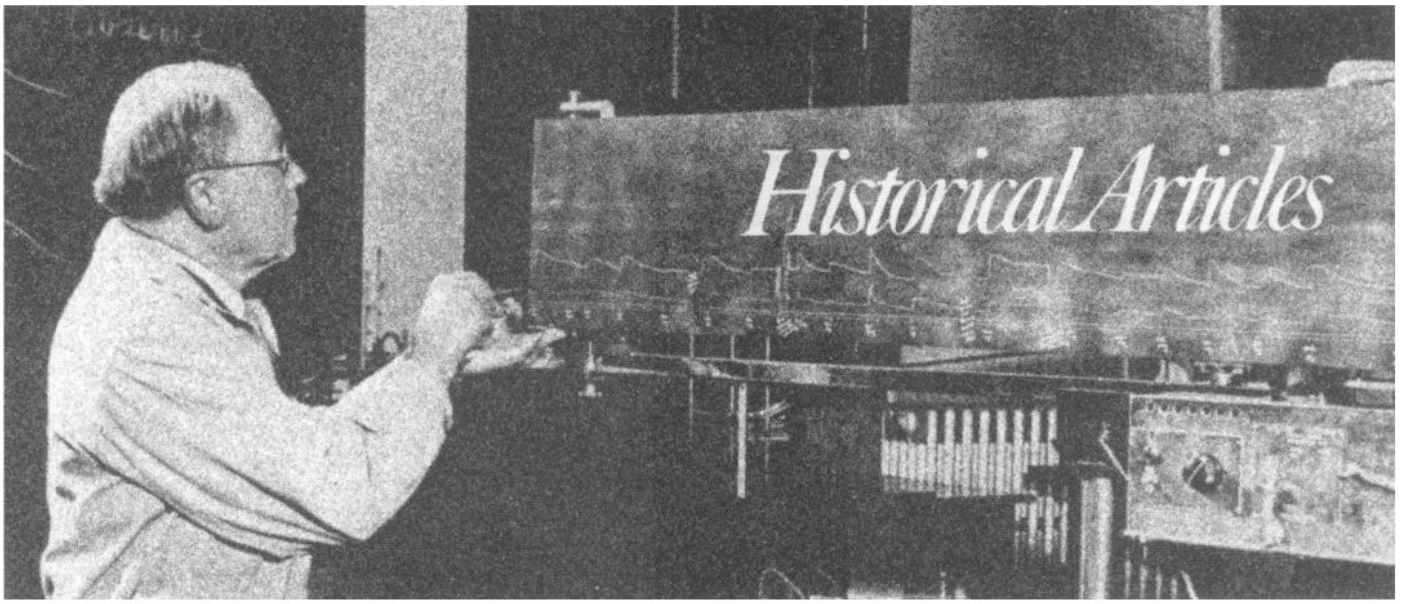
TABLE OF CONTENTS



Signs Of Anxiety, Rage, Or Distress

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This is the story of Walter B. Cannon's study of the sympathetic nervous system at the beginning and at the end of his scientific career (1). I am interested in the first because I was a gastrointestinal physiologist and in the second because, when I went to Harvard in 1943, I added Arturo Rosenblueth to my collection of characters.

Cannon began his experimental study of the effects of the sympathetic nervous system upon the digestive tract on November 28, 1897, when he was a second-year medical student at Harvard. The year before, on December 9, 1896, at the suggestion of Professor Bowditch, Cannon had begun his fluoroscopic observations on swallowing (2). Cannon finished his work on swallowing in the Spring of 1897, and he turned to the study of the stomach and small intestine. His paper (3), "The movements of the stomach studied by means of the Röntgen rays," contains his classical description of gastric peristalsis, and it marks the beginning of Cannon's masterly study of the mechanical factors of digestion summarized in his book of 1911 (4). Cannon had difficulties in his earliest work (5), "because in some animals the peristalsis was perfectly evident and in others there was no sign of activity. Several weeks passed before I discovered that this was associated with a difference in sex: the male cats were restive and excited on being fastened to the holder; the female cats, especially if elderly, submitted with calmness to the restraint, and in them peristaltic waves took their normal course."

On July 7 Cannon found "stomach still not moving. . . . Cat put down and very restless." On July 13 there was no movement in the stomach of a "big gray Tom." Two days later, "no movement – cat raging mad." And on October 23, "waves stopped after minutes. Cat raging Tom."

Those were the passively made observations. On Sunday, November 28, the Sunday after Thanksgiving, Cannon did his first experiment. He had a female cat with kittens, and he fed her 18 g of dry bread mixed with 5 g of bismuth subnitrate. At 10:04 movements of the stomach were clearly seen, and food first appeared in the duodenum at 10:15. But Cannon noticed "sev times very distinctly . . . that when cat passed from quiet breathing into rage w[ith] struggling the movements stopped entirely. . . ." Then, "Looked again – movements going ok. Cat breathing quietly. Placed handkerchief over cats mouth and stopped breathing. [Crossed out: as soon as breathing stopped – (movements stopped but constriction of the rings persisted)?] In a moment cat began to struggle. Then the handkerchief was removed and breathing resumed. . . . About ½ minute later, constriction took place at the end of pyloric region." Peristalsis started again, but it stopped in each of the eight times Cannon repeated the experiment.

When Cannon published his paper (3), the last conclusion was, "10. The stomach movements are inhibited whenever the cat shows signs of anxiety, rage, or distress." Cannon had been a pupil of William James (6), and he knew that he could not tell whether a cat was really anxious, angry, or distressed. He was not psychologically naive (7).

At the time Cannon began his work, the anatomical arrangement of the sympathetic nervous system had been determined, chiefly by J.N. Langley (8). A comprehensive account that Cannon could have read was Langley's chapter on "The sympathetic and other related systems of nerves" in Schäfer's *Text-Book of Physiology* (9). Cannon read Langley's papers in the *Journal of Physiology* and his review in *Ergebnisse der Physiologie* (10). Although some physiological actions of the sympathetic nervous system, for example, those on the heart, had been studied in some detail, Langley merely listed the effects on the muscle of the alimentary canal as being "chiefly inhibition, sometimes contraction."

Cannon continued his fluoroscopic observations until sometime in 1908. Amidst a large number of fruitful observations and the experiments suggested by those observations, Cannon

studied the role of both the craniosacral nerves and the sympathetic nerves on gastrointestinal motility. He concluded (11) "that the function of the vagi is that of setting the muscles in a tonic state, of making them exert a tension, so that in relation to the gastric contents they are as if stretched by those contents." On the other hand, depressive influences are exerted through sympathetic innervation. Naturally he was interested "to observe the result of physiological stimulation during emotion after different nervous connections had been destroyed. . . . When the vagus nerves were severed, and the splanchnic nerves alone remained, respiratory distress caused total cessation of the movements of the stomach and small intestine. Impulses along the splanchnic nerves, therefore, physiologically inhibit not only the intestine, but the stomach as well. When the splanchnic nerves were cut, and the vagi alone remained, respiratory distress had no effect upon the movements of the small intestine. . . ." Therefore, the objective correlatives are expressed chiefly through impulses in the sympathetic nerves.

Before Cannon had finished this work, T.R. Elliott (12) had observed that injection of the active principle of the adrenal medulla had no effect on an organ which had "at no time in its life been innervated by the sympathetic," but only on those which had been so innervated. He suggested that "Adrenalin (13) might be the chemical stimulant liberated on each occasion when the impulse [in a sympathetic nerve] arrives at the periphery." Accordingly, Cannon found (14) that "adrenalin, which stimulates as sympathetic impulses stimulate, causes relaxation of the entire gastrointestinal tract, except at the pyloric, ileocolic, and internal anal sphincters."

For the next thirty-five years, Cannon worked on many problems, ranging from traumatic shock to the electrophysiology of epilepsy, but his central interest remained the function of the sympathetic nervous system. Out of this work came his generalization of its emergency function. This part of Cannon's work, or at least his conclusion, is too well known to need description. If a student knows anything about Cannon, he knows three words, "Fight or flight."

When Cannon retired from Physiology at the Harvard Medical School he left Building C-1 on Longwood Avenue. He did not return until he was invited by his successor, Eugene Landis, to lecture to the first-year class. It must have been painful to return, to see the laboratories he had inhabited for thirty-six years gutted and his equipment and memorabilia discarded. However, he did return one morning in 1944, and he did lecture on the emergency function of the sympathetic nervous system. I sat in the back row along with the rest of the faculty. As I walked out with the students, I heard one say, "What's so great about that? We know all about it." He was too innocent to realize that the old man in the well of the lecture theater, an old man suffering from four kinds of cancer (15), was the one who had done it all.

In addition to being a useful mnemonic device, Cannon's conception of the emergency function of the sympathetic nervous system is a successful generalization. Like many successful generalizations, it has been subjected to captious criticism. Response to emergency is not the only function of the sympathetic nervous system; the numerous demands for adjustment occurring in minute-to-minute living can scarcely be called emergencies, and the major task of the sympathetic nervous system is to respond appropriately. Therefore, critics said, Cannon's conception is foolish. Even in an emergency, the response is not stereotyped. For example, the usual response includes dilatation of the pupil and accommodation for far vision. But consider an emergency occurring nearby in bright light; then the pupil is constricted, and the lens is shaped for near vision, although the heart may be accelerated, the clotting time reduced, and the blood sugar concentration elevated. Therefore, critics said, Cannon was wrong.

That which is not so well known is an enormous body of research on the control of the ductless glands. It is clear that in some way the thyroid gland is influenced by the nervous system. The thyroid's response to cold is an example. Cannon collected a series of anecdotes on thyroid hypertrophy immediately following severe emotional experience (16). His work, described in at least fourteen papers, didn't get very far, and in his old age Cannon regretted that he had wasted so much effort on the problem. Nevertheless, Cannon's interest in the nervous control of the ductless glands provides a striking example of how an unsuccessful piece of research can lead to a penetrating insight and how such an insight can be ignored.

Functions of the ovaries, like function of the thyroid gland, are controlled by the anterior pituitary, and the anterior pituitary, in the 1930's, was known to be influenced by the nervous system. One of Cannon's post-doctoral students, Harry Friedgood, a reproductive endocrinologist, set about trying to demonstrate that this influence is exerted through the sympathetic nervous system. He ended by concluding that the anatomical and physiological evidence for nervous control by way of either the parasympathetic or sympathetic system is, at best, inconclusive. In the atmosphere of Harvard, Friedgood couldn't quite bring himself to assert that such pathway of control does not exist. At that time, George Wislocki, Professor of Anatomy just across the quadrangle from Cannon's laboratory, demonstrated the portal vascular connection between the hypothalamus and the anterior pituitary, and he deduced that the direction of blood flow was from the hypothalamus to the pituitary gland (17). Friedgood summarized his work in a talk given during a symposium at Harvard on endocrine glands. The date was September 15, 1936. Friedgood concluded, "I conceive of this control in terms of a neuro-cellular secretion which is elaborated in the hypothalamus, whence it is transported to the anterior hypophysis via the infundibular portal system, as it has been described and interpreted by Dr. Wislocki." No one in Cannon's laboratory, or anywhere else for that matter, paid any attention, and Friedgood's paper was not published until humoral hypothalamic control of the anterior pituitary had been firmly established (18). Then it was published as an example of a missed opportunity.

Although Cannon was aware from the beginning of Elliott's suggestion that adrenalin is the mediator of sympathetic im-

Historical Articles

The photograph of Walter B. Cannon used for the masthead was kindly provided by A.C. Barger, Harvard University Medical School.

pulses, it was not until about 1930 that he undertook to demonstrate such mediation. Nevertheless, in the course of his extensive "Studies on the conditions of activity in endocrine glands" (19), Cannon encountered several signs of chemical mediation.

Cannon's chief method was to extirpate one or another part of the sympathetic nervous system and to determine the consequences. This was done in acute experiments, most often in cats, but it was also done on chronic preparations. Cannon was a superb experimental surgeon, and a cat would survive indefinitely after he operated on it. One of the sights of Harvard was a cat purring contentedly with her sympathetic nerves displayed on a card above her cage. It was in testing such chronic preparations with injections of adrenalin that Cannon discovered his Law of Denervation (20) and solved one of the scientific puzzles left over from the nineteenth century.

One such preparation was a cat with a denervated heart (21). When the extrinsic nerves to the heart were cut, one adrenal gland removed, and the other denervated, the heart was no longer under sympathetic control, and it did not increase its rate by 50 or more beats a minute when the cat was excited. However, there were occasions on which the denervated heart accelerated. In the early 1920s Cannon found (22) that about 15 s after stimulation of nerves to the liver, the denervated heart accelerated and the blood pressure rose. He demonstrated that these were due to some blood-borne substance coming from the liver, and he did a very thorough job (23) of eliminating most of the obvious candidates: glucose, amino acids, proteins, phospholipids, and so on. Having done so, Cannon said in no more than one sentence of a long paper that the substance responsible might be adrenalin.

Similar observations plus a knowledge of what was going on in Europe finally drove Cannon to attempt identification of the sympathetic transmitter.

In 1930, Cannon (24), working with two postdoctoral students, explored "the mystery of emotional acceleration of the denervated heart after exclusion of known humoral acceleration." In a cat whose heart had been denervated by "careful surgical technique," the heart accelerates greatly upon emotional stimulation. After exclusion of the adrenal glands by removing one and denervating the other, the immediate acceleration disappeared, but there was still a belated acceleration of a few beats a minute. In his search for the accelerating substance, Cannon excluded the effect of a rise in arterial pressure, a rise in temperature, escape of adrenin from the adrenal medulla, or accelerating substances from the liver, pancreas, gastrointestinal nerves, the semilunar ganglion, the pituitary gland, the male gonads, the thyroid gland, the parathyroids, or active muscle. In such a preparation, the sympathetic chain was left, but if all parts of the sympathetic chain were disconnected from the spinal cord, no acceleration occurred when the cat struggled.

At this point Zenon Bacq came from Belgium to work with Cannon, and much later he described the exciting time he had (25). Anesthesia confused the experiment, so Cannon and Bacq used a cat with chronically denervated heart but with acute spinal transection in the midthoracic region. Consequently, no anesthesia was needed when Cannon and Bacq stimulated the sympathetic nerves to the tail region. Intense piloerection, and doubtless vasoconstriction, was followed by a gradual increase in heart rate of 6 beats a minute. In addition, Cannon and Bacq measured flow from salivary glands that had been previously denervated and thus sensitized to adrenalin. To their delight, they found that salivary flow increased following piloerection. These responses were abolished if blood flow from the hind parts of the cat was hindered. Clearly, stimulation of the sympathetic chain liberated a hormone "like adrenin." Cannon, who wrote the paper rapidly (26), discussed briefly the similarity, but not having proved the identity of the hormone with adrenin Cannon called the transmitter "sympathin."

Cannon now made a trip to Europe, where he was reminded of Loewi's and Dale's work on the parasympathetic transmitter. Long before, Loewi (27) had demonstrated chemical transmission of vagal inhibition of the heart, and his "vagusstoff" had been identified as acetylcholine whose property of lowering blood pressure, but not the property of decreasing the heart rate, had been discovered by Hunt and Taveau (28). Dale, who had known acetylcholine's properties for a long time (29), was pretty certain that acetylcholine was the transmitter of all parasympathetic influences and probably the transmitter of all preganglionic impulses. Proof that this was so came later, chiefly as the result of Feldberg's experiments (30). While proof was accumulating, there was a heroic battle between the magisterial Dale and the brash young Jack Eccles over chemical versus electrical transmission of the nerve impulse (31).

When Cannon returned from Europe to undertake indentification of sympathin, he had a new collaborator, the Mexican physiologist Arturo Rosenblueth. Rosenblueth remained Cannon's disciple, collaborator, and dark angel for the rest of Cannon's life.

If you don't believe my oft-repeated declaration that most scientists disappear and are totally forgotten, ask yourself or your neighbor, "Who was Arturo Rosenblueth?" In his day he appeared to be a major physiologist. He published 74 papers in the *American Journal of Physiology* between 1930 and 1944 (32), but today only those who lived through the period have any idea who he was.

Arturo Rosenblueth was a man of striking intellectual ability. His friendship with Albert Grass and Norbert Wiener (33) testify to that. I am told he had been chess champion of Mexico, that he was a bridge player of Master rank, and that he had had difficulty deciding whether to be a physiologist or a concert pianist. He was widely and deeply read. I can't say how profound was his mathematical skill, but it was certainly far beyond that of most of the mathematically illiterate physiologists of the day.

Along with Rosenblueth's brilliance went almost total contempt for everyone who was not as brilliant as he. Rosenblueth always referred to the clinical staff as "goddamfoolclinicians," like "damnyankee." That did not endear him to powerful persons at Harvard. He said that out of the Harvard medical class there were only ten or so students worth a damn, and that was said about a class which for the next twenty years wrote a substantial portion of the *Journal of Clinical Investigation*. For those ten students, Rosenblueth conducted a special seminar, and I was allowed to sit in on it. I sought the opportunity as a means of cultivating Rosenblueth, and I was willing to put up with almost any insult for the sake of finding out what he was like. I also got him to teach me how to measure action potentials, using an early version of Albert Grass's double-pulse stimulators, and how to prepare the nictitating membrane, a major tool of physiological research in those days.

The one person for whom Rosenblueth did not have contempt was Cannon. In fact, he worshiped Cannon, and when he spoke of Cannon there was a tone of reverence in his voice. I once heard him refer to Bradford Cannon as The Son, as if Cannon were God. I suppose that Rosenblueth looked upon himself as the Holy Ghost, for he was not afflicted with disabling modesty.

Rosenblueth's devotion to Cannon was apparently reciprocated, and I have heard gossip to the effect that when Cannon retired he tried hard to have Rosenblueth appointed his successor. I never saw them together, so I can only speculate on what made so firm a bond between two such different persons.

Rosenblueth, of course, was not appointed Cannon's successor. In fact, he was not even given tenure. He must have antagonized too many "goddamfoolclinicians," but some of those who made decisions at Harvard may already have begun to see through his science. Rosenblueth had to leave Harvard some months after I got there. I inherited his desk in which he left some of his correspondence, and I saw what trouble he had in finding another job.

Cannon and Rosenblueth's methods for identifying sympathin were fundamentally different from those used by others to identify acetylcholine. Loewi, Dale, and Feldberg isolated an organ and perfused it with physiological salt solution. They then tested the perfusate for acetylcholine. The favorite test object was leech muscle, but others were used as well. Acetylcholine was identified by its properties: enzymatic hydrolysis prevented by eserine, disappearance in alkaline but not in acid solutions, and so on. Even Krayer and Verney (34), when they identified acetylcholine in mammalian coronary blood after reflex activation of the vagus, used external test objects: leech muscle and the blood pressure of a cat. Cannon and Rosenblueth, in contrast, used the animal producing sympathin as the test object. They measured arterial pressure, heart rate, pupil size, salivary secretion, contraction of the nictitating membrane, and relaxation of the nonpregnant uterus. An increase in blood pressure, heart rate, pupil size, or salivary secretion indicated stimulation by sympathin. A fall in blood pressure after ergotoxine or relaxation of the nonpregnant uterus indicated inhibition by sympathin. The sensitivity and nature of the response of test organs were often altered by means of drugs, and if physiologists think they have trouble with modern α- and β-blockers, they should try ergotoxine and yohimbine. Cannon and Rosenblueth stimulated various sources of sympathin and compared the effects. They also compared the responses to circulating sympathin with those to injected adrenalin. Cannon often wrote about injecting adrenalin, but he seldom specified its source. On a few occasions, but not on this, he said he used the Parke, Davis product (35).

It soon became clear that the responses differed, depending on the source of sympathin. For example, when hepatic nerves were stimulated, the nictitating membrane contracted, but the nonpregnant uterus failed to relax. The circulating mediator appeared to be purely excitatory. When nerves to the intestine were stimulated, the nictitating membrane contracted, and the nonpregnant uterus relaxed. The mediator appeared to be both excitatory and inhibitory. Injected adrenalin both excited and inhibited. There were many other differences, depending on the source of sympathin, the test organ, and the sensitizing drug used, all of which we youngsters were supposed to know. Cannon and Rosenblueth (36) reached an entirely reasonable conclusion, "The foregoing results are explicable on the assumption that two kinds of sympathin are produced—sympathin E, excitatory, produced by structures stimulated, and sympathin I, inhibitory, produced by structures inhibited by sympathetic impulses."

These words, "produced by," might be interpreted to mean that sympathetic nerve endings liberate one of two kinds of mediator, excitatory or inhibitory. However, Rosenblueth's rococo imagination was at work, and the theory of the two sympathins came out quite differently, "Sympathin is defined as the chemical mediator of sympathetic nerve impulses, ME or MI, which in the [Effector] cell induces the typical response, contraction or relaxation, *and which, escaping from the cell into the blood stream, induces effects elsewhere in organs innervated by the sympathetic.*" In their book on *Autonomic Neuro-Effectors* (32) it was more clearly stated that sympathetic nerve endings liberate M and that it acquires its E or I characteristics by combining in the effector cell with either E or I, upon which it becomes excitatory or inhibitory. That would be accepted today as a precursor of modern receptor physiology. But then came the odd part: after acting upon the receptor cell, sympathin E or I escapes into the blood and is then strictly excitatory or inhibitory.

Bacq wrote (25) about "this unlucky hypothesis," "It can be said that Rosenblueth was very fond of theoretical speculations and of mathematical analysis; all his work is impregnated with this spirit. When he wrote a paper or a monograph, he emphasized the discussion, not the facts. Cannon lived closer to the facts of classical physiology; he constantly invented and perfected new techniques. But neither of these two scientists had enough interest in biochemistry or pharmacology to avoid following the wrong path leading to the theory of the two sympathins."

This theory, which Rosenblueth continued to defend as late as 1950 (37), was accepted by almost no one. Bacq also wrote (25) about "the generaly poor acceptance of the two sympathin hypothesis" and that ". . . probably in 1936 W.B. Cannon failed to receive the Nobel Prize with O. Loewi and H.H. Dale, because this paper with Rosenblueth had made a bad impression on the jury." I have been told in corridor conversation that Liljestrand had said that Cannon did not get the Prize on account of his association with Rosenblueth. Perhaps. But selection of Nobel Prizemen is so capricious that the Prize hardly deserves to be considered the crown of scientific merit. I have often thought that if Cannon were to receive the Prize, he had earned it by the work described in *The Mechanical Factors of Digestion* (4).

I cannot say how far Cannon himself was taken in by sympathin E and I. He continued to work with Rosenblueth almost up to his death, and his name is first on the book expounding, elaborating, and defending the theory. In his Kober Lecture (38), Cannon spoke about the different sympathins liberated by tissues excited or inhibited, but he said nothing about the blood-borne distribution of the mediator combined with the receptor substance.

The attempt to indentify adrenalin as the sympathetic transmitter failed, because noradrenalin, or norepinephrine in the current usage, and not adrenalin is the "predominant" transmitter (39). Noradrenalin has the excitatory characteristics of sympathin E but not the inhibitory ones of sympathin I. After stimulation of the hepatic nerves, the nictitating membrane contracted, but the nonpregnant uterus failed to relax. These are the effects of circulating noradrenalin. Nevertheless, when the splanchnic nerves were stimulated after exclusion of the adrenal glands, the nonpregnant uterus indubitably relaxed. In this instance, the circulating mediator could be a mixture of adrenalin and noradrenalin.

The experiments of Cannon and Rosenblueth were further confused by something they did not anticipate: the adrenalin they injected in comparison with sympathin was probably a mixture of adrenalin and noradrenalin in variable proportions. Years after they finished their work, USP reference epinephrine was found (40) to contain 16-36% norepinephrine. One of two samples of USP epinephrine, the kind Cannon and Rosenblueth could have used, contained 12% norepinephrine, the other none.

Cannon freely admitted his mistakes (41). Years before he had trusted a mechanical device that turned out to give incorrect results. He did not live long enough to know that he shouldn't have trusted a pharmaceutical preparation.

NOTES

1. Dates and descriptions of observations are taken from Cannon's notebook preserved in the Countway Library. I have worked from a typed transcription, but I am grateful to Richard Wolfe, the Rare Books Librarian, for providing me with photographs of crucial entries.
2. Cannon, W.B., and A. Moser. The movements of the food in the oesophagus. *Am. J. Physiol.* 1: 435-444, 1898. The story of the Cannon-Moser collaboration is told in my book, *An Eagle-Feather: The Short Life of Albert Moser, M.D.* Boston: Francis A. Countway Library of Medicine, 1974.
3. Cannon, W.B. The movements of the stomach studied by means of the Röntgen rays. *Am. J. Physiol.* 1: 359-382, 1898.
4. Cannon, W.B. *The Mechanical Factors of Digestion.* New York: Longmans Green, 1911.
5. Cannon, W.B. The influence of emotional states on the functions of the alimentary canal. *Am. J. Med. Sci.* 137: 480-487, 1909.
6. Cannon, W.B. *The Way of an Investigator.* New York: Norton, 1945.
7. For example, Cannon did not believe, contrary to James and Lange, that a man is hungry because his stomach contracts. For a brief discussion of Cannon's mature views on hunger contractions, see my paper, Walter B. Cannon's contribution to gastroenterology. *Gastroenterology* 63: 878-889, 1973.
8. Langley's splendid accomplishment is summarized in his small book, *The Autonomic Nervous System.* Cambridge, UK: Heffers, 1921. There is also a brief account, *Lancet* i: 951, 1919, devoted to making certain Gaskell did not get too much credit.
9. Langley, J.N. The sympathetic and other related systems of nerves. In: *Text-Book of Physiology,* edited by E.A. Schäfer. Edinburgh: Young J. Pentland, 1900, vol. II, p. 616-696.
10. Langley, J.N. Das sympathische und verwandte nervöse Systeme der Wirbeltiere (autonomes nervöses System). *Ergeb. Physiol.* 2: 818-872, 1903.
11. This and following quotations are from Cannon's book cited in Ref. 4. Cannon's books were usually scissors-and-paste jobs in which the papers they were based on were repeated word-for-word and paragraph-for-paragraph. Consequently, the quotations are also from papers that can easily be identified through references in the book.
12. Elliott, T.R. On the action of adrenalin. *J. Physiol. London* 31: xx-xxi, 1904.
13. What to call the blood-pressure-raising principle of the adrenal gland was a problem throughout the period covered by this essay. In 1901 Takamine applied for a patent (granted in 1903) on the process of extraction and on the product which he called "Adrenalin." At first physiologists used the name without the capital A, but eventually they substituted adrenin, suprarenin, epinephrine (with and without the terminal e) or any of the thirty-four synonyms listed in the *Merck Index*. Sometimes, but not very often, they stated that they used the Parke, Davis product. In this article I quote the name used at the particular time.
14. Ref. 4, p. 208.
15. Aub, J.C., S.B. Wolbach, B.J. Kennedy, and O.T. Bailey. Mycosis fungoides followed for 14 years; the case of Dr. W.B. Cannon. *AMA Arch. Pathol.* 60: 535-547, 1955.
16. Cannon, W.B. The mechanism of emotional disturbance of bodily functions. *N. Engl. J. Med.* 198: 877-884, 1928.
17. Nowadays everyone knows about the portal system, but I indulge in an act of piety by quoting Wislocki. Wislocki, G.B., and L.S. King. The permeability of the hypophysis to vital dyes, with a study of the hypophyseal vascular supply. *Am. J. Anat.* 58: 421-472, 1936: "Evidence is adduced to demonstrate that the anterior lobe of the hypophysis, analogous to the liver, is supplied by afferent portal veins as well as by afferent arteries. . . . The portal veins have their origin in the region of the hypophyseal stalk from a plexus surrounding and in part penetrating the infundibular stem." And Wislocki, G.B. The vascular supply of the hypophysis cerebri of the rhesus monkey and man. *Res. Nerv. Ment. Dis. Proc.* 17: 48-68, 1938: "In so far as blood passes between these two regions via capillary anastomoses, the direction of flow is probably from hypothalamus toward the hypophyseal stalk."
18. Friedgood, H.B. The nervous control of the anterior hypophysis. *J. Reprod. Fertil. Suppl.* 10: 3-14, 1970.
19. Cannon wrote thirty or so papers under this general title, a practice editors frown on now.
20. Cannon, W.B., and A. Rosenblueth. *The Supersensitivity of Denervated Structures. A Law of Denervation.* New York: Macmillan, 1949). This posthumous book is largely Rosenblueth's.
21. Later work, particularly that of Donald David at the Mayo Clinic, indicates that to get complete denervation, the heart must be excised and reimplanted. Cannon did not do that.
22. Cannon, W.B., and J.E. Uridil. Some effects on the denervated heart of stimulating the nerves of the liver. *Am. J. Physiol.* 58: 353-364, 1921. Here and elsewhere I omit the general title of the series.
23. Cannon, W.B., and F.R. Griffith. The cardio-accelerator substance produced by hepatic stimulation. *Am. J. Physiol.* 60: 544-559, 1922.
24. Newton, H.F., R.L. Zwemer, and W.B. Cannon. The mystery of emotional acceleration of the denervated heart after exclusion of known accelerators. *Am. J. Physiol.* 96: 377-391, 1931.
25. Their paper is Cannon, W.B., and Z.M. Bacq. A hormone produced by sympathetic action on smooth muscle. *Am. J. Physiol.* 96: 392-412, 1931. Bacq's reminiscences are Bacq, Z.M. Walter B. Cannon's contribution to the theory of chemical mediation of the nerve impulse. In: *The Life and Contributions of Walter Bradford Cannon, 1871-1945,* edited by C. McC. Brooks, K. Koizumi, and J.O. Pinkston. New York: State Univ. of New York, Downstate Med. Center, 1975, p. 68-83.
26. According to Bacq, Ref. 25.
27. Loewi, O. Über humorale Übertragbarkeit der Herzennervenwirkung. *Pfluegers Arch.* 189: 329-242, 1921.
28. Hunt, R., and R. deM. Taveau. On the physiological action of certain cholin [sic] derivatives and new methods for detecting cholin. *Br. Med. J.* ii: 1788-1791, 1906.
29. Dale, H.H. The action of certain esters and ethers of choline, and their relation to muscarine. *J. Pharmacol. Exp. Ther.* 6: 147-190, 1906.
30. Feldberg, W. The early history of synaptic and neuromuscular transmission by acetylcholine: reminiscences of an eye witness. In: *The Pursuit of Nature.* London: Cambridge, 1977, p. 65-84.
31. Eccles, J.C. Synaptic and neuro-muscular transmission. *Ergeb. Physiol.* 38: 339-444, 1936.
32. And a book we all had to study, Cannon, W.B., and A. Rosenblueth. *Autonomic Neuro-Effector Systems.* New York: Macmillan, 1937. As for the multiplicity of papers, a student once asked Rosenblueth if he had read such-and-such a paper. Rosenblueth replied, "I don't read zem; I writes zem."
33. Albert Grass was, like his apparatus, first class, and Norbert Wiener was a genius who will be remembered by mathematicians and cyberneticists.
34. Krayer, O., and E.B. Verney. Reflektorische Beeinflusung des Gehaltes an Acetylcholin im Blute der Coronarvenen. *Arch. Exp. Pathol. Pharmakol.* 180: 75-92, 1935.
35. For example, Cannon, W.B., and H. Lyman. The depressor effect of adrenalin on arterial pressure. *Am. J. Physiol.* 31: 376-398, 1912-13. And Cannon, W.B., and H. Gray. Factors affecting the coagulation time of blood. *Am. J. Physiol.* 34: 232-242, 1914. Cannon wrote Parke-Davis with the hyphen, whereas the company called itself Parke, Davis with a comma.
36. Cannon, W.B., and A. Rosenblueth. Sympathin E and I. *Am. J. Physiol.* 104: 557-574, 1933.
37. Rosenblueth, A. *The Transmission of Nerve Impulses at Neuroeffector Junctions and Peripheral Synapses.* New York: Wiley, 1950.
38. Cannon, W.B. Sympathin E and I. *Trans. Assoc. Am. Phys.* 48: 236-238, 1933.
39. Koelle, G.B. Neurohumoral transmission and the autonomic nervous system. In: *The Pharmacological Basis of Therapeutics* (5th ed.), edited by L.S. Goodman and A. Gilman. New York: Macmillan, 1975, p. 404-431. The history is sketched in Euler, U.S. von. Twenty years of noradrenaline. *Pharmacol. Rev.* 18: 29-38, 1966.
40. Goldenberg, M., M. Faber, E.J. Alston, and E.C. Chargaff. Evidence for the occurrence of nor-epinephrine in the adrenal medulla. *Science* 109: 534-535, 1946.
41. In Ref. 6. The mistaken results were described in Cannon, W.B., and C.M. Gruber. Oscillatory variations in the contraction of rhythmically stimulated muscle. *Am. J. Physiol.* 42: 36-45, 1916-17.

Sosman Lecture

New Technology for a New Century: Walter B. Cannon and the Invisible Rays

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It was an unusual pleasure for me to accept the invitation to deliver the 19th annual Sosman lecture which honors an old friend and teacher, Merrill C. Sosman. The lecture provided the opportunity to speak of the contributions made to radiology by another teacher, fellow physiologist, and friend and colleague of Merrill Sosman, the renowned Walter Bradford Cannon, who was the George Higginson Professor and Chairman of the Department of Physiology at Harvard Medical School for 36 years.

I first came to know Dr. Sosman when I did my medical clerkship at Peter Bent Brigham Hospital in the summer of 1942. My admiration for Dr. Sosman grew during my internship there the next year. Dr. Sosman was a superb teacher who was always available for advice and help. His x-ray cubbyhole was the intellectual crossroad of Brigham. We sat in awe as he exchanged information and repartee with the clinical chiefs. My fellow students and I were convinced that Dr. Sosman was *the* master clinician of the hospital, and, as if to emphasize his role as clinician, he always appeared at grand rounds in his white coat (fig. 1). Although I held Dr. Sosman in great esteem, I had a cross to bear as well, that is, Dr. Sosman's attitude toward the student and house officer's badge of office, the stethoscope. In his office Dr. Sosman had mounted a stethoscope in a case with the inscription: "Rare and unusually well preserved fragments of an instrument known as the 'stethoscope' (diaural type circa 1918) formerly in common use in the diagnosis of pulmonary and cardiac disease. This contraption was developed by Laennec early in the 19th century and was actually in general use until the Roentgen era."

I forgave him his bias when I read Dr. Sosman's account of the uphill fight that the early radiologists had to wage to overcome the resistance to the new technology of x-ray. As Sosman [1] wrote of the era of 1896–1910—the very period when Cannon was active in the field of radiology—chest x-rays were used in the clinic:

> . . . but not much reliance was placed upon the findings, while the students were taught that careful physical examination was much more trustworthy than X-ray plates . . . . The best of the clinicians in those days were really experts in physical diagnosis, but it was the result of long years of patient study and constant practice . . . . They naturally resented any mechanical method which tended to supplant their hard-earned skills. For years the phthisiologists insisted that the physical findings were much more to be trusted than shadows on the photographic plate. Undoubtedly they were right at first, as no one had acquired the judgement and experience in reading chest X-rays in any way equal to or even approaching the clinical skill acquired by the best of the internists. Only recently the last surviving member of this cult, who believed that physical examination could detect pulmonary tuberculosis earlier and more accurately than X-ray, passed to his reward.

Sosman had noted that the ink was hardly dry on the paper reporting Roentgen's discovery in January 1896 before x-rays were being used in Boston—in

Fig. 1.—Merrill Clary Sosman, 1890–1959.

surgery, in medicine, and in physiology. Among the Boston pioneers he mentioned were Francis H. Williams, an internist at the Boston City Hospital (fig. 2); E. A. Codman, an orthopedic surgeon at Massachusetts General Hospital (fig. 3); Percy Brown at Children's Hospital (fig. 4); Walter Dodd, then the pharmacist at Massachusetts General Hospital (fig. 5); Elihu Thomson of Massachusetts Institute of Technology and the General Electric Company in Lynn, Mass. (fig. 6); and finally Walter Bradford Cannon, a student at Harvard Medical School (fig. 7). Poignantly, Sosman lamented that most of the pioneers in radiology received x-ray burns, some of them severe enough to cause death eventually.

How did Cannon, a first year medical student, become interested in x-rays and when did the brilliant idea strike him that the new technology could solve many of the problems of the physiology of gastrointestinal motility and provide a powerful new diagnostic tool for the gastroenterologist? In the fanciful world of Tom Swift, the first announcement of the discovery of x-ray would have stimulated our hero to set up his primitive apparatus the next day and make the great breakthrough. I was disappointed to learn that my hero, Dr. Cannon, a brilliant investigator and teacher, did not have the prescience to make this scientific leap. It was his aging mentor, Henry Pickering Bowditch, who had the vision. In her unpublished memoir, *Life with a Scientist*, Cornelia James, later to become Mrs. Cannon, recorded Walter Cannon's introduction to the miracle of x-rays in December 1895:

> I well remember the first time W. B. C. heard of the X-rays which were to play so important a role in his early investigation and, in the end, to be the cause of his death. It happened when I was in Radcliffe College. We were on a street car together on our way to a Lowell lecture. In front of us stood a man and a short-haired woman of masculine cast. She was talking to her escort about the 'new rays.' 'They say that you can see right through the body, make out the separate bones as if the flesh were transparent.'
>
> We looked at each other with understanding smiles, Some more Boston psychics' we thought. But the next day the papers were full of the news of the Roentgen rays and we recalled our scornful attitude with chagrin.

Walter Cannon was again exposed to the marvels of the x-rays 10 months later when he joined his classmates, including Percy Brown, in viewing Walter Dodd's x-ray demonstration given during the semicentennial celebration of Ether Day at Massachusetts General Hospital. However, Cannon made no mention of the exhibit in his diary. Brown wrote [2]: "The author will, perhaps, be pardoned a reference to his emotions on that memorable October 16, 1896, when, as a first year medical student, he was allowed to peer around the shoulders of the elders and betters at these wonders . . . in all, a great day for a very minor undergraduate, who unwittingly, was gazing from the remote past in surgery [i.e., the introduction of anesthesia] to its far future [radiology] by a mere turn of the head."

Shortly thereafter, Cannon and Albert Moser, a second year student, approached Dr. Bowditch regarding a research project. Bowditch suggested that they use the newly discovered x-ray to determine whether the Kronecker-Meltzer theory of deglutition was correct, that is, that liquids and semisolids are not conveyed down the esophagus by peristalsis, but are forcibly squirted into the stomach by the rapid contraction of the muscles of the mouth before the muscles of the pharynx or the esophagus have time to contract.

In a letter to John F. Fulton of Yale dated April 16, 1942, Dr. Cannon described the first experiment on the physiology of deglutition using the x-ray:

> The early apparatus used in Boston came altogether from Swett and Lewis of Bromfield Street. It was their tubes which were used in the early work by Dr. Codman and by me. They were trifling affairs compared with modern tubes and fairly soon became useless because of a hole burned through the very thin anode . . . . Dr. Amory Codman, however, brought a tube, a large secondary coil and an interrupter to the medical school early in December 1896. The apparatus was set up in the small prosector's room in the Anatomy Department of the Medical School at the corner of Boylston and Exeter Streets. It was thought best to try first a small dog as a subject, and I was commissioned to get a card of globular pearl buttons for the dog to swallow. Dr. Dwight, Professor of Anatomy, and Dr. Bowditch, Dr. Codman and I were the only witnesses. We placed a fluorescent screen over the dog's esophagus, and with the greenish light of the tube shining below we watched the glow of the fluorescent surface. Everyone was keyed up with tense excitement. It was my function to place the pearl button as far back as possible in the dog's throat so that he would swallow it. Nothing was seen! As intensity of our interest increased someone exploded: 'Button, button, who's got the button?' We all broke out in a sort of hysterical laughter.

Figure 8 illustrates the kind of apparatus used by Dr. Cannon. Figure 9 is a photograph of Cannon's handwritten notes on the early x-ray experiments on swallowing, including the December 9 experiment described above. On Monday, December 14, Moser and Cannon repeated the observations on a rooster whose neck was kept straight by fastening the head and body in fixed position. The pearl

Fig. 2.—Francis Henry Williams, 1852–1936.
Fig. 3.—Ernest Amory Codman, 1869–1940.
Fig. 4.—Percy Brown, 1875–1950.

Fig. 5.—Walter James Dodd, 1869–1916.
Fig. 6.—Elihu Thomson, 1853–1937.
Fig. 7.—Walter Bradford Cannon as a student at Harvard Medical School.

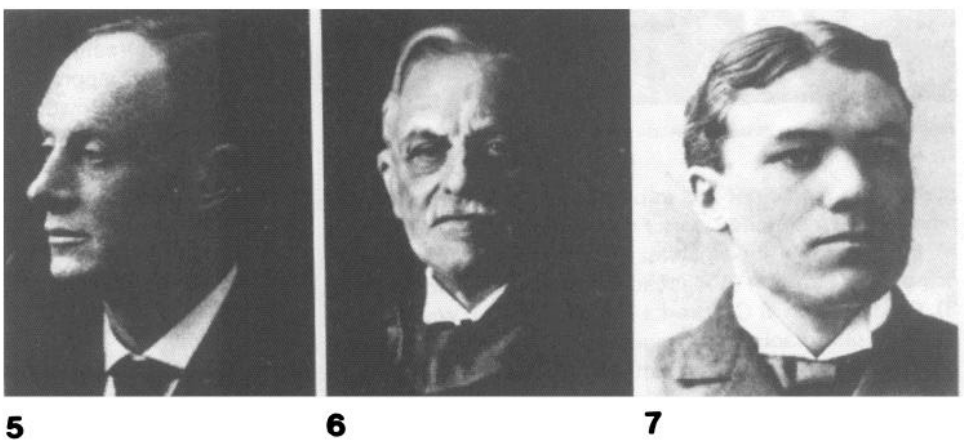
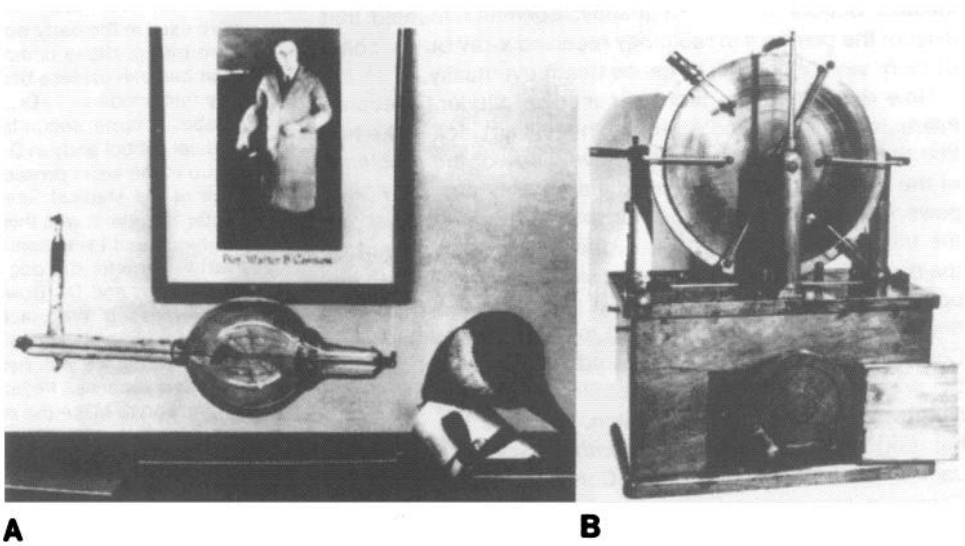


Fig. 8.—X-ray equipment used by Dr. Cannon.



button is indicated at A (fig. 9). Two days later radioopaque material, bismuth subnitrate in a gelatin capsule, was first used in the frog. When the swallowed capsules were dissolved, bismuth was liberated; in his notes I find a remark that a dark rounded area was produced as a stomach shadow. Then they procured a goose and made a box for it so arranged that the long neck reached up through the cover. A hard cardboard cover was then attached to the top of the box in such a way that it could be closed in front when surrounding the goose's neck. Thus, the goose, "with appearance of using the most stylish neckware, presented to the fluorescent screen a very satisfactory extended esophagus." At the meeting of the American Physiological Society in Boston, December 29, 1896, the phenomena of deglutition, as exhibited by the goose when swallowing capsules containing bismuth, were informally demonstrated to the

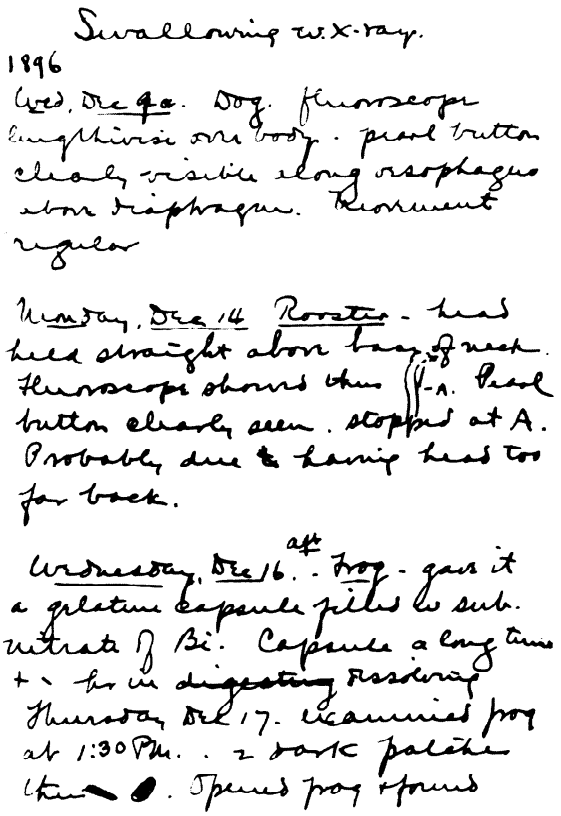
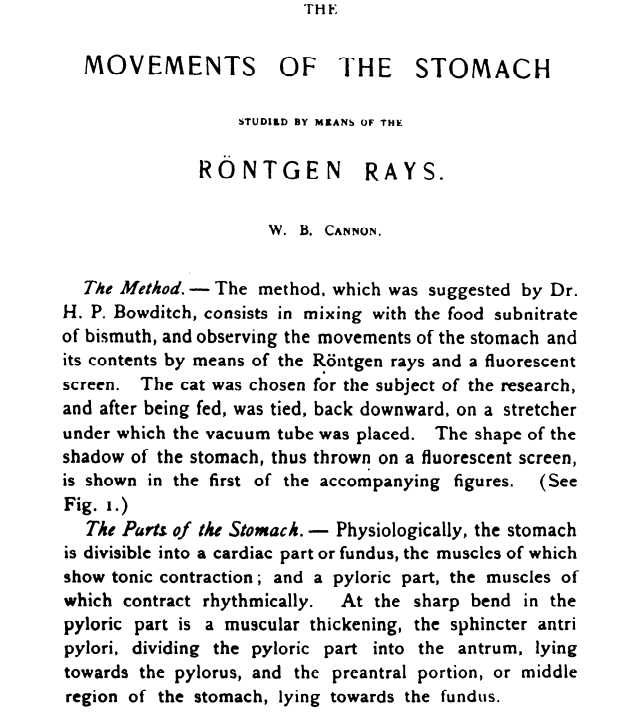

Swallowing w. X-ray.
1896
Wed. Dec 9a. Dog. fluoroscope
Esophagus and body. pearl button
clearly visible along oesophagus
above diaphragm. Movement
regular
Monday, Dec 14 Rotation - head
held straight above body of neck.
Fluoroscope shows when at A. Pearl
button clearly seen. stopped at A.
Probably due to head too
far back.
Wednesday, Dec 16. Dog - gave it
a gelatine capsule filled w. sub.
nitrate of Bi. Capsule a long time
+ - for in digesting passing
Thursday Dec 17. Examined dog
at 1:30 PM. - 2 dark patches
thin. Spread dog found

Fig. 9.—Cannon's handwritten notes on early x-ray experiments on swallowing, including the first experiment of December 9, 1896.

members by means of the roentgen rays. This was the first public demonstration of movements of the alimentary tract by use of the new technology.

In January 1897 Cannon and Moser began a series of experiments using bismuth mixed with foods of different consistencies, thus varying the physical state from a rather stiff mass to a very soft, nearly fluid mixture. In April 1897 they shifted their emphasis from studies in the goose to the mechanism of swallowing in the cat. On April 3, a cat was fed bread soaked in warm water and mixed with bismuth; about 1½ hr later peristaltic waves were clearly seen passing over the stomach, the first description of peristaltic waves passing over the organ as seen by roentgen rays in the unanesthetized animal. A preliminary note on the movements of the alimentary canal was presented to the American Physiological Society in Washington, D.C. in May 1897 by William Townsend Porter (cited in [3]). The title page of the first paper Cannon published on the movements of the stomach studied by means of roentgen rays [4] is illustrated in figure 10; the paper was published in the *Journal of the Boston Society of Medical Sciences* in February 1898, during Cannon's second year at medical school. Toilet paper, euphemistically called tissue paper in the text, was placed over the fluoroscopic screen and the outline of the stomach noted at various times after a meal was illustrated in figure 3 of the paper (fig. 11).

A more detailed paper on the same subject was published


THE

MOVEMENTS OF THE STOMACH

STUDIED BY MEANS OF THE

RÖNTGEN RAYS.

W. B. CANNON.

The Method. — The method, which was suggested by Dr. H. P. Bowditch, consists in mixing with the food subnitrate of bismuth, and observing the movements of the stomach and its contents by means of the Röntgen rays and a fluorescent screen. The cat was chosen for the subject of the research, and after being fed, was tied, back downward, on a stretcher under which the vacuum tube was placed. The shape of the shadow of the stomach, thus thrown on a fluorescent screen, is shown in the first of the accompanying figures. (See Fig. 1.)

The Parts of the Stomach. — Physiologically, the stomach is divisible into a cardiac part or fundus, the muscles of which show tonic contraction; and a pyloric part, the muscles of which contract rhythmically. At the sharp bend in the pyloric part is a muscular thickening, the sphincter antri pylori, dividing the pyloric part into the antrum, lying towards the pylorus, and the preantral portion, or middle region of the stomach, lying towards the fundus.

Fig. 10.—Title page of first paper Cannon published. (Reprinted from [4].)

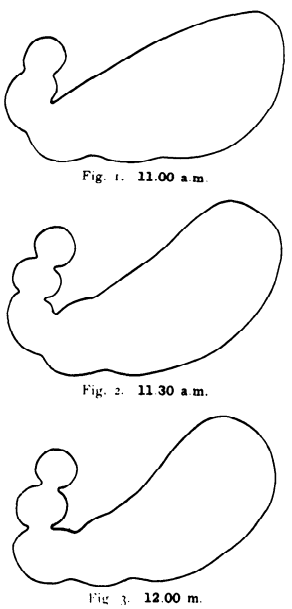


Fig. 1. 11.00 a.m.

Fig. 2. 11.30 a.m.

Fig. 3. 12.00 m.

Fig. 11.—Fluoroscopic tracings of outline of cat's stomach. (Reprinted from [4].)

in the *American Journal of Physiology* in May 1898 [5]. This classic paper reported on the movements of the various parts of the stomach in the unanesthetized animal and included studies of the pyloric sphincter. The last part of the paper, "The inhibition of stomach movements during emotion," is evidence of the kindling of Cannon's interest in psychosomatic medicine. These latter observations have

had such a profound influence on medicine that I should like to quote from Cannon's paper. He noted [5]:

> Early in the research a marked unlikeness was noticed in the action of the stomach of male and female cats. The peristalsis seen with only a few exceptions in female cats failed to appear in most of the males, although both had received exactly the same treatment. Along with this difference was a very striking difference in behavior when bound to the holder; the females would lie quiet, mewing occasionally, but purring as soon as they were gently stroked. The males, on the contrary, would fly into a violent rage, struggle to be loose from their fastenings, bite at everything near their heads, cry loudly, and resist all attempts to quiet them. On account of this difference only female cats were used for some time; and the significance at first attributed to the action of the males, was almost forgotten when the following incident recalled it, and suggested that the excitement caused the suspension of the stomach movements. On October 23, 1897, a male cat was fed at 12:00 but was not placed on the holder until 90 minutes later. The waves were passing at the rate of 6 a minute, the cat fell into a rage and the waves suddenly stopped. . . .
>
> . . . A few days later an observation on a female with kittens explained the absence of gastric movements in the males. While the peristaltic undulations were coursing regularly over the cat's stomach, she suddenly changed her peaceful sleepiness, began to breathe quickly and struggled to get loose. As soon as the change took place, the movements in the stomach entirely disappeared; the pyloric portion was relaxed and presented a smooth rounded outline. I continued observing and stroking the cat reassuringly. In a moment she became quiet and began to purr. As soon as this happened the movements commenced again in the stomach; first a few constrictions were visible near the end of the antrum, then a few near the sharp bend in the lesser curvature, and finally the waves were running normally from their habitual starting place. [5]

He noted that any distress was always accompanied by a total suspension of the motor activities of the stomach and a relaxation of the antral fibers and concluded: "It has long been common knowledge that violent emotions interfere with the digestive process, but that the gastric motor activities should manifest such extreme sensitiveness to nervous conditions is surprising."

The role of emotions in the digestive process repeatedly came to the fore while Cannon continued to work with Moser on movements of food in the esophagus. They were able to disprove the Kronecker-Meltzer thesis on deglutition and demonstrate the importance of peristalsis in movement of food down the esophagus in fowl, cat, dog, and man. However, with the early crude equipment they had available, the methods were not very successful in man in 1897 and 1898. As Cannon and Moser noted [6]:

> The X-ray method lends itself less successfully to the study of deglutition in man than in the other animals we have studied. The thickness of the thorax, the distance of the oesophagus from the surface, and the relation to dense tissues, render the observation of a swallowed mass difficult, especially when the mass is in rather rapid motion. The few observations which we have to report were made on a 7 year old girl placed in the sitting posture. Gelatine capsules containing bismuth were used for solids, and were traced to a point below the heart. The motion was very regular, and apparently due to peristalsis, for the bolus descended without a hitch or irregularity of any kind.

Later, in 1901, Francis H. Williams, in the first edition of his book, *The Roentgen Rays in Medicine and Surgery* [7], wrote: "Two or three years ago Dr. W. B. Cannon, then a student of the Harvard Medical School, who had made some excellent observations on the digestion of cats, assisted me in some observations on the stomachs of two children, the elder of whom, James W., was 10, and the younger M. W., was 7 years of age." This was the beginning of clinical gastrointestinal radiology.

Fig. 12.—Photograph of original tracings from Cannon's studies on gastrointestinal motility. (From archives of Countway Library.)

A long series of studies on gastrointestinal motility then ensued, and one of the original tracings preserved in the archives of the Countway Library is shown in figure 12. Cannon then went on to study the factors controlling the pyloric sphincter. Finally, in April 1909, Cannon published another pioneering paper, "The Influence of Emotional States on the Function of the Alimentary Canal" [8]. Here Cannon reviewed Pavlov's work on psychic gastric secretion, Pflüger's research on the inhibition of gastrointestinal motility produced by sympathetic nerve stimulation, and his own previous studies in animals. He emphasized that most of the emotional factors were also important in alimentary function in man and described a case in which he was associated:

> Indeed, the feeling of heaviness in the epigastrium commonly complained of by nervous persons may be due to the stagnation of food. That such stagnation occurs is shown by the following case: A refined and sensitive woman who had had digestive difficulties, came with her husband to Boston to be examined. They went to a hotel for the night. The next morning the woman appeared at the consultant's office an hour after having eaten a test meal. An examination of the gastric contents revealed no free acid, no digestion of the test breakfast, and the presence of a considerable amount of the supper of the previous evening. The explanation of this

stasis of the food in the stomach came from the family doctor, who reported that the husband had made the visit to the city an occasion for becoming uncontrollably drunk, and that he had by his escapades given his wife a night of turbulent anxiety. The second morning, after the woman had had a good rest, the gastric contents were again examined; the proper acidity was found, and the test breakfast had been normally digested and discharged.

Cannon became more and more intrigued by the effects of emotional factors on gastrointestinal motility while he was writing *Mechanical Factors of Digestion* [9], published in 1911 and summarizing 15 years of his work on x-ray of the gastrointestinal tract. The book remains a classic of gastrointestinal physiology and radiology. On October 1, 1910, Cannon wrote in his diary: "In morning wrote on end of chapter 12 and suggested research on adrenalin during emotion to Hoskins (by letter)." This entry and the letter to Roy G. Hoskins, who had just received his Ph.D. from the department of physiology, must have been the first written statements of Cannon's shift of interest to the study of the sympathetic nervous system.

Cannon, assisted by Daniel De La Paz, a research fellow from the Philippines, began a series of studies on adrenalin release into the blood during stress. In 1911 they published their paper on "The Emotional Stimulation of Adrenal Secretion" [10]. This was the first of a remarkable series of publications that led to Cannon's elaboration of the emergency function of the sympathetic nervous system. In 1921, at the same time that Otto Loewi was demonstrating the transmission of the peripheral effects of the vagus nerve by a chemical mediator, Cannon and Joseph Uridil reported the acceleration of the denervated and sensitized heart when the hepatic nerve was stimulated [11]. As Sir Henry Dale noted [12]: "Similar effects at a distance, transmitted by the circulation, were later recognized by Cannon and his colleagues as a result of stimulating other sympathetic nerves; and it seems clear that he had not been far from the discovery which later gained Loewi the Nobel Prize." Indeed, we have Cannon's own reaction to the announcement of the 1936 Nobel Prize in a letter to Uridil dated December 21, 1935: "If only we had taken the hint that came from the observations which we made in 1920, we should have been credited with a quite novel demonstration in the history of physiology. As it was, Loewi made his observations about the same time, and by following them up has the credit of establishing the fact of chemical mediation of nerve impulses."

Cannon's extraordinary manual dexterity and surgical skill enabled him to remove the entire sympathetic nervous system, a procedure that gradually led to the development of his ideas concerning the maintenance of a steady state in the internal environment. In a series of investigations continuing for almost a decade, Cannon showed that the function of the autonomic nervous system is the maintenance of a uniform condition in the body fluids, an elaboration of Claude Bernard's concepts of the constancy of the *milieu intérieur*. Cannon later coined a word to describe his concept, *homeostasis*, from the Greek *homeo* (like or similar) and *stasis* (condition) [13–15].

On June 11, 1927, Merrill Sosman wrote to Cannon informing him of his election to honorary membership in the New England Roentgen Ray Society. Cannon replied on June 13: "It was a great pleasure to receive your letter . . . . I look back upon the work which I did in the early days of roentgenology as if it were done by another person, so long ago were my experiences . . . ."

In 1934, Dr. Cannon sought Dr. Sosman's advice on a draft of his Caldwell lecture. The annual Caldwell lecture honors the physicist-turned-physician, Eugene Wilson Caldwell, a pioneer in radiology and former president of the American Roentgen Ray Society. Dr. Sosman replied to Dr. Cannon:

> My suggestion would be that you might with benefit deal a little more in detail on the effect of the emotions not only upon the gastro-intestinal tract but also upon the bodily organism as a whole and upon the individual organs and systems. Those of us in the teaching centers know your valuable works on this relation but I am sure that the majority of your audience in Pittsburgh will appreciate and profit by a sort of a resume of what you have done in this field . . . .
>
> . . . My minor contribution to your essay is in support of your statements as to the psychic factor in the control of gastric emptying. It has been our custom for several years when patients show weak peristalsis and poor emptying to talk to the patient while fluoroscoping them, particularly about some food which they like. It is quite striking to see the prompt increase in peristalsis and the opening of the pylorus when the particular food the patient craves is verbally offered to them. Women as a rule respond to salads, pickles and desserts. Men as a rule respond to roast beef, ham and eggs, or mince pie and ice cream.

Cannon chose as his title for the Caldwell lecture "Some Reflections on the Digestive Process" [16]. He was introduced by Percy Brown, his classmate and author of the soon-to-be published *American Martyrs to Science through the Roentgen Rays* [2]. Cannon began his lecture with a statement about:

> . . . Dr. Caldwell who died a martyr in his services to the progress of medicine. In the early days the pioneers in roentgenology had no inkling of the dangers to which they were subjected. Well do I recall the sage advice of Professor Henry P. Bowditch, when, in the spring of 1897, I showed him an area on my hand from which the skin, exposed repeatedly to the strange new rays, had come away in successive layers. He remarked that we were employing a quite novel agent which might have very dangerous properties and that we ought to be cautious until we learned more about its nature. At the time I was an eager first-year medical student, not pleased with being checked in my purposes. In order to avoid further harm I surrounded the tube with a metal box, leaving a small aperture at the top through which the rays could pass. The suggestion had been offered that the burns might be due to the brush discharge of the high tension current; you will be amused to learn that as a special precaution I grounded the metal box by a wire connection attached to the water pipes! Thus quite early I was protected. Consequently today only a few scars remain, although during a decade, I often sat for hours together watching with the fluoroscope the processes of digestion in different parts of the alimentary canal.

How well was Dr. Cannon really protected? In a letter to Walter C. Alvarez dated November 7, 1932, Dr. Cannon mentioned that he had also received rather severe burns on his knee from sitting close to the x-ray tube. The amount of gonadal radiation must have been enormous and it was little wonder that the Cannons, keenly desirous of starting a family, had no children until the administrative duties of the department, assumed in 1906, had taken Cannon away

from much of his radiologic research on the digestive tract. In 1907 a son was born. In 1909 the Cannons had their first daughter, followed by three more girls in 1911, 1912, and 1915. Marion Cannon Schlesinger, the fourth of the Cannon children, in her delightful Cambridge memoir, *Snatched from Oblivion* [17], noted the reaction to this parade of children by one of their neighbors on Divinity Street, a Mrs. Peirce, "a most gentle and proper lady, [who] thought it vulgar of Mrs. Cannon to have so many children."

In the summer of 1931, when Cannon was 59 years old, and 23 years after he had stopped his exposure to x-ray, there appeared itching of the skin and fiery red papular cutaneous lesions on his back, chest, thighs, knees, and elbows. The intense itching led to many sleepless nights and a chronic state of fatigue. On December 24, 1931, he wrote to Dr. Alvarez again saying:

> My erythema which you are so kind to inquire about continues with little change. I have had some relief from the itching by exposing my skin to ultra-violet light—just enough to produce a mild burn. Whether there will be after-effects from this treatment, I do not know. For the present we are assuming that the *Bacillus coli* may be the devil in the machine and we are proceeding about the same as in October. The possibility of getting relief by direct treatment of the skin was first suggested by Dr. [David] Edsall, who advised a hot shower followed by a cold. I have modified this to a luke-warm shower followed by a cold and find that it is a considerable relief, though of short duration. The exposure to ultra-violet light has given me relief for 4 or 5 days.

In 1932 a biopsy of the skin of Dr. Cannon was taken at Peter Bent Brigham Hospital and examined by his friend, Burt Wolbach. Dr. Wolbach made the diagnosis of mycosis fungoides, but in the hope that he might be mistaken, he sent the slides to several dermatologic pathologists. Unhappily, they confirmed his diagnosis. When Dr. Wolbach informed Joseph Aub, one of Cannon's closest associates and his personal physician for many years, of the diagnosis, they decided not to tell Dr. Cannon the nature of his illness. However, they did speak with his sister, Ida Cannon, who was director of social services at Massachusetts General Hospital. Some months later they also informed Mrs. Cannon of the diagnosis but the information was withheld from Dr. Cannon for many months. However, when Dr. Cannon became aware of the nature of his illness, "with the objectivity so well known to his friends and associates, he suggested that repeated biopsies be made whenever they could provide information on the development of this incompletely understood condition" [18].

Dr. Cannon reacted to the knowledge of his illness by resigning from his various dinner clubs whose meetings he had always enjoyed. Several months later he asked Dr. Aub if he could rejoin his colleagues, for he was quite lonely. Despite the illness he continued to work full time until his retirement in 1942.

In 1945 Cannon went to Mexico City to work with his former associate, Arturo Rosenblueth. There he developed a leg infection that necessitated his return to Boston where Dr. Aub hospitalized him at Massachusetts General Hospital. Upon his release from the hospital he went to his summer place in Franklin, N.H. to recuperate. On September 30, 1945, Dr. Aub was on his way to inspect his herd of deer with Don Fawcett, professor of anatomy. Dr. Aub was studying the hormonal control of antler growth and the possible relation to neoplastic growth. In Saul Benison's unpublished oral history he quoted Dr. Aub:

> I went down to the train and was just about to get on the sleeper—it was late in the evening—and I said to Fawcett, 'I have a feeling that Cannon's ill and I somehow have a feeling that he's going to die tonight. I think I won't go with you. You go up and do this and I will go up and see how Cannon is.'
>
> I got there quite late. He was very delirious, very sick and died about 3 hours after I got there. It was just a feeling that I ought to go up there. It was very lucky for Mrs. Cannon was all alone with Dr. Cannon in the house there.

Dr. Cannon died just short of his 74th birthday.

In 1955 Aub, Wolbach, Kennedy, and Bailey published a paper, "Mycosis Fungoides Followed for 14 Years," with the subtitle, "The Case of Dr. W. B. Cannon" [18]. In the introduction, they gave an account of the course of the illness and the repeated skin biopsies taken at Dr. Cannon's suggestion. They wrote: "The material thus obtained over a period of 14 years and that from the necropsy were carefully prepared for histologic study. They now afford an opportunity to trace the sequences involved in mycosis fungoides with development of lymphatic leukemia, . . . and to consider the relation of the condition to exposure to unfiltered X-radiation. Therefore, the record demands careful reporting, and it is coupled with Dr. Cannon's name because a great man who taught so many students so much should also be associated with the record of his instructive illness."

I have sought the advice and help of a number of my colleagues concerning this most interesting case, to determine whether, in the light of more recent information, the diagnosis would still hold true. Dr. Samuel Hellman, professor of radiation therapy at Harvard, wrote to me:

> I would agree almost completely with the interpretation of Dr. Aub and his colleagues . . . . The appearance of lymphocytosis does not mean leukemia but can mean that peripheral blood manifestations uncommonly seen in mycosis fungoidis which, when they are dominant, are described as Sezary's Syndrome. I know of no specific cases of this disease being induced by radiation. However, the history of the extensive radiation exposure and the development of radiation induced basal and squamous cell carcinomata makes this a likely presumptive diagnosis.
>
> All in all I would say that Dr. Cannon had mycosis fungoides with Sezary's syndrome and this was likely induced by radiation as were almost certainly his skin carcinomata . . . .

To the radiologists in the audience it comes as no surprise, I am sure, that many pioneers in clinical radiology died as a result of radiation-induced injury. But, why was the incidence of radiation damage so much lower among physicists? Otto Glasser, a well-known biophysicist, noted that [19]: "It is interesting that Röntgen himself made all of his experiments with the X-rays in a big zinc box . . . .These precautions probably were taken so that he could define his X-ray beam at will with diaphragms in the box and also to prevent fogging the photographic plates used in his experiments. By these experimental precautions, he himself was completely protected at the same time. Some other pioneers were equally careful."

In his *American Martyrs to Science through the Roentgen Rays* [2], Percy Brown stated that within a period of 90 days after Roentgen's preliminary communication suspicion was

aroused in the minds of a number of investigators, particularly Batelli in Florence, "that X-rays or something evolved in the production of X-rays might have some ill effect on living tissue exposed to them." As you may recall, Cannon had written to Fulton that the first tube he used was supplied by Dr. Codman and had been purchased from Swett and Lewis on Bromfield Street in Boston. Ironically, Swett too began to have x-ray dermatitis about 1897. In 1905 he had an ulcerative lesion that did not heal well. However, he continued to demonstrate and test x-ray equipment and according to Percy Brown sold much of the x-ray apparatus to hospitals, physical laboratories, and practitioners in New England. He had repeated operations for neoplasms from 1915 until his death in 1929 [2].

Dr. Codman, who supplied the equipment for Cannon's first experiment, had been warned by Elihu Thomson of the dangers of the irradiation by x-rays, but apparently he did not pass this information on to Bowditch and Cannon. On November 21, 1896, several weeks before Cannon began to use the x-ray, Thomson had written to Codman noting that he was:

> . . . nursing an X-ray finger, which is a striking example of what the rays may do if the exposure is long enough. Hearing of the effects of X-rays on the tissues, especially on the skin, I determined to find out what foundation the statements had by exposing a single finger to the rays. I used for this the little finger of the left hand, exposing it close up to the tube—about 1 and ¼ inch from the platinum source of the rays, for one-half an hour. For about nine days very little effect was noticed, then the finger became hypersensitive to the touch dark red, somewhat swollen, stiff, and soon after the finger began to blister. The blistering started at the maximum point of action of the rays, spread in all directions, covering the area exposed, so that now the epidermis is nearly detached from the skin underneath, and between the two there is a formation of purulent matter which escapes through a crack in the blister. It will be three weeks today since the exposure was made, and the healing process seems to be as slow as the original coming on of the trouble, while the pain and sensitiveness have largely left the finger within the last day or two, and the blister now covers the whole exposed back and sides of the finger. I think the finger will soon heal, but I assure you that I will make shorter exposures hereafter.

Codman must have continued to be a skeptic for on November 25 Thomson wrote again to Codman: "I received yours in relation to my X-ray finger, and notice that you are sceptical of the effect produced, or its cause." He went on to state: "I am strongly of the opinion that it is really a Röntgen ray effect, and that neither ultra-violet rays nor brush discharges have anything to do with it. I do not propose to repeat the experiment, however, under any conditions, at least not for the present, as the whole epidermis is off the back of the finger and off the sides of it also, while the tissue, even under the nail is whitened, and probably dead, ready to be cast off."

Finally, on December 1, 1896, Thomson wrote to Codman a third time: "I certainly have no objections to your publishing my letter to you concerning the effect of X-rays on the tissue, producing ulcerations, etc. I have lately made some inquiries and find that, so far as I can learn, two cases have been reported in Mr. Edison's laboratory, in which the effects are far more severe, since they took place over the hands and arms of the victims, and made it necessary for them to stop work altogether in connection with X-rays. The story goes that one of them was told by his physician that if he continued work it would be necessary to amputate his hands." These letters were published in the *Boston Medical and Surgical Journal* on December 10, 1896, the day after Cannon's first experiment with x-rays [20].

The two men in Thomas Edison's laboratory of whom Thomson wrote were probably the Dally brothers. Clarence Dally was closely associated with Edison in his work on the x-ray tube, and in particular on the proposed development of a fluoroscent tube using calcium tungstate. Percy Brown noted that, "while it was asserted at the time that these 'fluorescent lamps' gave off practically no X-rays sufficiently 'hard' to be effective outside the walls of the chamber, the cumulative effect of the radioactivity, both primary and secondary must have been considerable. In fact, concerning this lamp Mr. Edison concludes: 'I started in to make a number of these lamps, but I soon found that the X-ray had affected poisonously my assistant, Mr. Dally, so that his hair came out and his flesh commenced to ulcerate. I then concluded it would not do, and it would not be a very popular kind of light, so I dropped it'" [2].

Percy Brown denounced the manufacturers of x-ray tubes, who, he maintained, were more concerned with profit than with protection. He wrote [2]:

> At that moment, when not only scientific but lay interest was at its height, it was much to the advantage of fabricators of X-ray apparatus to preach simplicity as connoting, in their wares, both ease of purchase and ease of manipulation. Glasser quotes from the *Scientific American* of early 1896 the following advertisement, which was typical of many, commending a 'portable X-ray apparatus for physicians, professors, photographers, and students, complete in handsome case, including coil, condenser, two sets of tubes, batteries, etc., for the price of $15 net, delivered in United States with full guarantee.'
>
> . . . Such a detail as adequate protection for the operator in the form of a radiopaque enclosure for the Crookes tube was quite overlooked, although the need for it must have been apparent to every apparatus-manufacturer who read the engineering literature of the day. In fact, a considerable proportion of the physical damage to enthusiastic medical practitioners of this early era was inflicted by means of these portable apparatuses cheaply obtainable, wherein the output of radioactive energy was so low that long exposures were required to accomplish results even approaching those to be obtained from others of a more powerful type. Through this amazingly wide-spread, but happily short-lived, disregard of known danger on the part of commercial implement-manufacturers did the physical trials of the pioneer roentgenologist begin.

Thus, the discovery of x-rays at the dawn of the twentieth century provided the new technology that Cannon exploited so effectively for the solution of many problems of gastrointestinal motility and laid the foundation for the development of gastrointestinal radiology. However, the early development of radiology exacted far too high a price from the pioneers, in part because the physicians were unaware of, or ignored, warnings that appeared in the physical literature, and in no small measure because of the malpractice of the manufacturers of X-ray equipment. As an optimist, I hope that a future Sosman lecturer of the twenty-first century will not paint a similar picture with regard to nuclear energy. On

the other hand, some pessimists in the audience, fearful of a nuclear holocaust, may say: "let us hope that we still have a civilization in which the Sosman lectures may be delivered in the twenty-first century."

ACKNOWLEDGMENTS

I thank Birthe Creutz, Elin Wolfe, Saul Benison, and the members of the Cannon family for their invaluable help in the preparation of this lecture. Much of this presentation is based on original letters and source materials found in the Cannon Archive of the Countway Library during selection of documents for the forthcoming edition of *Cannon's Life and Letters*.

REFERENCES

1. Sosman MC. Roentgenology at Harvard. *Harvard Med Sch Alumni Bull* **1947**;21:65–76
2. Brown P. *American martyrs to science through the roentgen rays.* Springfield, IL: Thomas, **1936**
3. Bowditch HP. Movements of the alimentary canal. *Science* **1897**;5:901
4. Cannon WB. The movements of the stomach studied by means of the Röntgen rays. *J Boston Soc Med Sc* **1898**;2:59–66
5. Cannon WB. The movements of the stomach studied by means of Röntgen rays. *Am J Physiol* **1898**;1:359–382
6. Cannon WB, Moser A. The movements of the food in the oesophagus. *Am J Physiol* **1898**;1:435–444
7. Williams FH. *The Roentgen rays in medicine and surgery.* New York: McMillan, **1901**:360
8. Cannon WB. The influence of emotional states on the functions of the alimentary canal. *Am J Med Sci* **1909**;137:480–487
9. Cannon WB. *The mechanical factors of digestion.* London: Arnold, **1911**
10. Cannon WB, De La Paz D. Emotional stimulation of adrenal secretion. *Am J Physiol* **1911**;28:64–70
11. Cannon WB, Uridil JE. Studies on the conditions of activity in endocrine glands. VIII. Some effects on the denervated heart of stimulating the nerves of the liver. *Am J Physiol* **1921**;58: 353–364
12. Dale HH. Walter Bradford Cannon, 1871–1945. *Obituary Notices Fellows Roy Soc* **1947**;5:407–423
13. Cannon WB. Physiological regulation of normal states: some tentative postulates concerning biological homeostatics. In: *Jubilee volume to Charles Richet.* Paris: Editions Medicales, **1926**:91–93
14. Cannon WB. Organization for physiological homeostasis. *Physiol Rev* **1929**;9:399–431
15. Cannon WB. *The wisdom of the body.* New York: Norton, **1932**
16. Cannon WB. Some reflections on the digestive process (Caldwell lecture). *AJR* **1934**;32:575–588
17. Schlesinger MC. *Snatched from oblivion: a Cambridge memoir.* Boston: Little, Brown, **1979**:13
18. Aub JC, Wolbach SB, Kennedy BJ, Bailey OT. Mycosis fungoides followed for fourteen years. The case of Dr. W. B. Cannon. *Arch Pathol* **1955**;60:535–537
19. Glasser O. *Wilhelm Conrad Röntgen and the early history of the Roentgen rays* (Engl Trans). Springfield, IL: Thomas, **1933**: 293
20. Correspondence between EA Codman and E Thomson: the cause of burns from x-rays. *Boston Med Surg J* **1896**;135: 610–611

HONORS AND AWARDS

This Spring, at its 118th Annual Meeting, the Academy of Sciences honored 60 American scientists and engineers. Three APS members were recipients of this honor.

Michael V.L. Bennett, Director, Division of Cellular Neurobiology, Albert Einstein College of Medicine.

Eugene P. Cronkite, Chairman, Medical Department, Medical Research Center, Brookhaven National Laboratory.

Joseph F. Hoffman, Professor of Physiology, Yale University School of Medicine.

Symposium: Career Opportunities In Physiology

INTRODUCTION

The Career Opportunities Committee was established as a Standing Committee of APS Council by President Bohr in July, 1979, and it met first in New Orleans. The charge to the committee was that it be advisory to Council, serving as resource for current information regarding availability and need for appropriately trained physiological manpower. It reports annually to Council. It is charged to be informed concerning the nature of training processes and the quantity and quality of trained physiological personnel and is to recommend measures to ensure proper balance between supply and demand of physiologists.

The committee has met, with nearly 100% attendance, at *each* of the Spring and Fall Meetings of APS since its formation and has accepted responsibility to become informed upon manpower requirements and existing provisions to meet those needs within professional physiology. Individual members of the committee have accepted responsibility to accumulate actual data on this supply and demand, and this symposium is an outgrowth of those efforts together with a specific suggestion from Dr. Michael Gross representing one of the Society's Sustaining Associates. A first publication appeared in the December issue of *The Physiologist* (2). We hope you have carefully read that report. Additional factual reports are in preparation; one has already been published (1) and two appear in this issue of *The Physiologist*.

Authorities in each of four different career areas for professional physiologists have worked for several months in organizing the material for this symposium. We have convened the entire Careers Committee to form a panel together with the speakers, to discuss questions arising from the presentations as well as from the audience. It is the committee's hope that you will accept the challenge to consider the problems facing young scientists entering the competitive job market today. Are graduate training programs *in fact* training too many physiologists? Are the young trainees properly prepared to compete successfully in the existing job market? Are the areas of specialty training improperly biased? Are there a sufficient number of jobs available for the graduates and for those reentering the profession after temporary absence? Can additional attractive job opportunities be evolved out of existing employment resources? Is the quality of training in each of the training programs appropriate? Is there need for consideration of academic acreditation of training programs? Are you prepared to tackle realistically the questions of accreditation? Is APS the appropriate accrediting agency?

These are but a few of the questions with which the committee wrestled. We sincerely hope you will participate in the discussion and that you will offer either answers or additional questions in this critically important area.

REFERENCES

1. MacCanon, D.M., Careers for physiologists in Government. *Physiologist* 24(3): 48-49, 1981.
2. Saba, T.M., W.C. Randall, D. Bohr, J.E. Blankenship, D.M. MacCanon, D.J. Ramsay, P.T. Ridley, and O.E. Reynolds. Graduate training in physiology and its relationship to career opportunities. Report of Committee on Careers in Physiology. *Physiologist* 23(6): 9-12, 1980.

Walter C. Randall, Chairman
APS Committee on Career
Opportunities in Physiology

DO WE REALLY NEED MORE PHYSIOLOGISTS?

Theodore Cooper, Executive Vice-President
The Upjohn Company, Kalamazoo, Michigan 49001

A cynic might start this symposium with a suggestion to change its title to, "Do we really need more physiologists?" The question would be in vogue, since we seem to be questioning a lot of our values these days. Indeed, many of our values need to be questioned. In any case we must guard against pessimism. I am basically optimistic.

An analyst would approach our topic by asking, "What is a physiologist?" I am not certain what the agreed-upon description would be. Is is someone who has a Ph.D. in physiology? Or someone who works in a department of physiology? Some of you might think that it might be of small impact to the main issue at hand. I assure you the label is a large factor these days.

A modern-day budget official would start with the assertion that whatever they are, physiologists probably do not need much federal support, that physiologists should be "Stockmanized." That is only a slightly different way to express the view of many federal analysts for at least the past 10 years, which is why there are fewer and fewer training grants.

A practicing physiologist would no doubt like to open this symposium by asking, as he or she looked toward the northeast to Washington, DC, "Why hast thou rejected me? Have not we biomedical scientists been the best bargain of the past 30 years? Have we not produced spectacular changes in the practice of medicine and in the public health status?"

I approach this topic by asking for a clarification. (As you know, the best way to deal with a difficult question is to answer it with another question or maybe two.) Nevertheless, it will make a great deal of difference if you approach this problem with the purpose of providing our progeny with a future; or if you are seeking mutations (something different, but called a physiologist); or if you are really more concerned with the existing, anxious, unsupported physiologists in academia. Or all of the above.

Since I have not discussed this with the chairman or with any of the other speakers, and since I am first on the program, I will assume that the reason why the topic has been given important program space is because the leadership knows that the pivotal issue of the vigor of physiology for the next generation will *not* depend on restoration of the good old days. Nowadays a clarion call for the NIH program of 20 years ago does not even give the satisfaction that usually follows the catharsis of righteous indignation, much less any hope of reality.

I also assume that you are prepared to discuss certain aspects of the problem which only a few years ago might have been unacceptable topics for serious public talk at a meeting such as this, for example, program accreditation for the awarding of degrees or development programs with industry.

The life sciences are entering a major new era. Various labels have been attached to this expansion of avenues for research. A common one is "The New Biology." The promise is beyond anything that many of us ever hoped or dreamed could be seriously considered in our lifetimes. And as the new technologists called molecular and cellular biologists storm past us, those of us who are called physiologists, picking up our following of younger talent and our share of the public purse, are worried, for we are not ready to die.

In the past three months I have visited two distinguished academic institutions and one industrial laboratory of significant standing to discuss their plans for the future, and in each instance there was dwindling interest in what they individually called physiology (without definition) side-by-side with excitement for cellular and molecular biology and genetics. This is not a new trend. The erosion has been in process for some time. Ask faculties or research directors what they seek in order to bring their institutions to the first rank. They rarely will answer, "Send me a physiologist."

Indeed, the best press that I have seen for physiologists recently has been in connection with programs of preventive medicine, particularly programs highlighting exercise physiologists. The work of these people would rarely get mentioned in the "establishment" of high science. Interestingly enough, there are commercial interests seeking such experts to supervise a significant portion of the attempts of entrepreneurs to fill an interest of the consuming public. I ask you, Is this a decent career for a physiologist?

I read an analysis in the *New York Times* not too long ago which stated that senior corporate management could well benefit from more scientifically trained people in their ranks. Should such a career opportunity be a reflection of failure in the academic competition? In other words, go to industry if you cannot make tenure. Would you classify the president of a company a "successful" physiologist?

The writer for the *New York Times* did not mean that. He meant that good people who have a penchant for management and who also are trained in the basic sciences have a great deal to offer a spectrum of businesses. Second-rate people fare no better as managers in industry than they do in academia.

We also must ask whether we are graduating people who are not good enough to begin the academic ladder and who are advised to go to lesser institutions and to industry, people who their sponsors obviously feel will not meet the competition in academia. Those graduates were the slave labor you rewarded with a degree that had an asterisk.

Now I know that these assertions are an exaggeration, just as it is an exaggeration to assert that the programs of education of the recent past and of the present have not provided the elements that will facilitate future redirection of the technical interest of the individual scientist. Yet there is probably substantial truth in the assertion that the graduate programs have been less than concerned with quality and scope and more concerned with technical capability with existing methods of study.

The system has bred narrowness of total outlook. Strangely enough, this narrowness was fostered by wholesale adoption of the belief that federal grant support provides the greatest flexibility and the least restriction for intellectual endeavor. We forgot that old principle that has held up time and time again: NEVER PUT ALL YOUR EGGS IN ONE BASKET. We would like to believe that grant support for investigator-initiated research provides some sort of immunity against intellectual co-option. I think that most of us have learned that both of these beliefs are ill founded.

Let me make sure that you know where I stand on the issue of federal grants. I believe we should have them. Lots of them. And I spend a fair amount of time trying to encourage various branches of government to expand their support for the programs of the National Institutes of Health, the National Science Foundation, and the Veterans Administration.

My point is that the government is not enough. It should not do it alone. The so-called private (i.e., profit-making and nonprofit) sectors also should support the effort in academia. Most profit makers are honest people. I do not believe that they judge or fabricate any more than academics do. But they get checked more often. They have self-interest, indeed—but then few of us are nominees for sainthood.

The barrier to having enough baskets to enable continued growth of our enterprise has been, in large part, an attitudinal barrier which has estranged academia from industry.

We from academia were so preoccupied with our responsibility to "serve society" that we failed to prepare people for careers of distinction, of dignity, in industry. Indeed, we counseled *against* such careers. We sometimes took money from industry, but we usually felt the need to rationalize it through the confession of sins.

We fractured many strong and important intellectual bonds which brought great progress in the third and fourth decades of this century. We forced industry to seek self-dependence.

Fortunately, industry cannot afford to be offended by this. There is little room for foolish pride in the boardroom. Industry knows that it can thrive better when you are stable and vigorous, and particularly when there is active collaboration based on its money and your remarkable renewable assets (generation upon

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PROGRAM

SYMPOSIUM: Career Opportunities in Physiology
Sponsored by: APS Career Opportunities Committee and APS Sustaining Associates

Chaired: W.C. RANDALL

Introduction. W.C. RANDALL. *Loyola Univ. Stritch Sch. of Med.*

Keynote remarks. T. COOPER. *The Upjohn Co.*

Opportunities in industry. E. BLAINE. *Merck Sharp & Dohme.*

Opportunities in government. D. MACCANON. *Natl. Heart, Lung, and Blood Inst.*

Opportunities in clinical departments. A. FISHMAN. *Univ. of Pennsylvania.*

Opportunities in basic sciences. T. SABA. *Albany Med. Col.*

generation of brains and broad areas of experience in the aggregate). There are many opportunities. Many opportunities. We are seeing high-quality applicants now. The issue is not whether to dump outmoded technology, but rather the continuing need for cutting-edge technology.

The question, What is a physiologist? merits some attention. How is the designation decided? Does the label convey the same kind of information as does "biochemist" or "pharmacologist" or even "pathologist"?

And if the designation derives from having a Ph.D. from a department of physiology, does that mean that the department is called physiology because of what it teaches or what it investigates? What is the *special* philosophical perspective of physiology and how is it being passed on from generation to generation?

Is a Ph.D. the requisite to be called physiologist, or is it working in a department of physiology that makes an M.D., or taking pre- or postdoctoral courses in a department that gives the label?

Clearly it is a department that seems to be the pivotal position. So we must pursue how well the departments of physiology are meeting the needs and challenges.

It is an important time to examine the performance of departments. Resources will be limited. Reasons will be sought for reduction of resource allocations. There are two criteria that are fundamental to such evaluations and decisions. The first is the ability to explain why it is important to sustain the functions of the department in relation to the overall mission of the parent institution; the second is the question, "How good is the department?"

It is usually taken for granted that departments that have a great deal of federal support are training good physiologists. If the Liaison Committee for Medical Education team says a department is strong, people also assume that there is a quality graduate program; however, it is not clear what standards specify a quality program. Are graduate schools able to ensure quality?

You have all heard about "grade creep." Can we be accused of "degree creep"? Should the Society be thinking of *accreditation* of programs? Or will it be enough to characterize what a program should be to train the physiologists of the future—"good" physiologists, as the Career Opportunities Committee calls them.

Finally, I ask you to stretch your imaginations. Reconsider what is a good result. For on that rests what limits your ideas of what is a career. The brotherhood of physiology has given life to many of the new biologists who, as they say, are eating your lunch: biochemists, biophysicists, engineers, cellular scientists. We have to stop depending on what we know and seek what we can imagine.

PH.D.'s IN CLINICAL DEPARTMENTS

Alfred P. Fishman, Director
Cardiovascular-Pulmonary Division
Hospital of the University of Pennsylvania

and

Paul Jolly, Director
Division of Operational Studies
Association of American Medical Colleges

Between 1950 and 1979, medical schools underwent a remarkable proliferation and expansion. They increased in number from 72 to 126 and in full-time clinical faculty from 1,284 to 33,913. The increase in the number of faculty was not uniform. For example, in departments of medicine, the full-time faculty increased from 793 to 8,921 (3). Many of the additional faculty were trained by funds from the National Institutes of Health. Since most of the funds were earmarked for research, many clinical departments are now staffed by individuals who are not only skilled at the bedside but equally qualified in research.

The reader who was not born into clinical departments during this academic boom may find bewildering the nature of the research that is done there. Table 1, based on one issue of the *Journal of Clinical Investigation,* illustrates the problem. Departments of medicine, occasionally in association with basic science departments, are the major contributors to this journal. Table 1 shows that this research in clinical departments is far-ranging, that it cannot be categorized as "applied," and that it is not always related, or even extrapolatable, to human disease. Indeed, research in clinical departments extends from molecular and cell biology to human biology and disease, so that the subject matter often falls within the traditional purview of basic science departments.

Ph.D.'s as well as M.D.'s have been involved in this clinical research. In recent years (1968-1978), the number of physicians entering on a research career in clinical departments has decreased, while the number of Ph.D.'s in clinical departments has increased strikingly (1-5). This decrease in M.D.'s entering on research careers is viewed as a serious threat to the underpinnings of scientific clinical medicine. Others have attempted to explain the reasons for this decrease (3-5). Here, in dealing with the future role of Ph.D.'s in clinical departments, it is pertinent to note that the increase in Ph.D.'s in clinical departments, together with the decrease in the number of M.D.'s embarking on a career in research has faced clinical departments with three alternatives: 1) to ride with the tide, shifting away from clinical research to clinical practice and health care delivery; 2) to resist the swell toward clinical practice by enticing M.D.'s into careers in research; or 3) to strike a new balance in clinical departments by recruiting Ph.D.'s to continue the research effort.

Missions of Clinical Departments

A Ph.D. entering a clinical department usually moves into a strange academic community. The *general* ambience is set by the departmental obligations to patient care and teaching, with the individual subspecialties, such as cardiology and rheumatology, conducting "relevant" research. In certain departments within this setting, the clinical investigator is held in high esteem, not only because of intramural contributions to research, patient care, teaching, and administration, but also because the scientific

TABLE 1. Types of research in clinical departments*

Department	Test Material or Subject	Topic
Med	Mouse *S. Mansoni*	Inflammatory mediators (eosinophils)
Med	Toad bladder	Prostaglandins as modulators
Med/Physiol	Rabbit tubules	Renal metabolism
Med/Path/Biochem	Rabbit	Endothelium on thrombin
Med	Cat	Cholecystokinin receptors
Med	Human blood	Apolipoproteins
Pharm/Med	Toad bladder	Thromboxane on permeability
Med/Physiol	Rat lung cell culture	Glycolytic enzymes
Med/Biochem/Path	Human blood	Eosinophil stimulation
Med	Rat gut	Calcium homeostasis
Med/Path	Human biopsy (lymphoma)	Cytometry
Ped/Med	Dog hindlimb	Amino acid transport
Med	Human biliary cirrhosis	Lymphocyte reactions
Med/Biochem	Human thrombasthenia hybridoma	Platelet glycoproteins
Med	Human thalassemia blood	Molecular organization of α-globin
Med	Human jejunum (normal)	Chloride secretion
Med	Rat islets	Somatostatin binding
Med	Rat nephropathy	Complement
Med/Ped	Human blood	Apolipoproteins
Med	Human polycythemia vera cell culture	Hematopoiesis
Med	Human cardiopathy	Hemodynamics
Med/Surg	Human cerebrospinal fluid	Endorphin, adrenocorticotropin
Med	Human lupus erythematosus	Plasma DNA
Med	Human airways culture	Secretion of mucus
Med	Human neutrophils	Respiratory burst

* Exemplified by the table of contents of *J. Clin. Invest.*, December, 1980.

publications and presentations of the investigator shape the scientific image of the department and medical school in the outside world.

It cannot be overemphasized that the responsibility which is unique to clinical departments is patient care. Patient care requires licensure; patient care activities are monitored by the medical school, by the department, by the hospital, and by legally constituted public authorites. Only M.D.'s can render medical care. Distinct from, but related to, this responsibility are the other missions of the clinical departments: to teach medicine to students and house staff and to conduct biomedical research.

Not all clinical departments execute their responsibility and mission in the same way. Neither do medical schools: some stress patient care, others research; an occasional school devotes its major effort to health care delivery. Therefore, in attempting to analyze the roles played by Ph.D.'s in clinical departments, we subdivided medical schools in the United States into the categories shown in Table 2. This classification distinguishes a group of schools which would be recognized by most observers as research schools, new schools (since 1967-1968), and all other schools. Obviously, this classification is simply an expedient for handling data. As a second strategy for dealing with data from clinical departments, we have created the categories shown in the bottom half of Table 2.

Numbers of Ph.D.'s in Clinical Departments

According to data from the Faculty Roster System of the Association of American Medical Colleges (AAMC), there were about 4,600 Ph.D.'s in clinical departments of US medical schools in academic year 1978-1979, including departments of pathology (Table 3).[1] Approximately one-fourth of the Ph.D.'s in these clinical departments were in psychiatry, where there are many clinical psychologists. Moreover, about 600 Ph.D.'s were in pathology departments, where there is a long-standing tradition of commitment to both fundamental science and clinical pathology.

It is well known that radiology departments depend on physicists, that community medicine requires epidemiologists and computer experts, and that physical medicine needs bioengineers, but the existence of 2,800 Ph.D.'s in clinical departments other than pathology and psychiatry may be surprising to some. The fraction of the faculty of each department accounted for by Ph.D.'s varies considerably, ranging from 4% in anesthesiology to 25% in family and community medicine; only psychiatry with 30% has more.

TABLE 2. Grouping of Schools and Departments for Analysis

Medical School Groups

A. Selected research-oriented schools ($n = 20$)*
B. New schools since 1967-1968 ($n = 31$)
C. All other schools ($n = 73$)

Department Groups

Medical: Internal medicine, pediatrics, allergy, neurology, and dermatology
Family/Community: Family practice, community medicine, and preventive medicine
Surgical: Surgery, orthopedics, opthalmology, otolaryngology, neurosurgery
Ob/Gyn: Obstetrics and gynecology
Psychiatry
Anesthesiology
Radiology: Nuclear medicine and radiology
Physical Med/Rehab: Physical medicine and rehabilitation
Pathology

* Schools included in this designation were as follows: Baylor, Case Western, Columbia, Duke, Einstein, Harvard, Johns Hopkins, New York University, Rochester, Stanford, UCLA, UCSF, the Universities of Chicago, Michigan, Minnesota, Pennsylvania, Washington, Wisconsin, and Yale.

[1] In this and subsequent statements concerning Ph.D.'s, faculty members with both an M.D. and a Ph.D. are not included.

TABLE 3. Full-Time Faculty in Clinical Departments by Degree (1978-1979)

Departmental Classification	M.D. and M.D./Ph.D. No.	M.D. and M.D./Ph.D. % of Dept.	Ph.D. No.	Ph.D. % of Dept.	All Other Degrees No.	All Other Degrees % of Dept.	Total Faculty No.	Total Faculty % of Dept.
Medical	11,194	86.9	1,131	8.8	561	4.3	12,886	100.0
Family/Community	941	54.9	424	24.7	349	20.4	1,714	100.0
Surgical	3,974	82.4	529	11.0	318	6.6	4,821	100.0
Ob/Gyn	1,158	83.3	167	12.0	65	4.7	1,390	100.0
Psychiatry	2,358	58.1	1,208	29.7	496	12.2	4,062	100.0
Anesthesiology	1,472	92.7	65	4.1	51	3.2	1,588	100.0
Radiology	1,981	77.3	393	15.3	189	7.4	2,563	100.0
Physical Med/Rehab	284	57.7	85	17.3	123	25.0	492	100.0
Pathology	2,033	70.1	602	20.7	267	9.2	2,902	100.0
All clinical departments	25,395	78.3	4,604	14.2	2,419	7.5	32,418	100.0
Basic science departments (excluding Pathology)	1,213	15.0	6,456	80.0	406	5.0	8,075	100.0
All departments	26,608	65.7	11,060	27.3	2,825	7.0	40,493	100.0

TABLE 4. Full-Time Ph.D.'s in Clinical Departments (1970-1971 through 1978-1979)

Departmental Classification	1970-1971 Ph.D.'s No.	1970-1971 Ph.D.'s % of Dept.	1970-1971 Total Faculty	1974-1975 Ph.D.'s No.	1974-1975 Ph.D.'s % of Dept.	1974-1975 Total Faculty	1978-1979 Ph.D.'s No.	1978-1979 Ph.D.'s % of Dept.	1978-1979 Total Faculty
Medical	596	7.0	8,498	896	7.9	11,382	1,131	8.8	12,886
Family/Community	226	24.3	930	332	23.3	1,426	424	24.7	1,714
Surgical	350	10.3	3,393	469	11.0	4,283	529	11.0	4,821
Ob/Gyn	109	10.7	1,014	157	12.3	1,272	167	12.0	1,390
Psychiatry	856	29.0	2,956	1,154	30.7	3,761	1,208	29.7	4,062
Anesthesiology	18	1.9	937	41	3.1	1,344	65	4.1	1,588
Radiology	222	13.5	1,642	351	14.8	2,364	393	15.3	2,563
Physical Med/Rehab	77	17.4	442	78	15.8	4,951	85	17.3	492
Pathology	306	13.8	2,223	504	18.3	2,753	602	20.7	2,902
All clinical departments	2,760	12.5	22,035	3,982	13.7	29,080	4,604	14.2	32,418
Basic science departments (excluding pathology)	4,690	73.1	6,418	5,980	77.2	7,748	6,456	80.0	8,075
All departments	7,450	26.2	28,453	9,962	27.1	36,828	11,060	27.3	40,493

TABLE 5. Full-Time Ph.D.'s in Clinical Departments for Selected Research-Oriented Schools, Other Schools, and New Schools (1978-1979)

Departmental Classification	Selected Research-Oriented Schools No.	Selected Research-Oriented Schools % of Dept.	Selected Research-Oriented Schools Total Faculty	Other Schools No.	Other Schools % of Dept.	Other Schools Total Faculty	New Schools No.	New Schools % of Dept.	New Schools Total Faculty
Medical	352	8.7	4,069	681	9.4	7,243	98	6.2	1,574
Family/Community	94	26.6	354	284	26.0	1,093	46	17.2	267
Surgical	215	14.5	1,486	276	10.0	2,762	38	6.6	573
Ob/Gyn	57	14.0	408	92	11.2	819	18	11.0	163
Psychiatry	404	31.2	1,294	705	29.8	2,366	99	24.6	402
Anesthesiology	28	4.8	587	36	4.2	863	1	0.7	138
Radiology	151	17.6	860	221	15.4	1,435	21	7.8	268
Physical Med/Rehab	51	22.8	224	29	13.3	218	5	10.0	50
Pathology	164	18.5	886	360	21.7	1,657	78	21.7	359
All clinical departments	1,516	14.9	10,168	2,684	14.5	18,456	404	10.6	3,794
Basic science departments (excluding Pathology)	1,457	71.2	2,047	4,212	83.1	5,070	787	82.2	958
All departments	2,973	24.3	12,215	6,896	29.3	23.526	1,191	25.1	4,752

The traditional basic science departments have some M.D.'s and persons with other degrees, but they are predominantly (of the order of 80%) made up of Ph.D.'s. Yet Ph.D.'s in basic science departments outnumber Ph.D.'s in clinical departments only by a ratio of a little more than four to three.

Table 4 shows a steady increase in the numbers of Ph.D.'s in clinical departments, rising from 12.5% of faculty in those departments in academic year 1970-1971 to 14.2% in 1978-1979. In absolute numbers, 1,844 positions for Ph.D.'s were added in clinical departments in the 8-year period, a number greater than the increase of 1,766 for Ph.D.'s in basic science departments.

Selected Research-Oriented Schools

Since the Ph.D. faculty member is primarily an investigator, it might be expected that more positions for Ph.D.'s in clinical departments would be available in schools with a strong research orientation than in the other medical schools. Table 5 shows that this is not the case; the fraction of Ph.D. faculty in clinical departments is almost the same in both the research-oriented schools and the other schools. The fraction is less in new schools where, naturally, the first faculty in clinical departments are likely to be M.D.'s to teach and practice medicine.

New Appointments

The faculty roster allows the identification of new appointed faculty in a given year. Table 6 shows the fraction of these new Ph.D. faculty with a base in a clinical department. The trend is evident; there are now more Ph.D.'s appointed each year in clinical departments than in basic science departments. The trend is strongest in the selected research-oriented schools, where three out of five new Ph.D. faculty joined clinical departments in 1978-1979.

TABLE 6. Percentage of New Full-Time Ph.D.'s Appointed in Clinical Departments

US Medical Schools	1970-71	1974-75	1978-79
Selected research-oriented schools	48.6	56.4	60.3
Other schools	38.2	42.5	53.2
All schools	41.1	45.6	53.4

Role of the Ph.D. in Clinical Departments

According to the AAMC Faculty Roster, the major role played by Ph.D.'s in clinical departments is in research, often combined with teaching (Table 7). Only in certain departments, particularly psychiatry, radiology, physical medicine and rehabilitation, and pathology, are large numbers of Ph.D.'s committed to activities involving patient care. Unfortunately, the data do not provide any insight into the level of scientific activity at which the Ph.D.'s are operating: are they independent investigators, coequal members of a research team, or providers of technical skills?

Although reliable data describing in detail the activities of Ph.D.'s in clinical departments are not available, a few generalizations can be made from personal observations of one of the authors (APF). As a rule, the Ph.D.'s who conduct research in clinical departments seem to be members of a team. Rarely do they serve as independent heads of laboratories. More often, they serve as collaborators, generally charged with a project requiring a high degree of technical skill and specialized knowledge. Most of the research that they do is entirely within a clinical department; some cross departmental lines, usually either as part of an interdisciplinary program project grant or of a research institute sponsored by the National Institutes of Health.

Academic Advancement Within Clinical Departments

Many of the opportunities for Ph.D.'s in clinical departments relate to extramural research support, and often academic viability depends on continuation of this source of funding. Academic advancement for the Ph.D. is generally along one of two lines, a research track or the academic track; only the latter entails tenure.

As a rule, the road to tenure in a clinical department is more difficult for the Ph.D. than for the M.D. Nonetheless, a considerable number of Ph.D.'s do acquire tenure. Table 8 shows the distribution of Ph.D. faculty in clinical departments by tenure status. Twenty-eight percent of the Ph.D.'s in clinical departments have tenure, and another 32% are on a tenure track; 38% have no prospect for tenure, and a handful are in schools without tenure systems. By contrast, over half of all Ph.D.'s in basic science departments already have tenure, and only 14% are not on a tenure track.

TABLE 7. Roles of Ph.D.'s in Clinical Departments Distribution of Effort in Percent by Areas of Responsibility (1978-1979)

Areas of Responsibility	Medical	Family/Community	Surgical	Ob/Gyn	Psychiatry	Anesthesiology	Radiology	Physical Med/Rehab	Pathology	Basic Sciences
Research Related										
Research	32.5	15.7	27.7	28.2	11.5	27.5	14.1	20.0	16.1	8.1
Research & Teaching	40.1	53.3	51.2	56.3	27.9	56.8	46.6	18.8	45.0	83.3
Research, Teaching, & Patient Care or Research & Patient Care	16.2	12.4	12.3	12.0	33.7	10.6	30.1	40.1	24.8	2.9
Research-related subtotal	88.8	81.4	91.2	96.5	73.1	94.9	90.8	78.9	85.9	94.3
Nonresearch Related										
Teaching	3.1	9.7	0.6	1.2	6.4	1.5	3.5	4.8	4.5	3.7
Patient Care or Patient Care & Teaching	5.6	3.2	5.9	0	15.7	1.5	3.6	10.7	5.7	0.5
Other	2.8	5.4	2.5	1.8	4.9	1.5	2.8	5.9	4.2	1.5

TABLE 8. Tenure Status of Full-Time Ph.D.'s (1978-1979)

Departmental Classification	% of Ph.D.'s in Dept. with Tenure	% of Ph.D.'s in Dept. On Track	% of Ph.D.'s in Dept. Not on Track	% of Ph.D.'s in Dept. Tenure not Available
Medical	20.5	31.3	45.1	3.0
Family/Community	31.3	40.8	26.5	1.4
Surgical	32.3	29.7	36.3	1.7
Ob/Gyn	40.8	32.2	27.0	0
Psychiatry	28.8	25.1	42.6	3.6
Anesthesiology	16.4	36.4	43.6	3.6
Radiology	33.7	32.5	31.7	2.1
Physical Med/Rehab	30.0	28.6	41.4	0
Pathology	28.0	36.7	31.9	3.3
All clinical departments	27.9	31.5	38.0	2.6
Basic science departments (excluding Pathology)	52.8	30.4	14.4	2.4
All departments	41.9	30.9	24.6	2.5

TABLE 9. Full-Time Ph.D.'s in Clinical Departments with Joint Appointments in Basic Science Departments

Departmental Classification	Ph.D.'s	Ph.D.'s with Joint Appointments No.	%
Medical	1,131	206	18.2
Family/Community	424	15	3.5
Surgical	529	117	22.1
Ob/Gyn	167	67	40.1
Psychiatry	1,208	42	3.5
Anesthesiology	65	13	20.0
Radiology	393	30	7.6
Physical Med/Rehab	85	10	11.8
Pathology	602	99	16.4
All clinical departments	4,604	599	13.0

Important for the acquisition of tenure at many institutions is the endorsement of the professional competence of the Ph.D. by the relevant basic science department. This endorsement is more readily achieved if the Ph.D. has a joint appointment in a basic science department, but this occurs in only 13% of the cases (Table 9), varying widely from one clinical department to another. Not included in Table 9 are those faculty with a principal appointment in a basic science department and a joint appointment in a clinical department.

Concluding Remarks

The role played by the Ph.D. in a clinical department varies greatly, ranging from that of a principal investigator to collaborating investigator to a technical assistant. Tenure in a clinical department is more difficult to achieve for the Ph.D. than for the M.D. Opportunities exist for Ph.D.'s in clinical departments. Moreover, it seems likely that opportunities will continue in the years ahead, either at the same or increased rates depending on levels of federal funding.

The data included in this presentation were gathered from diverse sources, but primarily from the Faculty Roster System of the Association of American Medical Colleges. Thomas E. Morgan, M.D., participated in the discussions that led to this paper and suggested some of the analyses. Valuable assistance was provided by AAMC staff members Elizabeth Higgins, Director of the Faculty Roster, and Exequiel Seville III.

REFERENCES

1. Clinical Research Manpower. *The Report of the ad hoc Committee on Clinical Research Training.* Washington, DC: Assoc. Am. Med. Coll., 1980, p. 1-16.
2. Gillis, C.N. The role of the basic scientist in an academic clinical setting. *Federation Proc.* 38: 2355-2358, 1979.
3. Sipirstein, M.D. Training of internal medicine faculty, 1980. *Trans. Assoc. Am. Physiologists* 93: 1-13, 1980.
4. Whedon, G.D. Further analysis of research support at NIH. *Perspect. Biol. Med.* 23: S34-S43, 1980.
5. Wyngaarden, J.B. The clinical investigator as an endangered species. *N. Eng. J. Med.* 301: 1254-1259, 1979.

POSTDOCTORAL SCIENCE RESEARCH PROGRAMS

Deadline for Applications: January 15, 1982

The National Research Council announces its 1982 Research Associateship Awards Programs for research in the sciences and engineering to be conducted in 18 federal research institutions, whose laboratories are located throughout the United States. The programs provide Ph.D. scientists and engineers of unusual promise and ability with opportunities for research on problems largely of their own choosing yet compatible with the research interests of the supporting laboratory. Initiated in 1954, the Associateship Programs have contributed to the career development of over 3500 scientists ranging from recent Ph.D. recipients to distinguished senior scientists.

Approximately 250 new full-time Associateships will be awarded on a competitive basis in 1982 for research in chemistry, engineering and mathematics, and in earth, environmental, physical, space, and life sciences. Most of the programs are open to both U.S. and non-U.S. nationals, and to both recent Ph.D. holders and senior investigators.

Awards are made for a year with possible extensions through a second year; senior applicants may request shorter tenures. Stipends range from $22,400 a year for recent Ph.Ds to approximately $50,000 a year for Senior Associates. Allowances are made for relocation and for limited professional travel during tenure. The host federal laboratory provides the Associate programmatic support including facilities, support services, and necessary equipment.

Applications to the Research Council must be postmarked no later than January 15, 1982. Awards will be announced in April.

Information on specific research opportunities and federal laboratories, as well as application materials, may be obtained from the Associateship Office, JH 610-D3, 2101 Constitution Avenue, N.W., Washington, D.C. 20814, (202) 389-6554.

APS Sections

ENDOCRINOLOGY AND METABOLISM SECTION

A general meeting of the Section was held Sunday, April 12, 1981, during the FASEB Meetings in Atlanta. Dr. S.M. McCann, Chairman of the organizing committee, presided. He announced the following election results:

Chairman (1981-82)	Edward J. Masoro
Councillor (1981-83)	Howard Morgan
Councillor (1981-84)	Mary Dallman
Secretary-Treasurer (1981-84)	Jimmy Neill
Program Committee (1981-84)	M. Susan Smith

Dr. McCann turned the meeting over to Dr. Masoro, who opened it for a discussion of the goals of the Section and activities for the coming year.

On Monday, April 13, the Council of the Section met to plan the activities for the coming year in light of the discussions of the general meeting. The following were decided.

1. For the Section to be viable will require its promotion not only within the American Physiological Society, but with related societies. It was therefore decided that plans should be developed and executed for recruitment of members from the American Society of Biological Chemists, American Institute of Nutrition, American Diabetes Association, and American Society for Clinical Investigation.
2. The decision was made that for each Federation meeting the Section should develop a theme by *a*) concentrating symposia in a specific subject area, *b*) having a dinner meeting with a distinguished speaker in the subject area, and *c*) publishing the theme widely and soliciting abstracts for 10-minute papers and poster sessions in the subject area. The subject area for the 1982 FASEB Meetings will be "Metabolic Characteristics of Diabetes Mellitus and Related Metabolic Subjects."
3. Finally, it was concluded that the possibility of joint meetings of the Section in conjunction with the annual meeting of other societies (e.g., American Diabetes Association) should be explored by Council.

Another important function of the Section is its advisory role in regard to the *American Journal of Physiology: Endocrinology and Metabolism.* To carry out this function, a Section Publication Committee was appointed with the following membership: S.M. McCann, Chairman; Larry Ewing, Robert E. Fellows, Leonard S. Jefferson, Fred W. Turek, and Mladen Vranic.

We would like to encourage members of the Section with thoughts about activities that should be undertaken by the Section to contact us.

Edward J. Masoro, Ph.D., Chairman

CARDIOVASCULAR SECTION

The following report covers the Cardiovascular Section activities for the year ending with the 1981 Spring Meeting in Atlanta.

The organizational structure of the Cardiovascular Section has changed substantially in the last year. It became a section of the American Physiological Society rather than the undesignated Circulation Group, and it formally adopted Section bylaws. The organizational plan and categories for regular members and fellows have worked smoothly. Membership in the Section stands at 68 regular, 164 fellow, and 34 emeritus members.

Dr. Harvey Sparks of Michigan State University was elected as the new member of the Steering Committee. Dr. Douglas Griggs of the University of Missouri was appointed as the new member of the APS Program Committee representing the Cardiovascular Section. Dr. Griggs is already deeply involved with those activities, since he is planning the 1981 Fall and 1982 Spring Meetings. Dr. Griggs replaced Dr. Eugene Morkin of the Arizona College of Medicine.

Two organized groups within the Section requested and were formally established as subsections. The groups are the Cardiac Mechanics Group, with Karl T. Weber of the University of Pennsylvania as president, and the Splanchnic Circulation Group, with C.C. Chou of Michigan State University as president. Both groups have functioned for three to four years and have held successful symposia and workshops. Formal establishment of these subsections followed a series of Steering Committee discussions, which found an almost uniformly favorable response. Dr. Paul C. Johnson, a member of the APS Council, participated in the discussions on this subject; the Council also reached a general conclusion that subsections would strengthen the Section. It was felt that subsections would achieve the following goals.

1. Identify people with more specific common interests, rather than a loosely knit group working under a broad umbrella.
2. Improve Section program quality by increasing the input of people with special expertise.
3. Bring people together more effectively and improve the quality of the scientific programs, possibly providing a better mechanism for exchange of ideas.
4. Encourage others from outside APS to present papers at Federation Meetings rather than at clinical meetings.

Dr. Eric Feigl presented a draft of the amendment to the bylaws that included subsections, and both Dr. Weber and Dr. Chou spoke in favor of the motion. The formal motion was made to adopt an amendment to the bylaws establishing subsections as described by Dr. Feigl. This motion was seconded and formally approved by the Cardiovascular Section. Council subsequently approved the Section's revised Statement of Organization and Procedures, which was published in the June/July issue of *The Physiologist* [24(3): 37-38, 1981].

The Lamport Award was given to Dr. Glen Bohlen of the University of Indiana and the Carl J. Wiggers Award was given to Dr. Paul Johnson of the Arizona College of Medicine, who lectured on his pioneer studies on the microcirculation. The title of his formal lecture was "An Analysis of Local Regulatory Mechanisms of the Circulation."

James O. Davis, M.D., President

MINUTES OF THE MEETING

Held April 14, 1981 - Atlanta, Georgia
Dr. James O. Davis, presiding

1. New Fellows of the Cardiovascular Section:

J. Andrew Amour	George Grega
Lewis C. Becker	Marcos Intaglietta
Shu Chien	Joseph J. Janicki
Ching-chung Chou	Albert P. Shepherd, Jr.
Louis G. D'Alecy	Richard J. Traystman
Walter Ehrlich	Karl T. Weber

2. Dr. Harvey Sparks was elected to the Steering Committee.
3. Dr. Glen Bohlen received the Harold Lamport Young Investigator Award.
4. Dr. Paul Johnson received the Carl J. Wiggers Award and gave and address entitled "An Analysis of Local Regulatory Mechanisms of Microcirculation."
5. A symposium on "Pathogenic Mechanisms in Hypertension" was held in the afternoon of April 14, 1981.
6. The Cardiovascular Section approved the amendment to the By-laws which included establishment of subsections of the Cardiovascular Section.

Kiichi Sagawa, M.D., Ph.D., Secretary

RENAL SECTION

The annual dinner meeting of the Renal Section of the American Physiological Society was held in association with the FASEB Meeting on Tuesday, April 14, 1981, in the Paulding Room of the Atlanta Hilton Hotel. Ninety-five members were in attendance.

Support for the dinner, and for the awards which were presented, was provided by Abbott Laboratories, Hoechst-Roussel Pharmaceuticals, Merck Sharp & Dohme, and Smith Kline & French Laboratories. This support is very gratefully acknowledged by the officers and members.

After dinner, the guest speaker, Dick Malvin, presented an entertaining account of the personal and professional benefits of sabbatical leave in some of the more remote regions of the world. The title of his address was "Comparatively Speaking. . . ."

The talk was followed by the presentation of awards for excellence in research. These awards are made annually to students on the basis of their presentations at the Fall Meeting of the APS. This year's awards, for presentations at the 1980 meeting in Toronto, were made to Colin Robin Felder, a biochemistry student at George Washington University, for his presentation on "Glomerular Adrenegic Receptors"; and to Jay M. Goldman, a medical student at the University of Michigan, for his presentation on "Acute Effects of Lead on Plasma Angiotensin II and Hepatic Removal of Renin." Officers of the section will again attend student presentations at the APS Fall Meeting to be held in Cincinnati in order to choose next year's winner(s).

Nominations were opened for new officers of the Renal Section, and election was made by a show of hands. Fred Wright was elected President, Jim Schafer Secretary, and Paul Churchill was reelected as Treasurer. Dave Warnock was elected to serve as the Renal representative to the Program Advisory Committee of the American Physiological Society. His term, as established at last year's meeting, will overlap with that of the outgoing program representative, Ed Schneider.

The remainder of the meeting was devoted to a general discussion and two votes concerning the participation of the Renal Section in meetings sponsored by the American Physiological Society. Fred Wright raised the question of whether the Renal Section should support programs for both the APS Fall Meeting and the FASEB Meeting. In view of the fact that many members of the section attend the annual meeting of The American Society of Nephrology as well as international meetings, and in view of limited available travel funds, this has become an important question. Dr. Wright noted that several members of the Section had expressed the possibility that the Renal Section might discourage the submission of free communications to the APS Fall Meeting, or that we might elect not to program symposia at that meeting.

Art Vander, who is presently chairman of the APS committee to evaluate the meetings, expressed his opinion that the fall meeting might be discontinued after 1983. Of course, regional and topical meetings could still be organized within the auspices of the APS.

After discussion a motion was made and seconded that the Renal Section withdraw its support from the APS Fall Meeting. This action would have meant that the Renal Section would discourage the submission of abstracts to the fall meeting by its members and that symposia would not be programmed for that meeting. The vote showed that the members of the Section in attedance were divided about evenly on this issue. Since a consensus was not apparent, it was decided not to proceed with such action.

After more discussion a motion was made that the Renal Section convey to the Council of the APS a consensus of the Renal Section that the APS support only the FASEB Annual Meeting and discontinue the fall meeting. This motion was seconded and supported by a considerable majority of the members present upon vote. In accordance with this consensus, it was also decided that the Renal Section program representative would not automatically program symposia for the fall meeting. Instead, symposia for the fall meeting will be suggested to the APS Program Advisory Committee only in the event that a strong interest in a particular symposium topic is conveyed to the Program representative and the officers of the Section.

Further discussion of this topic is warranted by events subsequent to the Renal Section Dinner. At the APS Council Meeting on April 15, Art Vander conveyed the above consensus of the Renal Section during the discussion of the fall meeting. After a split vote, the Council decided to continue the fall meeting, at least for the foreseeable future. If any member of the Renal Section has additional suggestions for our further course of action, these should be forwarded to one of the officers.

Jim Schafer, Secretary

Letters To The Editor

To The Editor:

I read with great interest both the "Report on Proceedings of IBRO-UNESCO-NIH-ACADEMIC SINICA Workshop of Neurobiology in Shanghai" by H.T. Chang and the "Introduction to Shanghai Brain Research Institute" in April/May 1981 issue of *The Physiologist*. It has been with great satisfaction that I have witnessed the rapid progress in Sino-American scientific exchanges in the biomedical fields in the last few years.

I can still remember the days in early 1970's when the door to The People's Republic of China was just being reopened after over two decades of isolation. When I first met Professor H.T. Chang in Shanghai in 1973 and visited his laboratory (Figure 1), neither he nor I would have thought it possible to hold the IBRO-UNESCO-NIH-Academia Sinica Workshop on Neurobiology in Shanghai in October 1980, and to have Professor Chang himself as a Visiting Scientist at Fogarty International Center at NIH the same year.

Professor Chang was chiefly responsible for most of the basic research work that made it possible for successful clinical application of acupuncture anesthesia in various major operative procedures, including brain and heart surgery. As Professor Chang said in his report, despite the devastating effect of the decade of "Cultural Revolution" (1966-1976) during which students in neuroscience lived in almost complete isolation, physical as well as intellectual, from the scientific community of the world, great progress was made in those years. This is even more remarkable when one takes into consideration the poor laboratory facilities the Chinese scientists had to work with. In Figure 1, Professor Chang was performing a delicate experiment in which microelectrodes had to be inserted stereotaxically into various nuclei of the thalamus and hypothalamus of the laboratory animal; in order to steady the laboratory bench from vibrations transmitted from the street cars going by below, pails of sand were used to support and cushion each of the four legs of the operating table on which the animal lay. In spite of all these handicaps remarkable research work in neurophysiology has been accomplished in Professor Chang's laboratory.

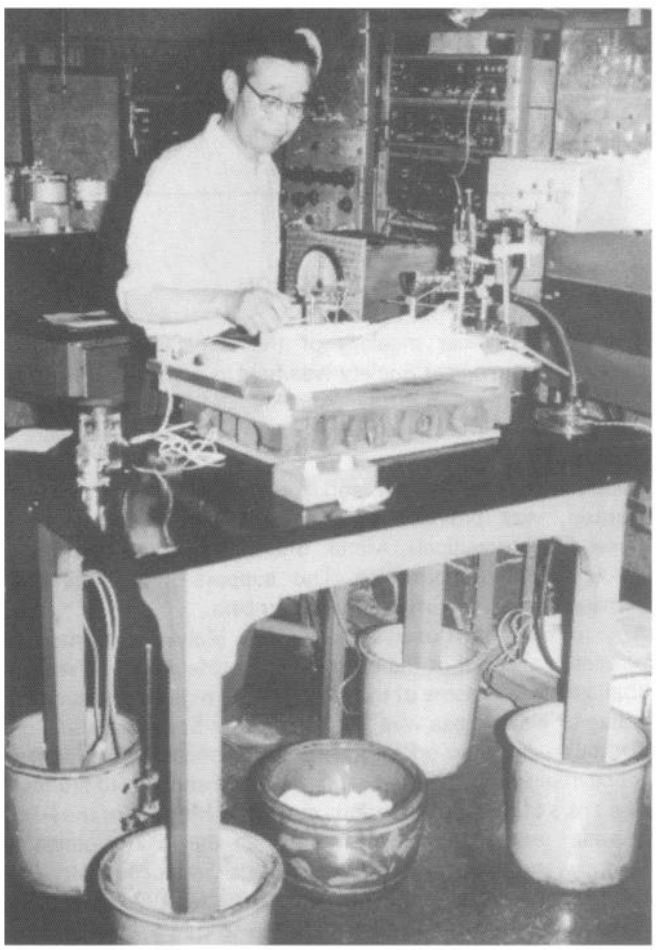

Fig. 1. Professor H. T. Chang of Shanghai Institute of Physiology, in order to insert the microelectrodes *(above)* stereotaxically into various nuclei of thalamus and hypothalamus of the laboratory animal, had to use pails of sand to support and cushion the legs of the operating table *(right)* to steady the later from vibrations from the streetcars going by below.

It is particularly noteworthy that through the effort of your president Dr. Earl Wood, who was a member of the American Medical Teaching Delegation which I led to China in 1979, formal contact was made at last with the Chinese Association of Physiological Sciences and the Institute of Basic Medical Sciences in Peking and the Shanghai Institute of Physiology in Shanghai where Professor Chang did all his work. As you know, Dr. Wood reported his China experiences in June 1980 issue of *The Physiologist*. I should also mention that, as a consequence of his visit, several Chinese physiologists are now working in various laboratories in the United States, including Dr. Wood's at Mayo. It would be very desirable to have more of these young Chinese scientists to come to the United States to spend time and exchange ideas with their colleagues in this country. As Dr. Wood concluded in his report, the future welfare of mankind will be best served by, and to a major degree be dependent on, the fostering and permanent maintenance of friendly, peaceful cooperation between our two great nations.

Tsung O. Cheng, M.D.
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INTERNATIONAL NEWS

IBRO-UNESCO-NIH-ACADEMIC SINICA WORKSHOP
New Techniques in Analysis of Neuronal Circuits

Due to the good offices of Dr. Clinton N. Woolsey, Organizer of the IBRO-UNESCO-NIH-ACADEMIC SINICA Workshop on "New Techniques in Analysis of Neuronal Circuits" held in Shanghai, China, October 7-17, 1980, the following pages represent abstracts of poster presentations made available for the benefit of interested American physiologists.

The following is excerpted from his letter of transmittal. "May I express to you my appreciation and that of our Chinese colleagues of your willingness to have these abstracts appear in *The Physiologist*. I think they will give our members a view of the range of topics and methods being used by our Chinese colleagues in nervous system research."

This material also serves as an appropriate introduction to a newly inaugurated International News Section of *The Physiologist*. In the future, this Section will be used to publicize physiological events occurring outside North America. Members and subscribers are invited to provide material for the new Section.

Orr E. Reynolds, Editor

SUPRASPINAL CONTROL ON NOCICEPTIVE MESSAGES IN DORSAL HORN OF CAT'S SPINAL CORD. Chao Chih-Chi, Yang Chun-Chien and Yang Huan-Qiao. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

Our previous work showed that electroacupuncture and brain stimulation could inhibit the nociceptive discharges of PO neurons of thalamus. This paper is concerned with the effect of the stimulation of raphe magnus nucleus (Rm), periaqueductal gray (PAG) and caudate nucleus (Cd) on nociceptive response of dorsal horn neurons of lamina V. Forty-nine dorsal horn neurons were responsive to radiant heating (<45°C) of the skin and electrical stimulation of sural nerve which excited the C fibers. Almost all units were strongly inhibited by Rm stimulation (100-600 μA). Most of the units were moderately inhibited by PAG stimulation (200-1000 μA), whereas only a few units were weakly inhibited by Cd stimulation. It indicates that the descending inhibition produced by Cd stimulation is not of importance in analgesia. Naloxone (0.5 mg/kg IV.) could partially antagonize the inhibition of Rm stimulation, but had no effect on those of PAG and Cd stimulation. The result suggests that different transmitter systems are involved in the descending inhibition of Rm and PAG. The fact that Rm stimulation could elicit IPSP in a few nociceptive neurons implies that postsynaptic inhibition might be involved in the inhibitory process induced by Rm stimulation.

PROJECTIONS OF HYPOTHALAMUS TO MIDBRAIN IN RAT. Chen Chi-Tang, Wang Pu-Shi and Chien Kuo-Chang. Department of Histology and Embryology, Second Military Medical College, Shanghai, China.

Cell bodies of the origin of the hypothalamic projection to the midbrain were studied in the rat with the method of retrograde axonal transport of horseradish peroxidase (HRP). When small amount of HRP was injected electrophoretically in the dorsolateral part of the central gray, the labeled cells were concentrated mainly in the anterior hypothalamic area, the dorsomedial nucleus, the ventromedial nucleus, the zona incerta, the dorsal premammillary nucleus and the prelateral mammillary nucleus. After injection of the enzyme in the centromedial part of the tegmental area, the labeled cells were found dispersed in the preoptic area and located in the lateral hypothalamus (dorsal to the supraoptic nucleus), the dorsomedial nucleus, the ventromedial nucleus and the dorsal premammillary nucleus.

IDENTIFICATION OF SPECTRAL PEAKS OF R1-6 AND R7-8 RETINULAR CELLS FROM ERG OF COMPOUND EYE OF HOUSEFLY. Chen De-Mao and Ma Wu*. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

Multiple-peaked S_λ curve of dark-adapted red eye of housefly (Musca domestica vicina) was determined by choosing different criterion sizes. At low criterion size (0.2-0.5 mV), the S_λ shows three peaks respectively at 488 nm, 517 nm and 358 nm (488 nm > 517 nm > 358 nm peak) and an additional shoulder at 623 nm. When the criterion size is increased to 1.5-3.0 mV, the 488 peak decreases more than the 517 peak and there is some broadening of the S_λ curve in the blue-green region. At still higher criterion size (4.0-5.0 mV), the spectral peak is shifted to 517 nm and the relative sensitivities of the blue region (425-458 nm) are increased. The spectral sensitivities of ERG of dark-adapted Drosophila melanogaster (wild red eye and mutant white eye) were also measured and compared with the results of Musca.

During adaptation to orange adapting light (579 nm), the S_λ of the blue-green region is depressed more than that due to violet adapting light (405 nm). The relative sensitivity at 623 nm, however, shows considerable increase in both these adapting lights but is depressed by a 630 nm adapting light.

The changes of the spectral peaks determined with the use of different criterion sizes and due to adaption to different monochromatic lights were discussed in regard to contribution of different types of ommatidum retinula cells to the compound ERG.

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A MICROCOMPUTER SYSTEM FOR AUDITORY RESEARCH. Chen Jun-Qiang, Wang Yi-Zhong, Deng Shu-Zhen, Hu Qi-Wei, Xie Jing-Guang and Zhang Guan-Hua. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

A microcomputer system built in 1979 for auditory research is described. It consists of a newly designed mainframe (including 3 microcomputer chips 8085, 8155 and 8755, a multiwaveform generator, a special keyboard, a display panel and interfaces) and peripherals (including a XY plotter, an oscilloscope, a camera, a microelectrode amplifier and a bioelectric pulse slicer). The system can generate the complex stimulating sound with programmable parameters, process the bioelectric pulses recorded from the experimental animal, change the way of experimental observation according to the result obtained, transfer the data of results to XY plotter and plot in the form of histogram. Several programs for routine experiments are available and easy to use. In addition, there is also a variety of subroutines in the EPROM. It is possible and convenient to make new programs according to user's intention. By combining digital and analog circuits the system can be built with little hardware resources and investment and have reasonable performance. The design ideas can also be used for systems applicable to other fields of research in neurophysiology.

AVERAGED EVOKED POTENTIAL IN CAT CEREBRAL CORTEX AFTER STIMULATING C-FIBERS OF SAPHENOUS NERVE. Chen Pei-Xi and Weng Ji-Wei. Department of Physiology, Zhong Shan Medical College, Canton, China.

In order to explore the possibility of recording the evoked potential produced by C-fiber stimulation from the cerebral cortex, the relationship between the appearance of different components of averaged cerebral evoked potentials (AEP) and the excitation of different kinds of afferent fibers in saphenous nerve was studied.

Experiments were performed on 30 cats under chloralose and Flaxedil. The saphenous nerve was stimulated with square wave pulses of various intensities and sometimes blocked by a galvanic current so as to excite selectively different kinds of nerve fibers. The evoked potentials in contralateral somatosensory cortex were averaged through a TQ-19 medical data processor and recorded with a X-Y plotter.

Intensive saphenous stimulation, which excited both Aβ- and Aδ-fibers usually brought forth A-AEP with an early and a late component (latency 9.6 ± 1.0 ms and 203 ± 10.9 ms). A less intensive stimulus, which could excite the Aβ -fiber only, made the late component smaller or even absent in most cases. However, a much higher stimulus above the C-fiber threshold usually elicited a response similar to A-AEP.

After blocking the A-fibers selectively, a stimulus above C-fiber threshold would produce a particular C-AEP at a latency of 147.1 ± 5.1 ms, and the A-AEP disappeared. C-AEP was a mono- or biphasic potential, and its amplitude depended on the amplitude of the afferent C-volley. The latency of C-AEP was shorter than that of the late component of A-AEP. C-AEP was more susceptible to the analgesic Demerol than A-AEP. The phase of C-AEP began to reverse at a depth of 1100μ beneath the cortical surface. Furthermore, C-AEP was depressed by a preceding A-AEP or C-AEP and a preceding C-AEP reduced the A-AEP also

The above results showed that the evoked potential presumably elicited by C-fiber stimulation could be recorded from the cerebral cortex. Usually the C-AEP could not be detected without blocking the A-fiber for the possible reason that the C-AEP could be depressed by A-AEP.

AVERAGED MIDBRAIN EVOKED POTENTIALS ELICITED BY HYPOTHALAMIC STIMULATION. Chen Yi-Chang and Chen Jun. Department of Physiology, Second Military Medical College, Shanghai, China.

Both hypothalamus and paramedian midbrain area have been implicated in pain modulation. The present work was undertaken to study the projections from hypothalamic tuberal region to paramedian midbrain area by average evoked potential (AEP) technique. The hypothalamus was stimulated by bipolar eccentric electrode with a tip-tip distance of about 0.5 mm. The midbrain AEPs were recorded with a fine insulated stainless steel-wire (diameter, 60 μ; resistance, 150 ± 10 kΩ). The midbrain AEP consists basically of two negative waves: N_0 and N_1. N_1 has a latency of 3-6 ms and could follow a PST with a repetition rate of 500 Hz. These results indicate that direct projections from hypothalamic tuberal region to the paramedian midbrain might exist.

EFFECTS OF PHOTIC AND SAPHENOUS NERVE STIMULATION IN PREOPTIC-ANTERIOR HYPOTHALAMIC UNITS IN CATS. Chen Yi-Chang, Wang Chi-Han, Chen Jun, Hsing Pao-Ren and Chen Jin-Gui. Department of Physiology, Second Military Medical College, Shanghai, China.

Cats were operated upon with an initial dose of chloralose-urethane, and then immobilized by flaxedil. The preoptic-anterior hypothalamic region (PO-AH) was approached transpharyngeally with the animal fixed in supine position. Extracellular recordings were made from PO-AH units by micropipette and its responses to photic and saphenous nerve stimulation were tested and analyzed by means of a medical data processor; 200 units were studied. The spontaneous discharge rate of units varied from <1 to <15/sec., but the majority fired at 1-15/sec. Among the 200 PO-AH units, 140 were tested with somatic nerve stimulation and 181 with photic stimulation. Of the 140 units, 69 (49.3%) were responsive to saphenous stimulation; among them 23 units gave excitatory responses, 36 units inhibitory and 10 units inconsistent responses. Four out of 69 somatic units were activated only by peripheral C-fiber inputs, which might be called "pain" units. Of the 181 units, 93 (51.4%) were responsive to photic stimulation; among them 21 showed excitatory response, 62 inhibitory response, and 10 units inconsistent responses. Ten out of 93 photic units reacted to bilateral light stimulations. A long-latency photic unit was noted in PO-AH region. The responses of PO-AH neurons attenuated when the stimuli were applied repetitively. Thirty-four units showed polysensory convergent responses. The "pain" and photic inputs to the PO-AH region and the resemblance of PO-AH to reticular formation neurons were briefly discussed.

INVESTIGATION OF COMMISSURAL FIBRES OF HIPPOCAMPUS AND DENTATE GYRUS IN GUINEA PIG. Dai Hong-Zuo, Wu Wen-Yao and Chunyu Li-Juan. Department of Biology, Fudan University, Shanghai, China.

The commissural fibres of hippocampus and dendate gyrus have been studied by the method of horseradish peroxidase (HRP) in guinea pig. The results are as follows:

1. The superior region (CA1) of hippocampus sends commissural fibres to the same field of the opposite side.
2. The inferior region (CA3) of hippocampus sends commissural fibres to all fields of hippocampus and dentate gyrus of the opposite side.
3. The cells of the polymorphic layer of the dentate gyrus send commissural fibres to the dentate gyrus or the inferior region (CA3) nearby the dentate gyrus of the other side, or perhaps to both of them.

SOME CHARACTERISTICS OF SINGLE CELL RESPONSE TO GRATING PATTERNS IN AREA 17 OF THE CAT'S VISUAL CORTEX. Diao Yun-Cheng, Wang Yung-Kai, Xie Jin-Tang* and Pu Ming-Liang. Institute of Biophysics, Academia Sinica, Beijing, China.

1. Extracellular single unit recordings were made with tungsten-in-glass electrodes in area 17 of the unanesthetized cat's cortex. Visual stimuli were presented in two ways: An overhead projector produced various light patterns on the screen for determining the position of the receptive field and the type of that cell, and a sine-wave and square-wave grating generator constructed from a television set was used for the investigation of spacial frequency characteristics and the contrast-response characteristics of the cell.

2. All cells that responded to and had spacial frequency selectivity for sine-wave gratings were responsive to and spatial frequency selective for square-wave gratings. The optimal frequency for both grating patterns was identical for each cell. The frequency tuning curves of the complex cells for square-wave grating were broader than those of simple cells.

3. The great majority of the recorded cells, of both simple and complex types, was more responsive to square-wave gratings than to sine-wave gratings. And the contrast thresholds for square-wave gratings were also lower.

4. The responses of a few cells (1 unidentified and 6 complex cells out of 54) to square-wave gratings were much higher than to sine-wave gratings in the lower spatial frequency region. The differences became smaller when the contrasts of the gratings were decreased to a level near the threshold for the optimal frequency. This is taken as an indication of the presence or absence of the contributions made by the higher harmonic components within the square-wave gratings.

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EFFECT OF NALOXONE ON INHIBITION OF VISCERO-SOMATIC REFLEX CAUSED BY BRAIN OR NERVE STIMULATION. Du Huan-Ji and Zhao Yan-Fang. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

It is well known that the endogenous opioid system plays an important role in the modulation of pain. The study was designed to answer: (1) To what extent is this system involved in acupunctural analgesia and brain stimulation-produced analgesia? (2) Is there any direct opiate-like action at the spinal cord level?

Experiments were performed on unanesthetized and immobilized cats. The evoked viscero-somatic reflexes were recorded from the 11th intercostal nerve by stimulation of the ipsilateral splanchnic nerve at an intensity strong enough to activate most of the afferent A-delta fibres.

The results were as follows: (1) Stimulation of the common peroneal nerve (to mimic the electroacupuncture) or different brain loci, including the nucleus raphe magnus (Rm), the periaqueductal grey, the central tegmental tract and the nucleus centrum medianum, could produce an inhibitory effect on the viscero-somatic reflexes. (2) Systematic administration of naloxone (0.07-0.80 mg/kg, i.v.) could partially, but never wholly, reverse the inhibitory effects caused by various brain and nerve stimulations. (3) Intrathecal administration of naloxone (0.016-0.1 mg/kg, T9) could also partially reverse the inhibitory effects. (4) After transection of the spinal cord (T6), all the inhibitory effects were almost abolished, but the inhibitory effects produced by stimulation of the dorsolateral funiculi (DLF) remained and could not be reversed by naloxone. (5) Bilateral sections of the dorsal part of DLF, which greatly reduced the brain stimulation-produced inhibition, prevented the naloxone reversals of the inhibition produced by both the Rm and the DLF stimulation, while the control sections made medially did not.

It seems that the endogenous opioid system does not play an important role in the supraspinal control of the transmission of visceral nociceptive messages, although it may partially produce an independent inhibitory action at the spinal cord level. The results suggest that a more powerful descending inhibitory system (probably the serotonergic raphe-spinal system) may be involved in such a control via the DLF.

THE IMPLICATION OF THE SURFACE NEGATIVE WAVE OF CEREBRAL CORTEX EVOKED BY ANTIDROMIC ACTIVATION OF THE BETZ CELL. Fan Shih-Fang and Hu Shi-Ling. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

In previous work, we have found that the cortical response of Betz cells to antidromic stimulation of the pyramidal tract in medulla contains a clear surface negative component of short latency with no sign of postsynaptic activity. As judged from other criteria, however, the antidromic impulse does not travel upwards to the terminal portion of the apical dendrite. Thus, there seems to exist an obvious contradiction, since it is commonly held that when an impulse ceased to conduct further somewhere along the nerve tissue situated in a volume conductor, the segment further on would only serve as a current source, around which only a positive potential change could be recorded. The results in this study, both from the qualitative calculation according to the volume conductor theory and from the model experiment done with peripheral nerve, show that, if the membrane properties of the segment, which the impulse has not invaded, are somewhat different from those of the segment, which the impulse has just passed through, and either the membrane potential of the former is lower and/or the membrane resistivity is higher, a negative potential could be recorded around the inactivated segment. Therefore, it is very likely that the terminal portion of the apical dendrite of a pyramidal cell possesses lower membrane potential and/or higher membrane resistivity as compared with the soma and basal portion of the apical dendrite.

UNIT RESPONSE OF CAT AUDITORY CORTEX TO SIMPLE AND FREQUENCY-MODULATED SOUNDS. Feng Jia-Zhen, Wu Shu-Huei and Lin Hua-Ying. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

Unit responses to white noise, click, tone burst and frequency-modulated (FM) tones were studied in anesthetized and paralyzed cats.

The tuning curves of the auditory neurons (total of 156) were classified into four types: I - wide-range, 52 units, 33%; II - intermediate-range, 30 units, 19%; III - narrow-range, 34 units, 22%; IV - no tuning curve, 40 units, 26%. Most type I units could be activated by click and white noise. Most type IV units were not responsive to any simple sound; however, some of them could be activated by FM tones.

The best frequency of the tuning curves varied with different units, but most were located between 8-32 KHz. Thresholds of units with best frequencies below 8 KHz tended to be higher than those of the high-frequency units.

The correlation between the responses to FM and to simple sound stimuli did not seem to be significant. Some units responded well to both simple and FM stimuli, but some units, having good responses to simple sound, might fail to respond at all to FM tones, and others, sensitive to FM tones of certain frequencies, could not be activated by tone bursts even of the very same frequencies. Responses to FM might be facilitatory or depressive. The great majority of the depressive responses occurred at or above threshold intensity for tone bursts, while about one-half of the facilitatory responses occurred at subthreshold levels.

No neuron was found responding exclusively to increase or decrease of frequency, nor was there a preferred direction pointing to the best frequency of the tuning curve of any of the neurons studied.

CENTRAL CONNECTION OF VENTRAL ROOT AFFERENTS AS REVEALED BY FINK-HEIMER METHOD. Wan Shuen-Tsae*, Shuen-Tsae*, Feng Shen-Yuen** and Feng Jia-Shen**. * Institute of Basic Medical Sciences, Academia Medica Sinica, Beijing, China; ** Lanzhow Medical College, Lanzhow, China.

Unilateral ventral root (Vr) rhizotomy was performed in 10 dogs. Unilateral dorsal root (Dr) rhizotomy, sympathectomy, and laminectomy were also made as controls. Using modified Fink-Heimer and Nauta techniques, degenerating fibers and terminals were traced in the spinal cord and brain stem. The following conclusions were drawn:

1. Degenerating fibers appeared regularly and characteristically in the spinal cord and dorsal column nuclei (DGN) in Vr rhizotomized animals. No degenerating fibers were found in the central nervous system of sympathectomized and laminectomized animals.

2. The diffusely distributed Vr afferents (Vra) could be traced in the spinal cord to more than 10 segments rostral from its entry. The terminal degeneration of VrA mainly distributed in the medial part of the dorsal horn (II-VII laminae). VrA joined the posterior funiculi interpolatedly and the Dr afferents laterally.

3. Experimental data suggest that VrA probably terminated in the reticular area, mainly on non-cluster cells of DCN.

4. The diffuse course of VrA and their termination in the reticular area imply that VrA may be a part of the extralemniscal system.

EFFECTS OF INFERIOR PREFRONTAL AREA LESIONS ON DELAYED-MATCHING AVOIDANCE RESPONSE IN MONKEYS. Hsu Ping-Hsuan, Liu Ren-Yi and Bao Chun-Yang. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

It is well known that cortex around the principal sulcus (PS) of the prefrontal lobe plays an important role in short-term memory in monkeys. However, this conclusion was derived from experiments with appetitive rewards. In this work, we aimed to study the role of various subregions of the prefrontal lobe in an aversive paradigm.

A pure.tone delayed matching avoidance response (DMAR) in a shuttle box was established in 10 monkeys. The alternative delayed response)appetitive reward) in Wisconsin General Test Apparatus, was tested in 3 other monkeys as control. The effects of the frontal lobe lesions on both responses were compared.

Our results showed that 7 out of 10 monkeys succeeded in learning the DMAR with 5 or 9-sec delay. The DMAR was seriously affected after inferior prefrontal (IP) lesions. The alternative delayed responses in another group of animals were retained after IP lesions and impaired only after PS lesions, which had nothing to do with DMAR. However, by increasing the matching samples, the DMAR of IP lesioned animals still persisted.

It is evident that the inferior prefrontal area plays an important role in delayed matching avoidance response. The fact that the destructive effects of IP lesions can be overcome by increasing the delayed-matching samples suggests a much larger brain area was excited and the brain circuit concerned with delayed matching avoidance response may not be stereotyped.

QUANTITATIVE CONSIDERATION OF THE POSSIBLE ROLE OF SARCOLEMMA IN THE REGULATION OF SARCOPLASMIC CALCIUM ION CONCENTRATION OF FROG CARDIAC CELL. Hu Shi-Ling and Fan Shih-Fang. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

It is generally accepted that the change of Ca ion concentration in sarcoplasm, which is regulated by the sarcoplasmic reticulum in the skeletal muscle cell, is the key linkage in the process of excitation-contraction coupling. In the case of the frog cardiac cell, the sarcoplasmic reticulum is poorly developed, the T-tubule may be absent completely and the diameter of the cell is rather small, thus it has been repeatedly proposed that in such a muscle cell, the sarcoplasmic Ca ion concentration may be controlled by the processes occurring in the sarcolemma. In this study, a quantitative test of the possibility of such supposition is made. Assume that the increase of

intracellular Ca ion concentration during activity is due simply to the inward transmembrane diffusion of the ions down their concentration gradient from the extracellular fluid into the cell and the decrease of concentration is attributed to a certain carrier involved in active membrane process. The latter process may be expressed as $Ca^{2+} + X \underset{K-1}{\overset{K1}{\rightleftharpoons}} CaX$. Based on above assumptions, the successive values of the intracellular Ca ion concentration during the course of repetitive stimulation at a given frequency and the asymptotic steady values of concentration under different stimulus frequencies have been calculated and then are compared with the experimental results of "staircase" phenomenon by making use of the known relation between the sarcoplasmic Ca ion concentration and the steady contractile force developed. Fairly good agreement has been obtained within quite a wide range of stimulus frequencies. It is entirely possible that the sarcolemma of frog cardiac muscle plays a crucial role in the regulation of sarcoplasmic Ca ion concentration even in the view of quantitative consideration.

THE CHANGES OF INTRAGANGLIONIC CATECHOLAMINE FLUORESCENCE OF RAT SYMPATHETIC GANGLION AFTER PREGANGLIONIC DEAFFERENTATION. Hua Zhong-Wei. Institute of Basic Medical Sciences, The Academy of Military Medical Sciences, Beijing, China.

The aim of this work is to study the changes of catecholamine (CA) fluorescence induced by glyoxylic acid (GA) in the superior cervical ganglion (SCG) after preganglionic denervation and to find out how they are influenced by age and postoperative time.

The right SCG of 46 rats of five age groups, i.e., 3, 10, 20, 30 and more days, were deafferentated, while the left sides were kept as controls. SCG of both sides were removed from 1, 2, 3, 4 and more than 15 weeks after the operation. They were frozen, sectioned and treated with GA. The sections were put under the fluorescence microscope for qualitative and semi-quantitative direct observations. The irides fluorescence of 15 operated animals were also observed.

The main findings are: (1) a redistribution of CA fluorescence in the intraganglionic neurons occurred as shown by a decrease in the fluorescence intensity in the perikarya and the axonal terminal plexus in the target tissue (irides) and a general increase of the size and number of fluorescent varicosities and fluorescent fibers; (2) all the changes mentioned above occurred in most cases of all groups except the 3-days group. They were found one week after the operation, and there was no definite tendency of increase or decrease in the subsequent observations; (3) the fluorescence intensity in the perikarya decreased more markedly in the younger groups, while in the intraganglionic varicosities and fibers it increased more markedly in the older groups.

It may be suggested that the deafferentation of the ganglion caused changes in the intrinsic modulation of the transmitters in the intraganglionic neurons resulting in the redistribution of CA; it also induced a general collateral sprouting of the nerve processes seen as an increase of the intraganglionic fluorescent fibers and varicosities. It seems that the plasticity of neurotransmitter varied with neurons of different developmental stages, which accounted for the different results in various groups.

CHARACTERISTICS OF CATALEPSIES INDUCED BY l-TETRAHYDROPALMATINE AND TETRAHYDROBERBERINE. Jin Kuo-Zhang (K. C. Kin), Xu Jiao, Wang Xiao-Li, Hong Geng-Xin and Yu Lei-Ping. Shanghai Institute of Materia Medica, Academia Sinica, Shanghai, China.

It was found that l-THP (I) and its analogue THB (II) could produce catalepsy in rats and mice. The THP-catalepsy was more severe than l-THP-catalepsy.

l-THP caused not only a catalepsy, but also a significant rise of 5-HIAA in brain and HVA in caudate nucleus. If the activities of 5-HT neurons were depressed by PCA or PCPA previously, l-THP-catalepsy in rats was augmented markedly. Cinanserine, a blocking agent of 5-HT receptor, also produced a similar but less significant augmentation.

Naloxone selectively antagonized the catalepsy induced by morphine in rats, but could not antagonize the catalepsy by l-THP, THB or haloperidol.

A small dose of AOAA (10 mg/kg) augmented the catalepsy produced by l-THP, a larger dose of AOAA (25/mg/kg) augmented the haloperidol-catalepsy as well. However, AOAA had no effect on the THB-catalepsy. Since AOAA is a well-known inhibitor of GABA-transaminase, it is suggested that l-THP-catalepsy might be related to the GABA-ergic system.

Scopolamine antagonized the haloperidol- and THB-catalepsy selectively, and physostigmine potentiated these catalepsies. But scopolamine potentiated the l-THP- or morphine-catalepsy. Apomorphine and l-dopa augmented the catalepsies induced by halaperidol and THB. These results suggested that the mechanism of haloperidol- and THB-catalepsy is very likely underlain by DA-ergic and ACh-ergic systems, where THB might be a DA-receptor blocking agent as haloperidol is.

CONNECTIONS BETWEEN SPINAL GRAY AND DORSAL COLUMN NUCLEI. A COMBINED ANTEROGRADE AND RETROGRADE HRP STUDY. Ju Gong. Department of Anatomy, The Fourth Army Medical College, Xian, China.

HRP was injected into C6,7 or L5,6 spinal gray in 21 adult cats and serial sections processed according to the benzidine blue reaction technique.

In L5,6 injections, labeled cells were concentrated mainly in the gracile nucleus (GN). Only a few were found in the medial cuneate nucleus (CN). After C5,6 injection most of the labeled cells were found in the CN, with only a minor number in the GN. In both C and L injections, labeled cells were more concentrated in the junctional zone between the GN and CN.

The non-primary spino-DCN fibers were found to project diffusely. After cervical injections the CN was packed with labeled terminal branches, but the GN was only mildy labeled. In CN,the labeled terminal branches were mainly distributed to the non-cluster regions, viz., the rostral one-third and ventral part of the caudal two-thirds of the

nucleus concentrating at the hilum region. A small celled area at the dorsolateral brim of the middle part of the CN was also found to be densely labeled.

After lumbar injections, the labeled terminals were much less than that after cervical injection. The terminals were predominant in the GN and few in the CN.

The areas of distribution of the labeled cells and the labeled terminal branches overlapped but did not coincide with each other. Most of the labeled cells were found in areas relatively clear of the terminal branches. Others were located right at the center of heaviest terminal labeling. The labeled cells were practically buried in pools of dense terminal branches; this indicates that the non-primary afferent fibers might connect directly with at least some of the DCN-spinal cells forming a spino-DCN-spinal feedback circuit.

TEMPORAL FREQUENCY TUNING PROPERTIES OF SUSTAINED AND TRANSIENT NEURONS IN CAT'S LATERAL GENICULATE NUCLEUS. Li Chao-Yi, Chang Yao-Ran and Xu Zing-Zhen. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

Using a sinusoidally modulated light spot stimulus we have observed that most of the geniculate neurons showed either "band-pass" or "low-pass" temporal tuning properties. The purpose of this study is to determine if any correlation exists between the temporal tuning properties and the neuron types. Sustained and transient neurons were identified by comparing the average unmodulated light-discharge rate (ULDR) with the spontaneous dark-discharge rate (SDDR) in each neuron. The ULDR is higher than the SDDR for sustained-on neurons and vice versa for sustained-off neurons. In the transient neurons (both on- and off-types), ULDR and SDDR are the same or their difference is insignificant. Of the 55 neurons studied, 26 were sustained (12 on-, 14 off-) and 29 transient (10 on-, 16 off and 3 on-off-). All the sustained neurons recorded showed without exception "band-pass" tuning properties with a maximum and pronounced declines at both the higher and lower frequency sides. On the contrary, most transient neurons showed "low-pass" tuning properties, which declined only at the higher frequency side but responded well to lower frequencies. Only a part of the transient neurons showed band-pass properties. No difference in temporal tuning properties was observed between the on- and off-response types, neither for sustained nor for transient neurons. The peak loci of the tuning curves of transient neurons were distributed mostly between 1-8 Hz, while those of sustained neurons were between 5-16 Hz. No difference was observed in receptive field size between sustained and transient neurons. In contrast, the receptive fields of the on-type neurons are significantly smaller than those of the off- type neurons, whether sustained or transient.

A STUDY OF THE TEMPORAL FREQUENCY TUNING PROPERTIES OF THE CAT'S LATERAL GENICULATE NEURONS. Li Chao-Yi, Chang Yao-Ran, Xu Xing-Zhen, Song Ru-Gai and Ruan Di-Yun. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

One hundred and twenty-six LGN neurons were examined in unanesthetized immobilized cats. The temporal frequency tuning curves of the single neurons were measured by stimulating the cat's eye with a sinusoidally modulated light spot, generated on a CRT and presented to the center of each neuron's receptive field. Average discharging rate was used as an index to judge the sensitivity to different modulating frequencies. By comparing the mean impulse rates responding to modulated light (modulated discharge rate) to those to unmodulated light (unmodulated discharge rate), two opposite tuning properties were observed. Majority of the cells (93.7%) showed modulation-excitatory curves, in which the modulated discharge rates were higher than the unmodulated ones. A minority of the cells (6.3%) showed modulation-inhibitory curves, in which the modulated discharge rates were lower than the unmodulated ones. The modulation-excitatory curves could further be classified into two subtypes, the "band-pass filters" and the "low-pass filters" according to the shapes and the bandwidths of the curves. Similarly, the modulation-inhibitory curves could also be divided into two subtypes, the "band-rejection filters" and the "low-rejection filters". Most of the tuning curves have only one peak. The peak loci for 110 curves show a normal distribution centered at 7 Hz. On both sides of the curves, side-bands opposite in direction to the main part of the temporal frequency tuning curve could often be seen. Some differences between the tuning curves due to stimulation of receptive field center and of periphery were also observed.

FM DETECTION IN HUMAN SUBJECTS AND IN GUINEA PIGS. Liang Zhi-An, Yang Qaing-Hua and Lin Hua-Ying. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

Frequency modulation (FM) detection is essentially a form of pitch discrimination. FM detection threshold (Δf) can be easily measured in human subjects by a psychophysical method and in guinea pigs by the cortical evoked response method with the aid of averaging technique. Relatively small values of the measured Δf indicate that these methods are accurate.

Results from human subjects and from guinea pigs are comparable. For high tonal frequencies, Δf increases linearly with the increase of frequency, while for low frequencies it remains more or less constant.

Δf is also a function of tone intensity. In guinea pigs, small Δf can be obtained usually in the intensity range of 70-90 dB SPL; below 50 or 60 dB, Δf becomes much larger. But in human subjects Δf increases slightly only when tone intensity decreases to as low as 30 dB.

The cortical response in guinea-pigs evoked by FM may be an "on-response", an "off-response" or an "on-off-response", which implies in essence the

sensitivity to the direction of frequency changes. The latencies for both the on- and the off-responses are very short; consequently, it is unlikely that modulation duration would exert any effect on Δf. In human subjects, however, Δf is definitely dependent on modulation duration.

ROLE OF SOMATOSENSORY AREA I IN OPERANT CONDITIONING AND ACUPUNCTURE ANALGESIA IN MONKEYS. Liu Jin-Long, Lu Yun-Yang, Liang Yun-Fei, Cheng Xiao-Zhong, Wang Xiao-Ming; Zeng Ya-Cai, Xie Hui-Ming and Han Guan-Yu. Department of Physiology, Guangxi Medical College, Nanning, China.

Experiments were carried out on six conscious, movable rhesus monkeys (Macaca mulatta) by using operant conditioning induced by noxious stimulation of the leg as an indication of pain. Single- or multi-unit activity was recorded simultaneously from the leg representation in the somatosensory area I of the cerebral cortex by tungsten microelectrode before, during and after acupuncture. When the threshold of conditioning (pain threshold) was elevated by acupuncture, the nociceptive discharge was inhibited in some of the cortical neurons and the background activity was increased. Intracortical stimulation of the leg representation in SI through the same recording electrode usually caused a decrement both of the pain threshold in the contralateral leg and of the analgesic effect of acupuncture, but the pain threshold in the ipsilateral leg was not affected. Blockage of the leg representation in SI by ice-saline first decreased and then increased the pain threshold in the contralateral leg, but the pain threshold in the ipsilateral leg was unchanged or only lowered slightly. It was suggested that the somatosensory area I might play a role in pain perception and acupuncture analgesia.

SOME PROPERTIES OF SYNTHETIC SLEEP-INDUCING PEPTIDE - PURE α - ASPARTYL DSIP. Liu Shi-Yi*, Zhang Wen-Yuen*, Wang Ze-Sheng* and Tai Xiu-Ju*, Ji Ai-Xue†, Li Chong-Xi†, Ye Yun-Hua† and Xing Qi-Yi†.
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Some sleep-inducing substances have been isolated from rabbits, goats and rats. Among all these substances only the structure of "delta-sleep-inducing-peptide" (DSIP) has been established. An attempt was made to synthetize DSIP, but the product was found to be a mixture of 20% [Asp^5] - α - DSIP and 80% [Asp^5] - β - DSIP. The present study was undertaken to investigate some physiological actions of the pure α - aspartyl DSIP ([Asp^5] - α -DSIP), which was synthetized with the liquid phase method and has preliminarily been evaluated by us.

Experiments were performed on rabbits and guinea pigs. The effects of [Asp^5] - α - DSIP on delta and sigma activity were evaluated on 40 adult rabbits of either sex during morning hours, to avoid the influence of the circadian sleep-wakefulness cycle. EEG signals were recorded and quantified by an automatic frequency analyzer and by "off-line" computer analysis. The results are as follows:

1. The effective dosages of pure α - aspartyl DSIP differ with different routes of administration (mesodiencephalic ventricle, lateral ventricle, i.v. and i.p.). Among them the mesodiencephalic route seems to be the most effective one, via which the appropriate dosage for inducing an increase of delta and sigma activity in rabbits is around 5 μg/animal.
2. In contrast with the usual dose-effect relationship of sleep-inducing drugs, higher doses of [Asp^5] - α - DSIP (50 or 100 μg/animal) produce less significant effects.
3. No obvious sign of adaptation was observed during six days of consecutive intravenous administration of [Asp^5] - α - (50 μg/kg).
4. Our results confirm that [Asp^5] - α - DSIP can pass the blood-brain barrier in rabbits and guinea pigs.

A STUDY OF THE "GROANING CENTER" IN CAT, ITS LOCATION AND CONNECTIONS. Lu Cheng-Lin and Zhu He-Nien (Chu Ho-Nien). Department of Physiology, Second Military Medical College, Shanghai, China.

Our present study is to ascertain the histological location and fiber connections of the "GROANING CENTER", which on excitation induced visceral and motor reactions.

According to microscopic study of sections, the "GROANING CENTER" is located in the lateral tegmental region. It lies at the ventrolateral side of the N. trochlearis, medial to the lateral lemniscus and the N. paralemniscalis (NPL, Jasper), dorsal to the N. pedunculopontile tegmentalis and ventral to the N. inferior colliculis. This center extends about 1 mm. anteroposteriorly, 1.5 mm. mediolaterally and about 2 mm. dorsoventrally. This area chiefly consists of fibers and scattered cells of medium and small size. A cluster of larger cells has been observed in this center.

By HRP retrograde transport study, we found that the "GROANING CENTER" has extensive connection with other brain areas. In the hypothalamus, labeled cells were found in various nuclei, such as the paraventricular nucleus, the dorsomedial nucleus, the posterior nucleus, the lateral hypothalamic nucleus and the anterior hypothalamic area.

EFFECT OF INTRAVENTRICULAR APPLICATION OF 3-QUINUCLIDINYL BENZILATE (QNB) ON DISCRIMINATION LEARNING IN RATS. Mei Zhen-Tong and Fu Cui-Zhen. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

A total of 33 rats was divided into 3 groups: one group received injection of QNB with a doze of 40 μg/20 μl and the other two groups were used as controls; one received injection of 20 μl of saline and the other no treatment. A stainless steel cannula was implanted chronically in the left lateral ventricle of the rat before training. The animals were trained to perform light-dark discrimination learning for a period of 5 consecutive days with 20 trials per day. Physiological saline of ZNB was administered into the ventricle

immediately after the completion of each training session. From the 3rd session of training, the percentage of correct responses in all control groups reached 90% or more, which was considered as the criterion of learning. However, the percentage of correct responses in QNB-injected group reached criterion from the 5th session. The difference between control group and QNB-injected group is statistically significant. Autoradiographical study of the distribution pattern of injected 3H-QNB showed an intense blackening around the lateral ventricle as well as in the hippocampus, and a minimal blackening was observed over the cerebral cortex. Under this condition, QNB delayed discrimination learning by its action as a muscarinic anticholinergic. It was suggested that the slowdown of discrimination learning in the QNB-injected group might represent the effect of the drug on memory consolidation and the muscarinic cholinergic receptors in hippocampus might play an important role in this memory process.

MIGRATION OF CERTAIN ORGANELLES IN CULTURED NEURONS. Pao Xuan, Zian Miao-Shen and Xu Wei-Qi. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

The aim of this work was to provide a detailed description of the movement of intracellular particles in the cultured neurons. The spinal cord and frontal cortex from 1-10 day old kittens were cultured and kept in good condition for a period of one month. The histological organization of these cultured neurons was still maintained and resembled that of the tissue of origin. The dendrites usually had many branches arranged in a certain geometrical pattern according to the neuron types they belonged to. The axon extended only for a short distance.

The migrating particles in the axon and the dendrite were detected and filmed under anoptral contrast microscopy. Film-by-film analysis of the migration of individual particles revealed the features of their movement:

1. The migrating particle could sometimes be seen to reverse its direction of motion, although most particles had a strong tendency to move in one direction, either somatofugally or somatopetally.
2. The speed of migration varied from 5 μm/min to 0.01 μm/min. It was observed that some of the particles would slow down or even stop their movement at the same region along the neurite. Sometimes the moving particle appeared to pulsate within the axon.
3. The size of moving particles ranged from 1.0 μm X 1.0 μm to 5 μm X 1.7 μm.
4. An electron micrograph of one migrating particle in a dendrite revealed that it contained a lysosome adjacent to a mitochondrion. Numerous microfibrils, parallel microtubules and a network of smooth endoreticulum were also seen in the dendrite.

ENDOCYTOSIS OF HORSERADISH PEROXIDASE IN CULTURED KITTEN NEURONS. Pao Xuan, Qu Fu-Jin and Dou Yue-Mei. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

Horseradish peroxidase (HRP) is an enzyme used for years to study endocytosis. The purpose of the present investigation is to study, by means of electron microscopic examination, the routes of uptake and intracellular distribution of HRP in cultured kitten spinal neurons.

The spinal cord tissue of 1-10 day old kittens was cultured in good condition for a period of one month. Cultured neurons were incubated with 0.25-0.5% HRP in serum-free medium for 5-20 min. or 1 hr. at 37°C. The fixative used was 2.5% glutaraldehyde in cacodylate buffer.

It was found that endocytosis occurred at the filopodia and vesicle-filled mound-like protrusions of dendrites, where accumulation of HRP labeled organelles can be identified. HRP was incorporated into vesicles, short tubules and small cup-shaped bodies distributed in dendrites as well as in perikaryon. Incubation with high concentration of HRP for a long period resulted in heavy labeling of the whole cell.

CHANGES IN THE MOTONEURONE RESPONSE AFTER INTRAMUSCULAR INJECTION OF BOTULINUM TOXIN. Rong Xin-Wei. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

Botulinum toxin (B.T.) type A was injected into the triceps surae group of muscles in the cat, causing chronic n-m block in these muscles. About three weeks after the injection, the electrophysiological responses of the motoneurones of the medial gastrocnemius (m.g.), lateral gastrocnemius (l.g.) and soleus (sol.) muscles, either to orthodromic stimulation of the dorsal roots, or to antidromic stimulation of their respective muscle nerves, or to a constant current passing through the soma membrane, were examined with the aid of intracellular microelectrodes. The main results obtained were: In comparison either with the typical responses in normal cat or with the responses of the contralateral unpoisoned side of the spinal cord of the same experimental animal, the responses of the motoneurones of the poisoned side showed in most cases a striking shortening of the afterhyperpolarization (AHP), a decrease in the duration of the action potential and a decrease in the prominence of the IS-SD spike inflection, and in general started to give repetitive discharges with the passage of weaker constant current. With two antidromic stimuli, the second SD response appeared at shorter stimulus intervals on the poisoned side. B.T. did not affect the conduction velocity of the motor axons and the resting potential of the motoneurone soma, and in general left the size of the action potential overshoot unchanged. On all these three points the effect of B.T. forms a striking contrast to that of axotomy. In relation to AHP, B.T. distinguishes itself by having a shortening effect on the motoneurones of all the three muscles - m.g., l.g. and sol., while axotomy and TTX block of nerve conduction only affect the AHP of the sol. motoneurone.

The mechanism underlying the B.T. effect calls for further study. Presumably the occurrence of motor nerve terminal sprouting in B.T. poisoned muscle is an important factor.

EFFECT OF ACUPUNCTURE OR NUCLEUS RAPHE MAGNUS STIMULATION ON INTERCOSTAL RESPONSE ELICITED BY STIMULATION OF MOTOR CORTEX. Shen E, Ouyan Shou, Ma Wei-Hsiang and Lan Ching. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

It was shown previously that acupuncture activated the bulbar medial reticular formation, including the nucleus raphe magnus, which in turn sent descending impulses to inhibit the viscerosomatic reflex (VSR, a splanchnico-intercostal response) and block the ascending transmission of the afferent visceral A-delta impulses at the spinal cord level. The present work deals with the question whether the descending impulses could inhibit the motor system as well as the sensory system. The effects of acupuncture or stimulation of the nucleus raphe magnus on motor cortex stimulation elicited intercostal nerve response (MIR) were observed and compared with the effect on the VSR. Unanesthetized, immobilized cats were used. It was found that electroacupuncture at the lower limb or sustained stimulation of the peroneal nerve (to mimic acupuncture, the intensity is adjusted just below the threshold of A-delta fibers) could not inhibit the MIR in 50 out of 65 trials, and sometimes even facilitated it, while the VSRs were always completely inhibited by the same stimulation. Stimulation of the nucleus raphe magnus gave approximately the same result.

It has been reported that morphine analgesic effect is largely due to activation of the descending inhibitory system. Intravenous injection of etorphine (8 ug/kg), a morphine derivative, enhanced the MIRs, but depressed the VSRs. Naloxone (0.15 mg/kg,iv.) reversed the etorphine effects.

It is therefore concluded that the descending inhibitory system involved in acupuncture or morphine effect exerts far less inhibitory influence on the motor system than on the sensory system.

FURTHER STUDIES ON DESCENDING INHIBITORY PATHWAY. Shen, E., Tung Hsin-Wen, Ye Wei-Ling, Chian Chi-Wa and Shan Hong-Ying. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

A few points have been added to the study of the bulbar descending inhibitory pathway, which is known to be situated in the dorsolateral funiculi (DLF) of the spinal cord. All the experiments were done on cats.

1. Taking the release of viscerosomatic reflex from the tonic descending inhibition as an index, we could see after various lesions in the DLF at T3 that the descending fibers might be diffusely scattered in the DLF, but they were relatively concentrated near the dorsal horn.

2. There were significant increases in 5-HT and NA content in the spinal segment just above the bilateral DLF sections (at T3 near the dorsal horn) on the 4th day after operation, suggesting accumulation of the monoamines in the central cut end of the descending fibers.

3. Fluorescent histochemical study also showed remarkable accumulation of 5-HT and NA in DLF above the bilateral sections (at T3 near the dorsal horn) on the 4th day after operation. Accumulation of 5-HT in the perikarya in the nucleus raphe magnus was also observed.

EPILEPTIC DISCHARGES OF CALLOSAL NEURONS. Shen Ke-Fei, Zhuang Yun-Shi and Xu Zhi-Chen. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

Intracellular events of cortical neurons were studied in an epileptic focus produced by topical application of penicillin (10^5 unit/ml) to the pericruciate cortex of cats with special reference to the effects elicited by various parameters of electrical stimulation to the corpus callosum. Three types of response were found in callosal neurons to callosal stimulation within the penicillin focus, namely the depolarized type, hyperpolarized type and depolarized-hyperpolarized type. Fully developed epileptiform discharges were evoked only when the strength of callosal stimulation exceeded a certain threshold, which was higher than that of eliciting an antidromic action potential. However, the epileptiform discharges could be provoked, when a train of subthreshold callosal stimuli (100 cps) was delivered. The results indicate that temporal and spatial summation are necessary for provoking an epileptic discharge.

TOOSENDANIN--A NEW PRESYNAPTIC NEUROMUSCULAR BLOCKING AGENT OF PLANT ORIGIN: 1. IT'S EFFECTS ON TRANSMISSION AND FINE STRUCTURE OF NEUROMUSCULAR JUNCTION. Shih Yu-Liang, Huang Shi-Kai, Sung Hsiu-E, Yang Ya-Qin and Wei Nai-Sen. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

Toosendanin ($C_{30}H_{38}O_{11}$) is a triterpenoid derivative extracted from the bark of Melia toosendan Sieb et Zucc used in Chinese traditional medicine as an anthelmintic against ascaris. We found that toosendanin had a selective and irreversible action on presynaptic terminals at the neuromuscular junction similar to that of botulinum toxin and β-bungarotoxin.

1. Toosendanin blocked the neuromuscular transmission without affecting the conduction of nerve impulses in nerve trunk and the resting potential and the acetylcholine sensitivity of the muscle. The tension of muscular contraction elicited by direct stimulation was augmented in the poisoned muscle. Bathing the preparations with toosendanin ($5X10^{-5}$,37°C) for only 5 min was sufficient for producing neuromuscular block.

During the development of toosendanin blockade, the tetanic contraction of muscle to indirect stimulation could not be maintained and posttetanic inhibition also appeared.

2. The neuromuscular blocking action of toosendanin was shown to be both concentration- and temperature-dependent. The paralysis time, i.e., the time from the addition of drug to the disappearance of muscular contraction, was inversely proportional to the biquadratic root of toosendanin concentration

and its temperature coefficient (Q10) was about 3.5.

The onset of paralysis was accelerated by repeated indirect stimulation and by increased CA^{++} concentration in the medium.

3. Electronmicroscopic observations on the neuromuscular junction of diaphragm after subcutaneous injection of toosendanin in mouse, showed an increase in the width of the synaptic cleft and a reduction in the number of synaptic vesicles at the nerve terminal.

TOOSENDANIN--A NEW PRESYNAPTIC NEUROMUSCULAR BLOCKING AGENT OF PLANT ORIGIN: 2. ELECTROPHYSICAL OBSERVATIONS ON IT'S PRESYNAPTIC BLOCKING EFFECTS. Shih Yu-Liang, Wang Wen-Ping and Hsu Ke. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

1. With the development of neuromuscular block due to toosendanin, the following sequence of changes could be recorded intracellularly from the end-plate region. A failure of muscle action potential occurred first, leaving alone the end-plate potential (e.p.p.) which then decreased progressively and finally disappeared. The e.p.p. elicited by a train of stimuli showed randomly varying amplitudes.

After addition of toosendanin to curarized preparations, a slight increase in e.p.p. amplitude could first be seen, then was followed by a gradual decrease until e.p.p. disappeared. The influence of toosendanin on the mean quantal content of e.p.p. was the same as that on the amplitude of e.p.p.

2. Toosendanin at first increased the frequency of m.e.p.p. but eventually abolished it. The duration of time with increased m.e.p.p. frequency was shortened by indirect stimulation.

3. In preparations treated by toosendanin, high Ca^{++} solution (8 mM) could increase temporarily the amplitude of e.p.p. in recently paralyzed neuromuscular junction. The frequency of m.e.p.p. increased after addition of guanidine (3 mM) to the medium. 4-Aminopyridine (2.6×10^{-6}) could augment temporarily the gradually decreasing amplitude and quantal content of e.p.p. and at the early stage of toosendanin poisoning it could even induce the recovery of contraction response to nerve stimulation.

THE EFFECT OF VENTRICULAR INJECTION OF PITUITRIN, OXYTOCIN AND ADH ON GROANING RESPONSE. Song Chao-You, Lin Bao-Cheng, Ouyang Gou-Shun, Wu Chong-Ren, Zhu Yan-Xiang and Zhu He-Nian (Chu Ho-Nien). Department of Physiology, Second Military Medical College, Shanghai, China.

We took the groaning response as a measure of pain response. The effect of intraventricular injection of pituitrin, oxytocin, ADH and saline on groaning response was observed.

23 cats under pentobarbital anesthesia were used. We stimulated the "Groaning center" once every 20 minutes within the period of 100 minutes. Each stimulation lasted 10 seconds. Groanings were recorded on tape and transformed into oscillographic records. Intensity of the groaning response was expressed in db. The first two responses are controls, followed by those produced by injection of different hormones.

The number and intensity of groaning responses before and after injection were compared.

Different kinds of humoral injections, all depressed the groaning response to a certain extent. The depressing effect of oxytocin and pituitrin on groaning is greater than that of ADH. Saline injection has no effect on the groaning response.

Our results suggest that the analgesic effect on the groaning response may be due to liberation of these hormones.

DYNAMIC PUPILLARY RESPONSE TO POSITIVE DIFFERENTIAL LIGHT STIMULUS. Sun Fu-Chuan, Liu Hao-Kun and Liu Yu-Min. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

1. Under low intensity background illumination, the pupil responds only to an increase in the intensity of light stimulation by a transient constriction, when the extent and rate of change of light exceed a certain value. We termed this response the dynamic pupillary response in order to differentiate it from the more sluggish and less pronounced response moeity that governs the static pupil size according to the level of light adaptation.

2. Pupillary response to frequency-modulated sinusoidal light stimulation shows that regular response can be elicited only over a limited range of frequency around 0.5 c/w. Both below and above this frequency, no regular or sine-wave approximated response can be obtained. Consequently no Nyguist diagram is derivable from such an experiment.

3. Analysis of a series of records at near threshold stimulation suggests that the dynamic response is light-precipitated congruence of a few hippi.

4. The dynamic response can be described by a third order differential equation based upon dynamic process analysis to an impulse function.

OBSERVATION ON SPONTANEOUS MINIATURE POTENTIALS AT THE NEUROMUSCULAR JUNCTION OF THE INSECT EUPOLYPHAGA SINENSIS WALKER. Sun Yi-An and Ma Wi*. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

In the levator tibia muscle of Eupolyphaga Sinensis Walker, the spontaneous miniature excitatory postsynaptic potentials (mepsp's) were studied with conventional intracellular microelectrode technique. The resting potential of the muscle fibers is 61±0.32 (S.E.) mV. The mean amplitude of the mepsp's is 0.67±0.18. This value is much larger than that reported for cockroach, which is about 0.18-0.3 mV. The amplitude distribution of the mepsp's in normal fiber displays a number of peaks that are integral multiples of the first peak. The smallest peak is about 0.22 mV. The number of the smallest mepsp's in the first wave normally amounts to 5-8% of the total. Treatment with Fenvalerate (an insecticide, s-5602) increased the percentage

of small mepsp's and reduced the mean amplitude of mepsp's, but the amplitude of the smallest mepsp's was not affected. For the statistical analysis of the frequency distribution of the mepsp's and the interval between two succeeding events the following methods have been used, that is, X^2-test, Kolmogorov-Smirov test, Dispersion test, Modified mean test, Variance-time curve and In-survivor function. All results showed that it fits with Poisson prediction.
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OBSERVATION ON DORSAL ROOT REFLEX CONVEYED BY C AFFERENT NERVE FIBERS. Tan De-Pei, Zhang Shu-Jie and Mao Jian-Ping. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

The dorsal root reflex conveyed by A afferent nerve fibers has been studied in detail, but that by C afferent nerve fibers was not reported in the literature. In this paper the dorsal root reflex conveyed by C afferents was observed by recording the unit discharges of C fibers from the fine filaments of the dorsal root. Among the 28 experiments, dorsal root reflex conveyed by C afferents could be identified only in 5 cases; thus its occurrence was a rarity. The activation of A-delta or C afferents was necessary for eliciting the dorsal root reflex conveyed by C afferents. This was in sharp contrast to that for eliciting the dorsal root reflex conveyed by A afferents, where A-delta or C afferent volleys were ineffective. Intraspinal latency of dorsal root reflex conveyed by C afferents ranged from 17-57 ms, which was extraordinary long as compared with that of A afferents.

AUTONOMIC NERVOUS ACTIVITY DURING ACUPUNCTURE IN THE RAT. I. CHANGES OF NEUROTRANSMITTERS IN SYMPATHETIC NERVOUS CENTERS. Wan Shuen-Tsae and Wei Yen-Go. Institute of Basic Medical Sciences, Academia Medica Sinica, Beijing, China.

The cholinesterase activity and the content of catecholamines in the sympathetic nervous centers (posterior nucleus and lateral area of hypothalamus, as well as intermediolateral nucleus of spinal cord) of 73 acupunctured rats were determined and compared with those in 36 control animals. The results were as follows: (1) The percentage of animals with strong acetylcholinesterase activity in these nuclei was higher in the acupuncture group than in the controls. The higher the elevation in pain threshold after acupuncture, the greater was the number of animals with strong acetylcholinesterase activities. (2) The relative number of animals with high intensity of noradrenaline fluorescence in the terminals of adrenergic fibers was found to be greater in acupuncture group than in the control group. These results seem to indicate that the activity of sympathetic centers was somehow depressed following acupuncture.

AUTONOMIC NERVOUS ACTIVITY DURING ACUPUNCTURE IN THE RAT. II. CHANGES OF NEUROTRANSMITTERS IN PARASYMPATHETIC NERVOUS CENTERS. Wan Shuen-Tsae and Wei Yen-Go. Institute of Basic Medical Sciences, Academia Medica Sinica, Beijing, China.

The cholinesterase activity and catecholamine content in the parasympathetic nervous centers (medial preoptic area and dorsal vagal nucleus) were determined with histochemical techniques in 19 acupunctured and 19 normal rats. The preliminary results obtained were as follows: (1) Animals with strong and moderate cholinesterase activity in these nuclei were fewer in number in the acupuncture group than those in the control group. The difference was more marked when the activities in dorsal vagal nucleus were compared alone ($P=0.05$). (2) No significant difference in noradrenaline or adrenaline content within the terminals of catecholaminergic fibers was found between these two groups. Our data suggest that acupuncture might induce activation of the parasympathetic nervous centers but catecholamines seem not to be involved in the process.

EFFECT OF MANGANESE AND ASPARTATE IONS ON HRP UPTAKE OF THE SYNAPTIC TERMINALS OF GEKKO RECEPTOR. Wang Hou-Hua, Liu Yu-Min, and Qu Fu-Jin. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

Effects of Mn^{++} and aspartate on the HRP uptake were studied in the rod terminals of a species of nocturnal gecko retina (Gekko japonicus). The results and conclusions are as follow:

1. 15% of the synaptic vesicles are typically stained by HRP in the dark-adapted preparation. Light depresses the uptake down to about 2%.
2. 5mM Mn^{++} inhibits the uptake of HRP by the rod synaptic vesicles to the same extent as that due to light adaptation.
3. 100mM aspartate accelerates HRP uptake, especially of the synaptic vacuoles.
4. In a minority of instances, Mn^{++} shows a slighter predilection to abolish ERG b wave than a wave, but usually both waves are affected simultaneously. It appears that the inhibitory effect of Mn^{++} on the HRP uptake is mainly due to synaptic blockage. Whether this is also aided by some direct action by Mn on the receptor is uncertain.
5. The present work supports the prevailing theory concerning the mode of transmission of visual information from receptor to second-order neurons in the vertebrate retina.

FUNCTIONAL CONNECTION OF HABENULA TO LOCUS COERULEUS AND ITS RELATED TRANSMITTER. Wang Shao and Yei Lin. Bethune Medical College, Changchun, China.

Our previous work demonstrated that the discharge rate of neurons of nucleus raphe magnus could be decreased by electric stimulation of the habenular nucleus (HN) and increased by destruction of HN. Since HN is an important relay nucleus connecting the limbic structures with the brain stem nuclei and the function of raphe nucleus is antagonistically related with locus coeruleus (LC), it is worthwhile to study the functional relation of HN

to LC. The unit discharges of LC neurons were recorded by glass microelectrode in rats. The discharge rate of LC neurons was increased by noxious stimulus (pinching the tail or hind paw) and inhibited by iontophoretic ejection of etorphine to the LC neurons. The inhibitory effect of etorphine could be reversed by iontophoretic ejection of naloxone. Electric stimulation of HN could increase the discharge rate of LC neurons. Electric coagulation of ipsilateral H (2mA, 15sec) could temporarily depress the discharge rate of LC neurons for a period of 20-30 min.

The effects of different transmitters on the discharge rate of LC neurons was decreased by GABA (0.2M, 60nA) and increased by ACh (0.2M, 27nA). When ACh and electric stimulation of HN were applied simultaneously the discharge rate of LC neurons increased still further. Iontophoretic ejection of atropine (0.2M, 30nA) not only decreased the discharge rate of LC neurons, but also offset the excitatory action of HN stimulation on the LC neurons. On the contrary, iontophoretic application of eserine (0.3M, 30nA) could increase the discharge rate of LC neurons and also facilitate the excitatory action of HN on LC neurons. These results suggested that HN, the relay nucleus of limbic system, could activate the LC neurons and the transmitter involved might be ACh.

EFFECTS OF NALOXONE ON UNIT FIRING IN RAT DORSAL RAPHE NUCLEUS. Wu Ben-Jie, Xu Jia-Ling, Li Ding-Zhao, Chen Ting-Fu and Nei Shu-Gin. Department of Biophysics, Beijing Medical College, Beijing, China.

The effect of injecting naloxone, both iontophoretically and intraperitoneally (ip), on the electrical activities of the neurons of rat dorsal raphe nucleus (DRN) in response to electro-acupuncture was studied. No significant difference was observed between the effects of naloxone iontophoresis on (DRN) units excited by electroacupuncture (UEEA) and units not responding to electroacupuncture (UIEA). Most of these two kinds of units were not affected by naloxone iontophoresis. On the contrary, the responses of all 12 UEEA were partially reversed by ip administration of naloxone (1 mg/kg). These facts were interpreted preliminarily as follows: The unresponsivness of the neurons in DRN to naloxone iontophoresis might be related to the low density of the opiate receptor on these neurons, and the reversive effect of ip injection of naloxone showed that enkephalin was involved in the neuronal pathway mediating the DRN response to electroacupuncture, although it may not directly act on DRN neurons.

DISTRIBUTION OF AXONAL COLLATERALS OF CAT PYRAMIDAL TRACT NEURONS AS REVEALED BY INTRACELLULAR HRP STAINING. Wu Jian-Ping, Zheng Ze-Hui, Mao Jin-Biao, Lu Jin-Gen and He Xiao-Wen. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

The distribution of axonal collaterals of pyramidal tract (PT) neurons in cat motor cortex was studied by means of intracellular injection of horseradish peroxidase (HRP). Glass microelectrodes were filled with 10-12% HRP solution (Boehringer, Grade I, in 0.3 M Nacl). PT neurons were identified by antidromic stimulation at medullary pyramid and direct current was then passed through the recording microelectrode to inject HRP into the neuron. The amount of injecting current ranged from 104 to 220 nA minute. The survival time of the animal after injection was 0.5-3.5 hours. The preliminary results obtained from 6 PT neurons indicate:

1. In area 4γ axonal collaterals of PT neurons were mainly distributed in layer V and VI of the cortex.
2. Collaterals of slow PT neurons tended to spread densely within an area along the longitudinal axis of the neuron, while those of fast PT neurons often had additional horizontal branches to more distant region.

INTERACTION OF SOME NEW GLYCOLATE ESTERS WITH MUSCARINE CHOLINERGIC RECEPTORS IN MOUSE BRAIN. Ye Shu-Zhen, Xu Heng, Jin Wen-Qiao, Xia Xing-Lin, Li Gui-Fen and Chi Zhi-Qiang. Shanghai Institute of Materia Medica, Academia Sinica, Shanghai, China.

In order to study the relationship of muscarine cholinergic receptor affinity and anticholinergic effect of anticholinergic drugs, some new glycolate esters synthesized by our laboratory with different anticholinergic potency were tested. In the muscarine receptor binding assay, these compounds competitively inhibited stereospecific binding of ^{3}H-QNB with muscarine receptor in p_2-fraction of mouse brain. Some drugs with strong anticholinergic effect, such as 7811, 7803, exhibited high receptor affinity. Some with weak effect, such as 7702, 7804, 7810, exhibited low receptor affinity. Those with moderate effect, such as 7701, B-7601, exhibited moderate receptor affinity. If plotted for ED_{50} (the drug dose giving 50% antitremor effect) against IC_{50} (the drug concentration giving 50% inhibition of ^{3}H-QNB binding), good linear correlation between IC_{50} and ED_{50} (correlation coefficient is 0.981) was obtained

Autoradiographic localization of ^{3}H-QNB in mouse brain, and competitive displacement of glycolate esters for the specific ^{3}H-QNB binding were studied. It was found that high densities of autoradiographic grains were over the corpus striatum, hippocampal formation and cerebral cortex. The greatest densities of ^{3}H-QNB site were in striatal regions. If the animals were pretreated with strong anticholinergic drug, such as 7811, the density of grains in striatum was markedly reduced. The effect of 7811 was more potent than or equal to the effect of Scopolamine. When examined quantitatively, the nucleus caudatus-putamen had 41.56 grains per 500 um^2 in control tissue, and 1.86 grains per 500 um^2 in 7811-pretreated tissue. If the animals were pretreated with weak anticholinergic drug, such as 7810, the density of grains in striatum was reduced too. The results indicate that the ^{3}H-QNB binding in these areas is the specific, pharmacologically relevant binding. These results agree with the results in muscarine receptor binding assay in vitro.

It can be concluded that the anticholinergic effect of these glycolate esters is closely correlated with their muscarine receptor affinity.

NUCLEUS RAPHE DORSALIS, LOCUS COERULEUS AND LIP-ACUPUNCTURE ANALGESIA. Yu Guang-Di, Liu Shi-Yu, Gu Feng, Di Shi, Yin Wei-Ping and Yin Qi-Zhang. Suzhou Medical College, Jiangsu, China.

It has been demonstrated that the raphe-serotonergic neuronal system plays an important role in lip-acupuncture analgesia (LAA). Midbrain raphe lesion or PCPA administration could decrease LAA, while raphe stimulation or 5-HT intraventricular injection resulted in enhancement of LAA. There are also evidences that the coerulo-noradrenergic neuronal system can effect acupuncture analgesia. In this communication the interaction between nucleus raphe dorsalis (RD) and locus coeruleus (LC) in lip-acupuncture analgesia was studied in rats by lesion and/or stimulation of these nuclei in various combinations. Methods of electroacupuncture, pain threshold measurement, brain lesion and brain stimulation have been described elsewhere (Zhonghua Yixue Zashi, 1979, 59 (9): 534-538).

1. Bilateral LC lesion + RD stimulation: LAA was decreased 3 days after LC lesion, and increased significantly ($P<0.05$) to subsequent RD stimulation.
2. RD lesion + unilateral LC stimulation: 7 days after RD lesion LAA was decreased significantly ($P<0.01$), and increased subsequent to LC stimulation.
3. Bilateral LC lesion + RD lesion simultaneously: 3 days and 7 days after simultaneous lesion of these nuclei, LAA was decreased significantly ($P<0.05$).
4. RD lesion followed by bilateral LC lesion: LAA was decreased significantly ($P<0.05$) 3 days after RD lesion. No further significant effect on LAA was observed after LC lesion.
5. Bilateral LC lesion followed by RD lesion: LAA was decreased significantly ($P<0.05$) 3 days after LC lesion. No further significant effect on LAA was observed after RD lesion.

From the above-mentioned experiments it is evident that LAA was decreased after RD or LC lesion, and increased after RD or LC stimulation, and no reciprocal antagonistic interaction was observed between these nuclei in LAA. It is suggested that lip-acupuncture may activate both descending raphe-spinal serotonergic and coerulospinal noradrenergic systems which, in turn, inhibit nociceptive neurotransmission at spinal level.

THE EFFECT OF ALDOSTERONE ON THE FUNCTION OF THE COCHLEA. Zeng Zhao-Lin, Wu Da-Zheng and Lu Yuan-Yuan. Experimental Research Laboratory of Traditional Chinese Medicine, Shanghai College of Traditional Chinese Medicine, Shanghai, China)

There are evidences that similarities in some features of the physiological functions, the morphological structures, as well as the characteristics in response to certain drugs were found to exist between certain tissues of the kidney and cochlea. In view of these facts, we hold that it is reasonable to find out some clues concerning the physiological mechanism in regulating the function of the cochlea from the known physiological process in the control of the kidney. Aldosterone, an effective humoral factor of the organism in regulating the function of renal tubule, was verified by us as showing some beneficial effect in promoting the function of the cochlea.

Experiments were carried out in guinea pigs with a pathological model of the cochlea induced by ethacrynic acid, using microphonic potential and action potential of the auditory nerve as indices in reflecting the function of the cochlea. The results indicated that the depressing effect of the ethacrynic acid on the electrical potentials of the cochlea was reduced markedly in animals treated with aldosterone, whereas a significant enhancement of the depressing effect of this drug on the electrical potentials of the cochlea was found in animals receiving antisterone --- an aldosterone receptor competitive antagonist. We believe that aldosterone is an important humoral factor in regulating the function of the cochlea.

INTERACTION OF NOXIOUS DISCHARGES OF DIFFERENT SOMATIC ORIGINS IN MIDBRAIN RETICULAR FORMATION. Zhang De-Xing. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

The effects of noxious stimuli applied to different somatic areas on unit discharges of midbrain reticular formation (RF) neurons were studied. The experiments were carried out on rats and cats. After operation the animals were paralyzed with Flaxedil and artificially ventilated. Glass microelectrodes filled with 2 M NaCl were used to record the unit discharges. The noxious stimuli included transcutaneous electrical stimulation of hind paw or tail, electrical stimulation of sural nerve, pinching and intraperitoneal injection of bradykinin. The responses of the midbrain RF neurons to different noxious stimuli were essentially the same, most of them being characterized by an increase in discharge frequency, others by a decrease. The increase of unit discharges of some midbrain RF neurons provoked by noxious stimulation of some somatic areas could be inhibited by noxious stimulation of other somatic areas. Similarly, the decrease of unit discharges of some neurons in response to noxious stimuli of some somatic areas could be diminished by noxious stimuli applied to other somatic areas. Thus, it might be suggested that the responses of certain midbrain RF neurons to noxious stimulation could be inhibited by another noxious stimulus delivered somewhere else.

CONTENT OF SOME NEUROTRANSMITTER AMINO ACIDS IN THE CAUDATOPUTAMEN IN NEWBORN, ADULT AND AGED MICE. Zhang Jin and Wang Zi-Mian. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

The contents of r-amino-butyric acid, taurine, alanine, aspartate, glutamate and glycine in the caudatoputamen of newborn, adult and aged mice were determined, using an ultra-micro dansyl method with polyamide TIC and fluorescence measurement. The results (expressed in μmole/g. wet weight) were as follows:

	GABA	Tau.	Ala.	Asp.	Glu.	Gly
Newborn	0.5.	16.23	0.36	1.20	1.99	1.03
Adult	1.24*	14.31**	0.92*	2.84*	9.79*	1.04
Aged	1.52**	14.11	0.92	3.01	9.89	1.30

* $p<0.001$ **$p<0.05$

The results indicate: (1) The r-amino-butyric acid content in the caudatoputamen increases significantly with age. (2) The taurine content in the caudatoputamen decreases, while alanine, aspartate, and glutamate significantly increase during postnatal development up to adulthood. However, there is no change in these amino acids from adulthood to old age. (3) There is no change in glycine content with age in caudatoputamen.

EFFECTS OF MICROIONTOPHORETICALLY APPLIED MORPHINE ON RESPIRATORY NEURONS IN THE REGION OF THE SOLITARY TRACT, THE NUCLEUS AMBIGUUS AND THE NUCLEUS PARABRACHIALIS MEDIALIS OF RABBIT. Zhang Jing-Ru, Yao Tai, Lin Hui-Jin, Sun Zhong-Han, Xu Ning-Sha, He Ju-Ren and Gong Qian-Ling. Department of Physiology, Shanghai First Medical College, Shanghai, China.

Experiments were carried out on 90 anesthetized or conscious paralyzed rabbits. Unit discharges and phrenic discharges were recorded simultaneously so as to differentiate the respiratory and the non-respiratory neuronal activity. A medical data processing computer was used on line to generate the spike frequency histograms. The effects of morphine given iontophoretically on the unit discharge were examined.

Of the 61 respiratory units recorded in the region of the solitary tract, 6 were excited and the remainder were without effect. Neither the spontaneous activity nor the glutamate-induced excitation of the respiratory units were seen to be depressed by iontophoretic application of morphine. Naloxone did not block morphine-induced excitation.

Of the 54 respiratory units recorded in the region of the nucleus ambiguus, 10 were depressed, 1 was excited and the remainder were without effect. Naloxone blocked morphine-induced depression in five out of six trials.

Of the 67 respiratory units recorded in the region of the nucleus parabrachialis medialis, 40 were excited, 4 were depressed and the remainder were without effect. Naloxone blocked morphine-induced excitation in twelve out of eighteen trials.

Our results indicate that the effects of microiontopheretically applied morphine on the brain stem respiratory neurons are quite different in different regions.

AFFERENT CONNECTIONS OF THE CENTROMEDIAN NUCLEUS OF CAT'S THALAMUS. Zheng Ze-Hui and Mao Jin-Biao. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

1. 0.1 µl of 50% HRP in 5% polyvinyl pyrolidone saline was injected unilaterally into the centromedian nucleus (CM) of cat's thalamus. After 48 hours HRP-labeled neurons were found widely but loosely scattered in the ipsilateral cerebral cortex. They were mainly the large pyramidal cells of layer V. The labeled small cells of layer VI were only found in some regions. The numbers of HRP-labeled cells in the rostral one-third of the cerebral cortex were greater than in the caudal two-thirds. Two longitudinal strips, which contained moderate amount of labeled cells denser than their surrounding region, could be observed on the lateral and medial cortical surfaces respectively, one in the anterior, middle and posterior suprasylvian gyrus, the other in the cingular gyrus.

2. Large numbers of labeled cells were found ipsilaterally in the rostral part of reticular nucleus and entopeduncular nucleus dorsal to the optic tract, but none in the caudate nucleus.

3. Many sensory nuclei of the brain stem projected to CM. They are the central gray, superior colliculus, dorsal raphe nucleus, locus coeruleus, main sensory trigeminal nucleus, dorsal medial vestibular nucleus and the dorsal horn of spinal cord C1 and C2.

4. CM bilaterally receives nerve fibers from some areas of the reticular formation including those where the gigantocellular and parvocellular reticular neurons are located.

5. These results indicate that CM receives its afferent fibers from the cerebral cortex as well as from various sensory nuclei. Therefore, this intralaminar nucleus may well be taken as a part of the reticular system for integrating the inputs from different sources at the thalamic level.

EFFECTS OF TELESTIMULATION OF CAUDATE NUCLEUS ON OPERANT CONDITIONING RESPONSE EVOKED BY NOXIOUS STIMULI IN CATS. Zheng Zin-Ze, Li De-Rong and Huang Ye. Shanghai Institute of Physiology, Academia Sinica, Shanghai, China.

The regional difference of the function of the head of caudate nucleus in modulating pain sensation was studied by using the telestimulation technique and the operant conditioning procedure in unrestrained cats; 9 cats were used and 25 points in the head of caudate nucleus (A 16-19) were tested. Constant current electric shock applied to cat's paws was used as noxious stimulus. The animals were trained to end the shock by pressing a lever. The duration of the shock was taken as the response time and the mean value of three successive response times was used as the control. A radio-controlled stimulator carried on the head of the animal delivered electrical pulses (5 cps) to the head of caudate nucleus through implanted electrodes. The change of response time was observed during the course of caudate stimulation. Stimulation of marginal and central zones of the head of caudate nucleus could both increase the response time to noxious stimulation. The effect of stimulation of the marginal zone, however, was much stronger than that of the central zone. The difference between the two was highly significant ($P<0.01$). It was found that stimulation of some of the points in the central zone often elicited motor responses, such as cycling movement or tremor, but the response time to noxious stimuli in these cases was usually not affected.

ANATOMICAL CONNECTIONS OF CAUDATE NUCLEUS, DORSAL RAPHE NUCLEUS AND SOME RELATED NUCLEI IN ALBINO RAT. Zhou Jing-Xiu, Huang Deng-Kai, Li Kuan-Yan, Zhu Dan, Zhou Si-shun* and Cao Si-Yun. Laboratory of Neuromorphology, Research Department of Acupuncture Analgesia, Shanghai First Medical College, Shanghai, China. * Department of Anatomy, Shanghai Second Medical College, Shanghai, China.

Physiological studies on acupuncture analgesia indicated that caudate nucleus, dorsal raphe nucleus, periaqueductal gray, medial preoptic area, entopeduncular nucleus, nucleus accumbens and substantia nigra were related to either pain perception or pain modulation. The aim of this work is to study the anatomical connections of these neural structures. The experiments were carried out on 277 adult rats with retrograde transport of horseradish peroxidase (microinjection and microelectrophoresis) and Nauta degeneration method. Our main results are:

1. Caudate nucleus receives direct projections from cerebral cortex, centromedian nucleus, parafascicular nucleus, interpeduncular nucleus and dorsal raphe nucleus. The degenerating axons and terminals can be seen in parafascicular nucleus, cingular cortex and nucleus raphe magnus after caudate lesion.
2. Dorsal raphe nucleus receives direct projections from substantia nigra, periaqueductal gray, interpeducular nucleus, nucleus raphe pontis, nucleus raphe medianus, locus coeruleus and nucleus raphe magnus. The degenerating terminals can be seen in parafascicular nucleus, substantia nigra, periaqueductal gray, nucleus raphe magnus and the dorsal horn of spinal cord after lesions made in dorsal raphe nucleus.
3. Periaqueductal gray receives direct projections from paraventricular nucleus, anterior hypothalamic nucleus, locus coerulcus, substantia nigra and dorsal raphe nucleus.
4. The medial preoptic area receives direct projections from paraventricular nucleus, anterior hypothalamic nucleus, interpeduncular nucleus, periaqueductal gray, septal nucleus, locus coeruleus and dorsal raphe nucleus.
5. Entopeduncular nucleus receives direct projections from caudate nucleus, frontal cerebral cortex, medial amydaloid nucleus, preoptic nucleus, periaqueductal gray, locus coeruleus, substantia nigra and dorsal raphe nucleus.
6. Nucleus accumbens receives direct projections from caudate nucleus, septal nucleus, periventricular gray, paraventricular nucleus, locus coeruleus, substantia nigra and dorsal raphe nucleus.
7. Substantia nigra receives direct projections from caudate nucleus, cerebral cortex, periaqueductal gray, central amygdaloid nucleus and dorsal raphe nucleus.

Our results indicate that the nuclei under study are closely related to the central gray system of CNS and most nuclei receive fibers from dorsal raphe nucleus as well as from locus coeruleus. The descending inhibitory pathways arising from dorsal raphe nucleus and caudate nucleus make access to the dorsal horn of spinal cord via nucleus raphe magnus and the dorsal raphe nucleus also projects directly to the dorsal horn and the central gray of spinal cord.

AN INHIBITORY EFFECT OF AMYGDALOID STIMULATION ON UNIT DISCHARGES OF THE MEDIAL GENICULATE BODY (MGB). Zhou Shao-Ci, Yin Hui-Zhen and Lu Xiang-Yue. Brain Function Research Laboratory, East China Normal University, Shanghai, China.

The present research on 82 rabbits has shown that stimulation of the anterior amygdaloid nucleus, the medial amygdaloid nucleus and the central amygdaloid nucleus can all have an inhibitory effect on the neuronal discharges of the MGB. When these nuclei were stimulated, 33 out of 48 MGB units responding to click stimulus (that is 66.8% of the total number) were markedly inhibited. The latent period of the inhibitory effect was 5-12 msec, the duration of inhibition being 2-13 msec. Furthermore, 19.3% of the spontaneously firing units of MGB were also inhibited by amygdaloid stimulation. Such an inhibition manifested itself as temporary interruption of the discharges. Evoked responses to stimulation of medial amygdaloid nucleus with a latent period of 2-4 msec could be recorded from temporal and parietal cortex. On the other hand, stimulation of the temporal cortex (Woolsey's auditory areas I and II) resulted in a distinct inhibition of the spontaneous as well as the evoked discharges of MGB neurons in response to sound stimulation. In view of the reciprocal connection between the amygdaloid complex and the auditory cortex, and that between the latter and the MGB as demonstrated by P. Gloor (1976) and J. Winer (1970), it seems probable that the auditory cortex may be an important link in the neuronal pathway responsible for the inhibition produced by amygdaloid stimulation. The results of the present study also indicate that under normal physiological conditions the amygdaloid complex may play a distinct role in the modulation of afferent messages at the specific thalamic relay of the auditory system. This provides further evidences suggesting that the limbic system is in some way involved in sensory functions of the nervous system.

From the Publications Desk

New Journal Developments and Two New Books

The Publications Committee is pleased to announce two new developments in the journals and the publication of two new books.

Rapid Communications are now accepted for the *Cell Physiology* and *Heart and Circulatory Physiology* journals of the *American Journal of Physiology.* Howard E. Morgan and Ernest Page, the Editors of these journals and their Editorial Boards are convinced of the need to publish such papers in their fields. Rapid communications should contain results of unusual interest. These communications must not exceed four journal pages in length, including figures, tables, and references. Review of rapid communications will be accelerated, and such papers will appear in the next available issue after acceptance. In general, one printed page is equivalent to four double-spaced typewritten pages, or to three figures or tables. Authors should indicate that papers are submitted as rapid communications. See the individual journals for further details as procedures vary slightly between the two journals.

The Modeling Methodology Forum is a new department in the *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology,* for the publication of articles and letters concerned specifically with the techniques of modeling in physiology. The major objective is to provide a lively forum for presenting, comparing, and assessing pertinent methodologic approaches to physiological modeling, borrowed from the physical, mathematical, and engineering sciences. Manuscripts may be original research contributions, critiques, reviews, survey papers, or tutorials. Letters to the editor also are encouraged. The only restriction on content is that the paper or letter must be concerned with some applied physics, mathematical, or engineering method, with its pertinence or application in physiology clearly delineated. Mathematics and technical jargon are welcome, but they must be relevant and clearly explained and presented. Also, papers should be reasonably self-contained; they should not depend on a series of highly technical previous publications, unless these dependencies are generally well known. All manuscripts will be reviewed by a special international Editorial Board, whose names are included along with preparation and submission rules in every issue of the journal. See also the May 1981 issue of this journal for an editorial by Joseph J. DiStefano III, the Associate Editor, who is heading this department.

New Perspectives on Calcium Antagonists, edited by George B. Weiss, is another timely book in the Clinical Physiology Series. Although a wide variety of compounds has been identified as directly or indirectly altering some action of Ca^{2+}, increasing attention has been focused on those newer groups of agents that have specific inhibitory actions on the inward Ca^{2+} current in the heart and on the voltage-sensitive Ca^{2+} channels of smooth muscle. *New Perspectives on Calcium Antagonists* reflects these interests; many of the chapters primarily deal with the delineation of the actions of inhibitors of Ca^{2+} uptake. But the broader range of actions of other types of Ca^{2+} antagonists is also considered.

The eighteen chapters are divided into four sections: Molecular and cellular parameters for activity of calcium antagonists; Effects of calcium antagonists on excitation-contraction coupling; Effects of calcium antagonists on stimulus-secretion coupling; and Effects of calcium antagonists on specific physiological functions.

Motor Control is the second volume in the section of the *Handbook of Physiology, The Nervous System.* Written by experts and edited by Vernon B. Brooks, Volume Editor, and John M. Brookhart and Vernon B. Mountcastle, Section Editors, each chapter is a monograph, the volume an encyclopedia. It is composed of two books, totaling more than 1500 pages.

The volume presents a systematic interdisciplinary view of the control of posture and movement. It is designed for those who want to assess current knowledge of the field and the directions in which it is heading. The authors have summarized concepts, facts, and methods of current research in their chapters and have deftly bridged physiology, anatomy, the behavioral sciences, control theory, and related areas. The relevance of motor control to human performance is kept in view throughout. This volume is a natural follow-up to the first volume of *The Nervous System, Cellular Biology of Neurons.*

The overall theme of *Motor Control* is today's emphasis on how the individual deals with an environment that dictates the dimensions of both motor efforts and their controls. This topic has generated numerous questions, What are the controlled variables in different circumstances? How are the contributions of diverse neurons encoded? How is intent translated into action by present programs and ongoing controls with optimal use of the available information and the neurons processing it? Much pro-

gress has been made in the last twenty years in relating structure to function, observations to theory, and "unknowing" neurons to a "purposive" brain and to heuristic performance. It is unrealistic to expect all these aspects to have fused in so short a time. The promise and the approaches, however, are evident in *Motor Control.*

Topics are grouped to take the reader on a journey that begins with peripheral conditions and events, moves inward through automatic, unconscious adjustments, proceeds to voluntary conscious adjustments, and ends with an analysis of behavioral motor performance. If an anatomical orientation remains in the sequence, it is merely because many neuroscientists still labor to unravel the functional mysteries of the components of a "computer" that arrived without explanations for either hardware or software. The volume is divided into sections only for convenience: there are no real boundaries between the thirty-three exciting and authoritative accounts.

Society members should order the books from the subscription office, American Physiological Society, 9650 Rockville Pike, Bethesda, MD 20814.

New Perspectives on Calcium Antagonists, $31.00 for APS members ($38.50 for nonmembers).

Motor Control, $196.00 for APS members ($245.00 for nonmembers).

An Analysis Of Foreign And Domestic Responses To Reprint Requests

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The use of reprints to keep abreast of the current literature is potentially attractive. For instance, the reprint is of better quality and less expensive than most photocopies made from the original published paper. However, these advantages could be offset if only a low percentage of the requests were eventually filled or if excessive time were required to receive a reprint. This report describes our experience in obtaining reprints from requests sent to authors of journal articles cited in *Current Contents* during the period of January 1, 1979 to December 31, 1979.

METHODS

Requests were made from a review of *Current Contents/Life Sciences.* Most articles were referenced in sections devoted to Experimental Biology & Medicine, Clinical Medicine, and Neurosciences & Behavior; a few additional requests resulted from articles listed in the Multidisciplinary and Pharmacology sections of this publication. The requests were all mailed within one week of receipt of the *Current Contents* in which the article was cited. Addresses were taken directly from the Author Index and Address Directory. Requests were made using a first-class postcard with the return address of one of the authors (*DCR*) on the upper portion. Response time was determined by calculating the number of days elapsing between the mailing of the reprint request and its subsequent receipt; a T1-59 Days-between-Date program was used to perform this calculation. Data were compiled in April 1981, approximately 15 months after the last request was mailed in December 1979.

RESULTS AND DISCUSSION

Two hundred fifty reprint requests were mailed during this one-year period. Two hundred five reprints were received, so that approximately 82% of the requests were eventually filled. Figure 1 presents our analysis of response times; results are shown for the number of reprints received (ordinate) as a function of the weeks elapsed since mailing the request (abscissa). Five requests filled at 40, 43, 53, 56, and 58 wk after mailing, respectively, are not shown. The mean response time was 9.7 ± 10.4 wk; one-half of the requests had been filled within 7 wk of mailing.

Of the 45 requests that were not filled, 26 were from domestic institutions with the remaining 19 from foreign sources. There were 18 reprints received in excess of one standard deviation from the mean (i.e., having a turnaround time longer than approximately 20 wk). Of these, 9 were from domestic sources and 9 from foreign.

We conclude that use of reprints to keep abreast of the literature is quite efficient for those articles not requiring immediate attention.

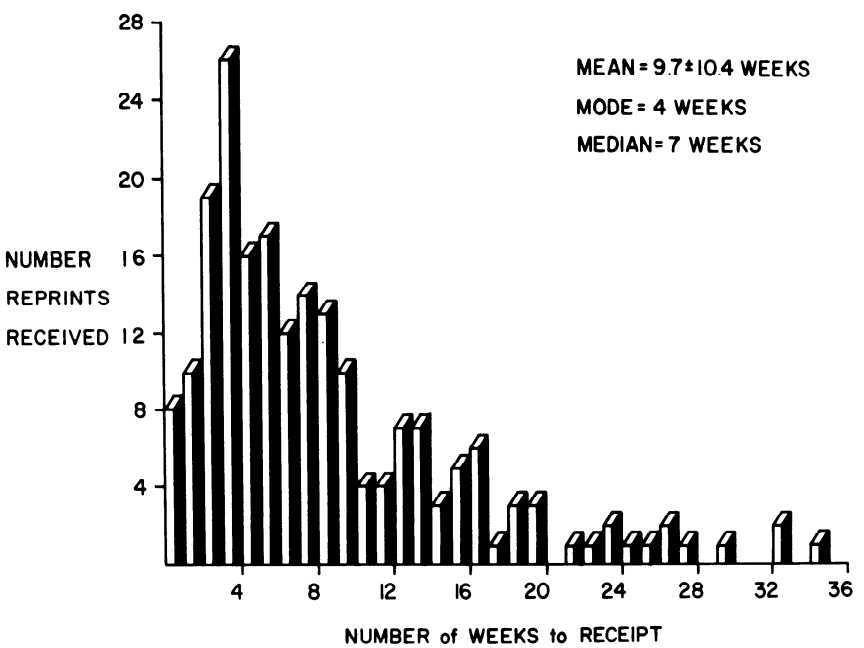

Fig. 1. Number of reprints received vs. weeks. Data show number of reprints received as a function of time elapsed from mailing reprint request to subsequent receipt of reprint. Five requests received more than 36 wk after mailing are not shown.

News From Senior Physiologists

J.P. Holt to Hallowell Davis:

Thank you for your letter regarding my activities. Since retiring four years ago I have continued limited activity in collaboration with Dr. E.A. Rhode and my younger son, Dr. W.W. Holt at the University of California, Davis, on studies of the cardiovascular system of large and small mammals as related to the Principle of Similarity. Several papers have been presented at spring and fall meetings and one manuscript will soon appear. I am in good health, my wife and I spend the cold months in south Florida mostly fishing and enjoying the climate, and in summer stay at my farm in southern Indiana where I garden and do general farm work several hours each day. I enjoy associations with my children, grandchildren, friends and former colleagues; but am saddened by our culture's "confusion of goal and perfection of means"* and man's increasing disharmony with nature.

*Quote, A. Einstein.

R.R. 1, Box 129
Depauw, Indiana 47115

Richard Eckstein to Hal:

I retired from the animal cardiovascular laboratory in July of 1979 when we were working in a new field for me, namely, recording from the aortic and/or the carotid sinus nerve. Since then I continue to go into University Hospitals regularly on Tuesday, Thursday, and Friday when I manage to see a few patients whose problems are of a psychiatric nature and attend meetings devoted to therapeutics and/or psychiatry. I am able to obtain the hours of instruction needed to renew my medical license in Ohio and maintain my membership in the American Psychiatric Association.

I have the use of my office in the Wearn Research Building. It is adjacent to my former laboratory which is now being used by others to study various approaches to the problem of recovery from cerebral ischemia. Now and then I am able to lend a hand by explaining how we used to do things and showing how our equipment works. In addition, I am a member of the committee to assess proposals for human research in the Department of Medicine.

My wife and I are in good health and continue to live on our 1.5 acres in Orange Village which is 11 miles from my research and teaching home at Case Western Reserve University. I am not doing any research or scientific writing but seem to have no end of interesting things to do. It seems very nice even now to continue to look forward to having spare time.

I do considerable reading but find that my understanding of many modern techniques is rapidly and increasingly more limited. In this brief period I am amazed to see the names of so many young authors that I do not recognize. I wish that I had some words of wisdom to spell out for younger colleagues, perhaps a method by which they might stay on top of the flood of new information with which they will have to deal.

University Hospitals of Cleveland
Cleveland, OH 44106

Harold Wiggers to Hal:

Unfortunately, Vero Beach is academically sterile, so I have had to adopt non-scientific pursuits. Having devoted my last 24 academic years to administrative and medical educational activities, I now find it extremely difficult to comprehend the highly technical and chemical aspects of today's published research. In its place, I have become an avid reader of historical biographies and novels. I conclude that the human race hasn't change much over the centuries. Selfishness and "me"-itis prevail as in the past – only today the generally irresponsible media are better equipped to disseminate all that is amoral, violent and depressing – with little concern for the innocent they deprecate in the process.

Most of my physical energies are spend on golf and working in the yard. I am particularly proud of the gorgeous roses which receive my TLC almost daily. I have never seen any more beautiful but have elected to enjoy rather than display them in competition. They are very sensitive to fungi and require periodic application of fungicidal applications. Also have lovely amyrillis, bouganvillea, Bird of Paradise, gardenias, oleanders, hibiscus and flamevine.

Of all the mentors I had during my climb up the academic ladder, I find in retrospect that I learned more positive things under your warm tutelage in one year than during several years under others. I shall always treasure that delightful learning experience with you. In particular I learned that distinguished scientists don't have to be aloof to their trainees to command respect. Being accessible for the problems of colleagues stood me in good stead during my 21+ years as President and Dean of the Albany Medical College (1953-1974). When we moved to Albany in 1947, I realized that my outlook had been greatly broadened by my varied encounters and experiences at Harvard, Columbia, Western Reserve University and Illinois. I realized how unfortunate those are who preclude such varied environments by remaining at one institutions most of their academic lives. I appreciate that no one or two institutions have a monopoly on talent, motivation and excellence. I also learned that timing – or being in the right place at the right time – has much to do with success and personal happiness.

I guess one of my greatest satisfactions during my Deanship and Presidency was in my ability to recruit superb people to Albany as Dept. Chairman and to again assist them in recruiting their faculty staffs. It is unbelievable to look back now and realize what totally inadequate facilities we started with. Also the growth of the Medical College transformed our continguous general hospital into a super medical center which provided secondary and tertiary care for 22 countries. This had been a remarkable resource for the health of the region. As you can see, I have 27 exciting years at AMC prior to retirement in 1974.

During one of our visits to our younger daughter's home in Greenville, N.C. we purchased a residence. East Carolina U. in Greenville has been trying to get funds to start a medical school since 1967. They succeeded in November 1974. Learning of our empty residence there, the Vice Chancellor for Health Affairs asked me to serve as a consultant – and two months later as "acting" Dean to provide the leadership to get the "show on the road." By September of 1975, we recruited a Dean. He insisted

that I remain as special consultant to assist in recruiting Dept. Chairman, plan temporary and permanent facilities, negotiate an agreement between the County Hospital and the E.C.U. Medical School and help develop a curriculum which would meet accredited tuition standards. Ginny and I spent 2½ delightful years in Greenville and made a host of friends. I retired a second time when the school was granted preliminary accreditation and admitted its first four year class.

Thank you for getting me off to a wonderful start on a career which has surpassed all I anticipated back there in the lab with Alex [Forbes] and Jean Reboul in 1936-37.

711 Iris Lane
Vero Beach, FL 32960

W.T. Liberson to Hal:

I am still quite active in both clinical neurophysiology (EMG and EEG) as well as Rehabilitation Medicine. My academic apointment is now limited to Senior Lecturer at Downstate Medical School, and I am the Chairman of the Rehabilitation Medicine Department in the Brooklyn-Cumberland Medical Center.

I was rejuvenated by recent studies confirming my early findings of the upper cervical somato-sensory evoked potentials. I am now pursuing the same line of research.

Thank you for thinking of me, and I am happy to know you are immersed in the research of neurological auditory brainstem potentials.

The Brooklyn Hospital
121 DeKalb Ave.
Brooklyn, NY 11201

Richard J. Bing to Horace Davenport:

Thank your for remenbering the oldsters. I am still Director of Experimental Cardiology & Scientific Development at the Huntington Institute of Applied Medical Research, a fine Institution with good work and great plans. I am continuing my research in atherosclerosis, cardiac metabolism and microcirculation. I am also continuing to compose music, and I have my first comprehensive record coming out in Germany on a choral work with orchestra, soloist, etc. My music was also played in Australia, Cleveland, and Los Angeles.

Pasadena, CA

Louis B. Jaques to Sid Robinson:

In response to your recent letter, I am happy to say that after two years of retirement, I am still active in research. The College of Dentistry at the University of Saskatchewan has provided me with a base and I am busy publishing more articles on heparin. What is particularly satisfying is that the new methods and resulting observations have confirmed the suspicions of the original investigators with whom I worked 45 years ago that heparin is much more than a simple direct anticoagulant drug. I suppose if there is any moral in this for younger people, it is that if you stay with a project long enough, you are bound to find something that is new to the current generation.

I deposited my back files with the University of Saskatchewan archivist in 1979. His staff will decide what is archival material. I thought a novel solution was that of our late prime minister, the Hon. John G. Diefenbaker, who appointed literary executors for his papers, separate from the estate executors. However, this has resulted in a court case involving the two sets of executors with the chief beneficiary, the University of Saskatchewan as a third party. Evidently, even a lawyer can not foresee the consequences of his own will.

Saskatchewan, Canada

Richard L.Riley to E.B. Brown:

I have discovered that the only way to pursue your academic interests is to retire from academic life. I keep in touch with people working in my fields and have time to ponder what they say. I also do just enough speech-making to keep me at my typewriter. I prefer thinking about work accomplished rather than bragging about results that may be forthcoming if a grant is approved.

The Luft Symposium was great fun and a wonderful opportunity to see old friends.

Petersham, MA 01366

Dan H. Moore to E.B.:

In response to your recent inquiry, I was born in 1909 and officially retired last year, but I continue to work every day. Although I do not carry out laboratory experiments any more, it is a pleasure to be around where the work goes on without having to provide funds and worry about progress. For many years, I have been interested in the etiology of breast cancer and have used mice as an experimental model; but, although the development of mammary tumors in mice is interesting and informative, mouse physiology is very different from human physiology insofar as the development of mammary cancer is concerned.

The incidence of breast cancer in different populations of the world varies all the way from zero to one women in ten, but the reasons for this variation are not known. Last year, I spent a great deal of time collecting data on the life style of the Zulu living in their natural habitat in Zululand, Natal, South Africa, where some two million women seem not to have the disease at all. I also collected data on Zulu women living in townships in the Durban area and also on white women in Durban. The Durban Zulu women have a breast cancer incidence one-third that of the white women, whose breast cancer incidence is very high. I am now collecting data on the Amish farmers of Lancaster County, Pennsylvania, who have a very high incidence, and the Hassidic Jews of Brooklyn, New York, who seem to have a low incidence, although the incidence in the total Jewish population of New York City is very high. It seems there may be as many as fifty factors concerning heritage and life style, sex life and reproduction, diet, stress, etc., which affect human physiology in such a way as to prevent or permit or cause breast cancer. (So far, nipple fluid specimens have caused no mutations by the Ames test.)

I am quite aware that this problem will probably not be solved in my lifetime, but it is so like unraveling a murder mystery (which it really is) that it is fun to pursue the clues. I am in good health (I jog a couple of miles each day), for which I am most thankful, and I plan to continue working (or playing) indefinitely.

Hahnemann Medical College
Philadelphia, PA 19102

William L. Doyle to E.B.:

I reached Emeritus status in the Department of Anatomy, University of Chicago, in 1976. Until last year I continued teaching Histology to first year medical students. For many years I have spent summers in research at the Mount Desert Island Biological Laboratory in Salsbury Cove, Maine.

This research has been concerned with the cytology and find structure of salt regulating organs in marine vertebrates including the nasal salt gland of seagulls, the rectal gland of elasmobranchs and the chloride cell of the teleost gill. I have enjoyed the collaboration of several physiologists.

For the last several years I have served as Editor of the Bulletin of the Laboratory for its annual research reports.

Chicago, IL

Willem J. Kolff to E.B.:

I am pleased to bring you up-to-date on my present activities. I am Director of the Institute for Biomedical Engineering of the University of Utah and as a Distinguished Professor, I do not have to resign for reasons of age. My greatest satisfaction is to see how my younger associates have developed or are developing into independent investigators, so that from an Institute led by one person, it gradually evolves into a consortium of independent investigators.

The Wearable Artificial Kidney has finally found a Japanese producer. It is used by John Warner our Administrator, for 20 Dialysis in Wonderland trips one year: camping in Canyonland National Park in Southern Utah, going down the Colorado River on rafts, fishing from houseboats at Lake Powell, and even swimming in Hawaii.

The artificial heart is almost ready for clinical application. It is waiting for approval from the F.D.A. I myself am spending a major portion of my time in designing a novel shape and developing new manufacturing techniques for Left Ventricular Assist Devices and Right Ventricular Assist Devices, that together can take over the function of the human heart.

The experimental Artificial Heart Program is led by Dr. Don Olsen (Implant-Transplant). Dr. Robert Jarvik's Electrohydraulic Artificial Heart is very promising, and he has a strong group of engineers.

The Utah Arm developed by Dr. Steve Jacobsen and his group is a marvelous piece of equipment that moves as soon as the wearer thinks about making a motion.

The artificial ear by Dr. Don Eddington has now progressed so far that some totally deaf people can understand 85 percent of spoken words without seeing the speaker's mouth.

Very exciting is the administration of insulin by Dr. Robert Stephen via the peritoneal-portal route. This results in an incredibly smooth glucose curve in diabetics who are otherwise virtually impossible to regulate.

The intra-aortic balloon pump, which was developed in our laboratories in 1961, has now been adapted for use in babies. Dr. Jeff Peters' Transapical Left Ventricular Bypass has saved a patient in Utah.

We are advancing over the entire field that covers artificial organs-blood-material interface (Dr. Joseph Andrade); degeneration of materials (Dr. Dennis Coleman); leaching of antibiotics or other medication from elastomer surfaces (Dr. Sung Wan Kim).

Presently there are 200,000 people in the world dependent on artificial kidneys. It is my prediction that between 50,000 and 100,000 people will want artificial hearts per year in the United States. We will be happy to treat the now skeptical cardiologists when they have their first very serious heart attack.

Salt Lake City, UT

COUNCIL OF ACADEMIC SOCIETIES BRIEF

ASSOCIATION OF AMERICAN MEDICAL COLLEGES • 1 DUPONT CIRCLE NW • WASHINGTON DC
(202) 828-0400 SUMMER, 1981 VOL. 6., NO. 4

The CAS Brief is prepared by the staff of the AAMC Council of Academic Societies and is distributed through the auspices of your member society.

CONGRESS ADOPTS RECONCILIATION BILL. The long and complex reconciliation battle finally ended in late July when Congress adopted a final Omnibus Reconciliation Act calling for cuts of $8.5 billion in health programs over the next three years. In most cases, programs important to medical school faculty fared as well or better than expected considering the extremely austere Senate approach to most of these programs and the early predictions that the health conference committee would be hopelessly deadlocked over widely disparaging House and Senate positions on crucial issues.

One of the most troubling proposals on the Senate side--establishing an overall funding ceiling for the NIH, the NIMH, and other Federal health agencies--never came to fruition. The conference committee fortunately accepted the House approach of reauthorizing programs within these agencies, thus negating the "cap" approach. Provisions of the bill in areas of particular interest to faculty are:

Research Training: The NRSA program is reauthorized for two years with a funding ceiling of $182 million in FY82 and $195 million in FY83. If money is appropriated at this ceiling in FY82, NIH is likely to receive about $164 million--$12 million below the current NIH training budget. How this decrease will affect numbers of trainees or the size of institutional allowances is left up to the discretion of DHHS, with the caveat that neither is to be significantly reduced.

Student Aid: The bill includes reauthorization of Health Professions Student Loan programs for the next three years at $12, $13, and $14 million. The Exceptional Financial Need Scholarship program was retained and authorization was provided for new starts in the National Health Service Corps. The Health Education Assistance Loan program was reauthorized for three years at $200, $225, and $250 million.

Medicaid: The Medicaid "cap" concept was rejected, but Federal matching payments to states will be reduced by 3%, 4%, and 4.5% in the next three years.

The next hurdle in the process of gaining adequate support for medical research and education programs will be in the Appropriations Committees where final spending authority is decided. In September, these committees will begin marking up their bills, working within the tight guidelines imposed by the First Concurrent Budget Resolution. Since competition for shrinking Federal support will be intense, the academic medical community will have to be particularly compelling in urging full funding of medical education and research programs.

AAMC REPORTS FOCUS ON PREPARATION FOR GRADUATE MEDICAL EDUCATION AND EVALUATION FOR LICENSURE. The AAMC's Executive Council adopted two important committee reports at its June 25th meeting. "External Examinations for the Evaluation of Educational Achievement and for Licensure" and "Quality of Preparation for the Practice of Medicine in Certain Foreign-Chartered Medical Schools" are complementary documents that focus on the issues raised by the Federation of State Medical Boards' proposal to require all candidates for entry into graduate medical education to pass a preliminary licensure examination (FLEX I) and a later licensing examination (FLEX II) for an unrestricted license to practice.

1981 FALL MEETINGS—NOVEMBER 1-2—WASHINGTON, D.C.

Concerns have been expressed about the readiness of medical school graduates--particularly those of foreign-chartered schools--to continue into graduate medical education. The report on external examinations points out that the critical evaluations of clinical skills and personal professional qualifications required of students in LCME accredited schools are not known to be required of students in non-LCME accredited schools. Evaluation of these essential qualities, which are not easily measured by written examination, is a responsibility of U.S. medical school faculties.

The reports urge that the Federation of State Medical Boards not require passage of the FLEX I examination (the preliminary examination at the interface between graduate and undergraduate medical education) by graduates of LCME accredited schools. They recommend that for the purpose of ensuring adequate evaluation of graduates of non-LCME accredited schools at this stage, the Accreditation Council for Graduate Medical Education (ACGME) should request the Educational Commission for Foreign Medical Graduates (ECFMG) to apply more appropriate evaluation methods and raise its standards for determining the educational preparation of these individuals. The proposed methods are: (1) a rigorous written examination equivalent to Parts I and II of the National Board of Medical Examiners certification sequence followed by (2) a practical hands-on evaluation of clinical skills in prepared testing centers. For graduates of LCME accredited schools, final licensure for unrestricted practice still would require either passing the NBME Parts I, II and III examinations or the FLEX examination. For graduates of non-LCME accredited schools, passing the FLEX examination would be required.

The Association's Executive Committee has met with representatives from the Federation of State Medical Boards and discussions to resolve the concerns of the academic community are in progress. The Accreditation Council for Graduate Medical Education has referred the question of modifying the evaluation methods and the standards for ECFMG certification to a standing committee.

Copies of both reports have been distributed to CAS society representatives and officers. Additional copies are available by writing August G. Swanson, M.D., Director of the Department of Academic Affairs. Societies are urged to inform the Federation of State Medical Boards, the ACGME, and the ECFMG of their views and to send copies of such communications to Dr. Swanson.

1981 CAS FALL MEETINGS. The 1981 CAS Fall Meetings, held in conjunction with the AAMC Annual Meeting, will begin on November 1 with an afternoon program devoted to discussion of the issue of basic science education as the foundation for advanced medical practice. Dr. Frederick E. Shideman, Chairman of the Department of Pharmacology at the University of Minnesota, will contrast the content and scope of instruction in pharmacology in 1960 compared to 1980 and speculate on changes that may occur in this area by 1990 as a result of the virtual explosion of basic science knowledge currently underway. Dr. Rubin Bressler, Chairman of the Department of Medicine at the University of Arizona, will address the challenge of selecting the essential basic science knowledge students should learn during this period of rapid scientific advancement and change when it is difficult to identify concepts which will remain relevant for future practitioners of medicine. These presentations will be followed by small group discussions on underlying topics. On November 2, Dr. Robert W. Berliner, Dean of the Yale University School of Medicine,will discuss science in medical practice in the year 1990. The CAS Business Meeting, including election of officers and Administrative Board Members, will also be held on November 2.

COMPETITIVE APPROACH TO CONTAINING HEALTH CARE COSTS. At its March meeting, the AAMC Executive Council approved a discussion paper entitled "Price Competition in the Health Care Marketplace: Issues for Teaching Hospitals." Copies may be obtained by sending $3.00 to the AAMC Office of Membership and Subscriptions. Also currently available, at a price of $3.00, is a booklet prepared by the Association's Department of Teaching Hospitals: "Toward a More Contemporary Public Understanding of the Teaching Hospital."

ANNOUNCEMENTS

SCIENTISTS CENTER FOR ANIMAL WELFARE

The First Conference on Scientific Perspectives in Animal Welfare will be held at the National 4-H Center, 7100 Connecticut Avenue, Chevy Chase, Maryland, on November 11-13, 1981. The conference, the first of its kind, is sponsored by the Scientists' Center for Animal Welfare.

The intent of the meeting is to discuss scientists' responsibilities in animal experimentation. Participants will assess the state of the art, identify areas for special consideration, and make recommendations in the four topic areas of responsibility: investigator, institutional, funding agency and review groups, and editorial.

Invited speakers represent a wide range of scientific interests and viewpoints. Dr. Jean Dodds, Vice President of the Scientists' Center, is the Program Chairman of the conference.

Attendance will be limited to scientists. Preregistration is required; registration materials will be sent upon request. The registration fee is $85.00 before September 15 and $100.00 thereafter, payable to Scientists' Center for Animal Welfare (S.C.A.W.) and mailed to the administrative office of S.C.A.W., listed below.

Scientists interested in attending may contact:

Administrative Information:

Ms. Marcia Feinleib
Scientists' Center for Animal Welfare
11325 Seven Locks Road, Suite 221
Potomac, Maryland 20854
(301) 983-0544

Scientific Information:

W. Jean Dodds, D.V.M.
Division of Laboratories and Research
New York State Department of Health
Empire State Plaza
Albany, New York 12201

REPRODUCTIVE BIOLOGY STUDY SECTION WORKSHOP

A workshop on "The Role of Proteins and Peptides in Reproduction," sponsored by the Reproductive Biology Study Section, Division of Research Grants, National Institutes of Health, will be held on February 15 and 16, 1982, at Bethesda, Maryland. The program of the workshop will start at 8:00 a.m. on February 15 and will end at 5:30 p.m. on February 16. The proceedings of this workshop will be published.

Observers are invited and there will be room for approximately 250 persons on a first-come basis. Each person desiring to attend will be responsible for his travel, lodging and meals. Written requests to attend this workshop should be sent to:

Dharam S. Dhindsa, D.V.M., Ph.D.
Executive Secretary
Reproductive Biology Study Section
Room 307, Westwood Building
National Institutes of Health
Bethesda, Maryland 20205
Telephone: (301) 496-7318

FIRST SOUTHERN BIOMEDICAL ENGINEERING CONFERENCE

LOUISIANA STATE UNIVERSITY MEDICAL CENTER
SHREVEPORT, LOUISIANA

JUNE 7-8, 1982
CO-SPONSORS

Biomedical Engineering Society
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The American Society of Civil Engineers
Society of Experimental Stress Analysis
Association for the Advancement of Medical Instrumentation

and in collaboration with IEEE Engineering in Medicine and Biology Society

FORWARD ALL ABSTRACTS AND REQUESTS FOR INFORMATION TO:

Dr. S. Saha, Program Chairman
First Southern Bioengineering Conference
Department of Orthopaedic Surgery
Louisiana State University Medical Center
P.O. Box 33932
Shreveport, Louisiana 71130 USA
(318) 674-6187

AUTHORS ARE INVITED TO SUBMIT PAPERS ON ANY ASPECT OF BIOENGINEERING INCLUDING THE FOLLOWING AREAS:

Artificial Organs/Prosthetic Devices
Biochemical Engineering
Biocontrol Systems
Bioelectricity
Bioinstrumentation
Biomaterials
Biomechanics
Biomedical Education
Biophysical Measurements
Biosignal Processing
Cardiology/Hemodynamics
Clinical Engineering
Computers in Medicine
Imaging
Modeling and Simulation
Occupational Injury & Safety
Rehabilitation Engineering
Thermal Regulation in Biological Systems
Ultrasonics

Instructions For Authors	Deadline Dates
Receipt of Abstract (500 words)	December 5, 1981
Notification of Acceptance	January 15, 1982
Receipt of Completed Photo-ready Paper (4 pages)	December 20, 1982

Papers will be reviewed. Accepted papers will be included in a proceedings to be published by PERGAMON PRESS which will be available at the time of the meeting.

GASTROENTEROLOGY RESEARCH GROUP SYMPOSIUM

Time & Place: November 6, 1981; 8:00-10:00 PM
Place: Hyatt Regency, Chicago
Title: Cellular Protein and Membrane Processing
Moderator: Dr. Robert Glickman, Chief GI Unit, Columbia University College of Physicians & Surgeons
1st Speaker: Dr. Gunter Blobel, Professor of Cell Biology, Rockefeller University
Title: Translocation and Integration of Proteins Across & Into Membranes.
2nd Speaker: Dr. Marilyn Farquhar, Professor of Cell Biology & Pathology, Yale University School of Medicine
Title: Multiple Pathways of Intracellular Membrane Traffic.

BELTSVILLE SYMPOSIUM

On May 16-19, 1982, the Beltsville Agricultural Research Center of the U.S. Department of Agriculture will sponsor the seventh annual Beltsville Symposium in Agricultural Research entitled "Genetic Engineering: Applications to Agriculture." The program will include invited lectures, poster papers, and a tour of the research facilities at Beltsville.

The main subject areas to be covered included molecular genetics, DNA cloning, genetic modification, production of new plants via tissue culture and commercial applications. Specific topics within these areas will be covered by 20 speakers.

For further information, contact Dr. Lowell D. Owens, USDA-ARS, Room 116, Bldg. O11A, BARC-West, Beltsville, MD 20705. Phone—(301) 344-4072.

USA NATIONAL COMMITTEE FOR THE INTERNATIONAL BRAIN RESEARCH ORGANIZATION

ANNOUNCEMENT OF TRAVEL AWARDS

The USA National Committee for the International Brian Research Organization (IBRO) is sponsoring a travel grant program to benefit American scientists who could not attend the First World Congress of IBRO in Lausanne, Switzerland, April 1-6, 1982, without such assistance. A limited number of grants will be available. Those eligible to apply for awards are qualified scientists who are citizens or permanent residents of the United States of America, and who plan to participate fully in the Congress; Federal employees are not eligible for this award program. Each applicant will be judged on the merit of his contribution to the Congress in Lausanne, and also on his training, experience and potential. Priority will be given to young scientists. Grants will be in the range of $700-$900 depending upon airport of departure and return.

Requests for application forms should be addressed to:
USA National Committee for IBRO
Attention: June S. Ewing, Staff Officer
Division of Medical Sciences
National Research Council
2101 Constitution Avenue, N.W.
Washington, D.C. 20418

Deadline for postmark of completed application in November 6, 1981. To the degree that it is possible, successful applicants will be notified by December 15, 1981.

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THE PHYSIOLOGY TEACHER

Salivary Gland Secretion

H.L. Dorman†, L.L. Bellinger, L.W. Frazier, and F.E. Williams
Department of Physiology
Baylor College of Dentistry
Dallas, Texas 75246

Saliva is produced in several specific glands, including the parotid, submandibular, and sublingual, and numerous accessory glands. Modulation of salivary secretion is under strict autonomic nervous system control.

Parasympathetic stimulation greatly increases the volume of salivary secretion. First it causes vasodilation, which promotes increased permeability of blood vessels in the glands. However, blood flow to salivary glands is only a supportive influence and not the primary factor increasing salivary secretion. It appears that the second and primary cause for enhanced salivary secretion is the direct stimulation of intracellular acini guanosine 3′,5′-cyclic monophosphate (cGMP) formation by parasympathetically released acetylcholine. The elevated cGMP leads to enhancement of the acinar cell, ionic, active transport mechanism, which promotes increased secretion by the glands.

Sympathetic stimulation of the salivary glands also promotes increase in viscous salivary secretion. However, the volume increase is small and is not considered in detail in this exercise.

At the acini cells a primary secretion is formed through the active transport of Na^+, HCO_3^-, K^+, and Cl^- into the lumen of the duct (1). Water moves passively due to osmosis. As the primary secretion moves down the duct the ionic composition is modified, with Na^+ being reabsorbed from and K^+ secreted into the lumen. At higher secretion rates HCO_3^- concentration in luminal fluid increases due to conversion (via carbonic anhydrase) of enhanced metabolic CO_2 into HCO_3^-.

MATERIALS AND PROCEDURES

Materials

Dog, polyethylene tubing (1.25 mm OD), dissection set, acetylcholine (0.02 mg/ml), atropine (0.1%), string, stimulating and small stimulating electrodes, osmometer, pH meter, flame photometer, blood pressure transducer, 10-ml graduated cylinder, heparin (10 mg/ml), 20- and 26-gauge needles, centrifuge, pentobarbital sodium (33 mg/ml).

Cannulation of Submandibular Gland Duct

Anesthetize the dog and clip the hair from under the jaw and neck. We have found it best to supply the student with a previously anesthetized dog. Ideally, we use a dog approximately 15 kg in weight and anesthetize the dog with pentabarbital sodium (33 mg/kg).

Make a skin incision on the ventral surface of the jaw about midway between the midline and the mandible, starting from the angle of the mandible and extending forward about 7.5 cm (Fig. 1).

By use of a blunt dissection (i.e., repeatedly push the points of hemostats or round-pointed scissors into the area and then gently open) and scissor retractors, separate the digastric from the mylohyoideus muscle (Fig. 2). The fibers of the mylohyoideus will extend diagonally from the area of the digastric toward the midline; the digastric fibers are parallel to the mandible. The mylohyoideus is very thin (2-3 mm).

Bluntly separate the fibers of the mylohoideus at a point about 3 cm from the angle of the jaw and look for the lingual nerve (Fig. 3). The mylohyoideus is only about 3 mm thick; therefore, care must be taken not to dissect too deep or the muscle layer below will also be separated. The lingual nerve will pass almost perpendicularly from the mandible toward the midline.

Locate the structure shown in Fig. 4. They include the lingual nerve, the chorda tympani nerve, and Wharton's duct. Blunt dissection in the area of the gland may damage the chorda tympani nerve and/or accessory salivary ducts; therefore, do not attempt to isolate the chorda tympani but merely visualize it. Stimulation can be applied to the upper surface of the nerve. The duct is translucent and passes diagonally from near the angle of the jaw toward the nose. It will be necessary to stimulate [5 ms duration, 3 V, 5 pulses per second (pps)] the chorda tympani so that the duct will fill with saliva and thus be more apparent.

†Deceased 6 June 1981.

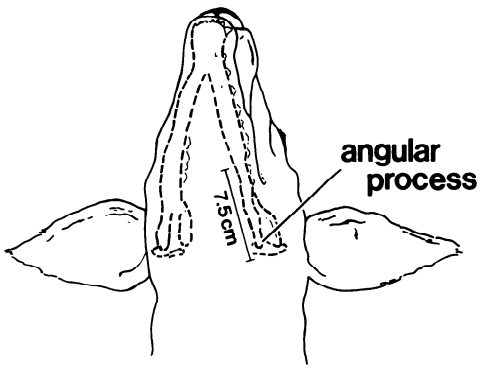

Fig. 1. Diagram showing approximate location and size of incision for salivary duct and chorda tympani exposure of the dog.

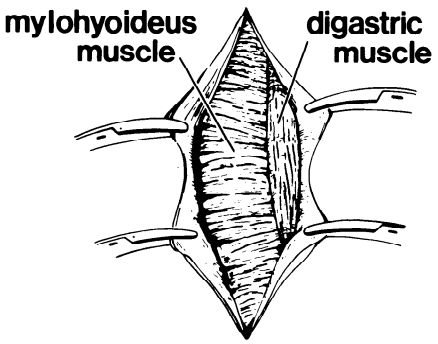

Fig. 2. Diagram showing exposure of digastric and mylohyoideus muscle layers. Top of diagram is cephalad.

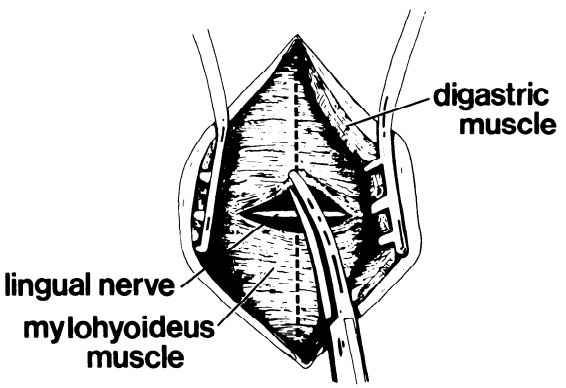

Fig. 3. Isolation of lingual nerve. Top of diagram is cephalad.

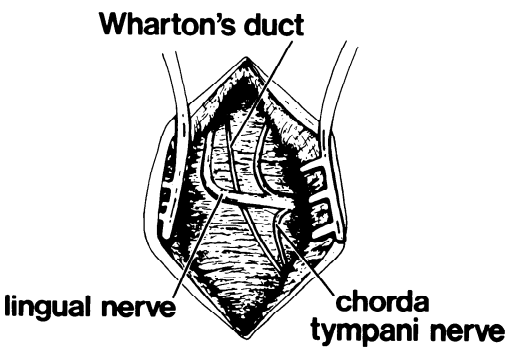

Fig. 4. Isolation and exposure of Wharton's duct and chorda tympani nerve in the dog. Top of diagram is cephalad.

By use of careful blunt dissection pass a ligature beneath the duct on the side of the lingual nerve opposite the gland. Cannulation is accomplished by carefully snipping the duct (expanded by chorda tympani stimulation) and passing the cannula into the duct toward the gland. The cannula tip will have to be tapered (but not sharp). Once the cannula is inserted stimulation of the chorda tympani should produce saliva flow. Secure the cannula into the duct with a moderately tight string ligature.

Additional Procedures

Expose the carotid arteries and place a string under each artery, but leave the vessels in place so as not to restrict the blood flow. Cannulate the femoral artery (for blood pressure measurement) with a clamped cannula filled with heparinized saline *but do not* connect it to a blood pressure transducer at this time. Expose the femoral vein.

EXPERIMENTAL PROCEDURE

Remove 10 ml of blood from the femoral vein using a syringe containing 0.1 ml of heparin (10 mg/ml) and 20-gauge needle. Centrifuge the sample and save the plasma for [Na^+], [K^+], pH, and osmolarity determinations.

Comparison of Stimulation Rate on Salivary Constituents

1. Determine the salivary flow rate for 2 min without chorda tympani stimulation (use a 10-ml graduated cylinder to determine volume).
2. Stimulate the chorda tympani at a rate that gives a flow near 0.5 ml/min. *Stimulation parameters:* approximately 3.0 V, 5 ms duration, 2-4 pps; voltage and frequency may have to be adjusted. Collect at least 2.5 ml of saliva for [Na^+], [K^+], pH, and osmolarity determinations. It is important that extreme care be taken during stimulation to not stretch or otherwise damage the nerve.
3. Stimulate the chorda tympani to obtain a flow rate near 2.0 ml/min. *Stimulation parameters:* 3 V, 5 ms duration, 20-60 pps. Record the time and begin saliva collection once the flow is rapid. Note the stimulator setting utilized. Collect 2.5 ml for analysis and save 2 ml of saliva for later use. Calculate the salivary flow rate (ml/min). Increase stimulation and try to attain a flow rate near 3.0 ml/min, and again collect saliva for analysis.
4. Take plasma and salivary samples and determine [Na^+] and [K^+] with a flame photometer. To determine osmolarity saliva will have to be diluted (1:10 with distilled water). The pH can be determined with any standard pH meter.

Effect of Reduced Blood Flow on Saliva Secretion

Tighten the strings on both carotid arteries by pulling upward on them until the flow of blood through the arteries is stopped. With the blood flow to the head restricted by carotid artery occlusion, stimulate the chorda tympani nerve for 15 s with the same setting as used to obtain a saliva flow of 2.0 ml/min. Record the amount of saliva formed and compare the rate of saliva formation with that obtained without carotid artery blockage. Release the carotid arteries. It should be noted that the dog has a very substantial vertebral blood flow; thus occluding the carotid arteries does not completely stop the blood flow to the salivary glands.

Maximum Secretory Pressure of the Submaxillary Glands

Place a piece of rubber tubing on the sidearm of the blood pressure transducer and fill the pressure transducer with heparinized saline by injecting it into the sidearm of the transducer. After filling, clamp the rubber tubing shut. Calibrate the pressure transducer. Insert a tight-fitting needle into the open end of the salivary duct cannula; then fit the needle hub onto the

second connector arm on the blood pressure transducer. Stimulate the chorda tympani nerve (4 V, 10 ms, 5-60 pps) until the pressure rise reaches its maximum and levels off. Stop the stimulation and detach the pressure transducer and needle from the salivary duct cannula. To demonstrate that the nerve is still functional stimulate the nerve with the same settings that produced a flow rate of 2.0 ml/min. Record the flow for 1 min.

Connect the femoral arterial cannula to the transducer and record arterial blood pressure. Compare the maximum saliva secretion pressure with the recorded systolic blood pressure. If two pressure transducers are available the blood pressure and salivary gland secretory pressures should be measured simultaneously.

Salivary Secretory Response to Acetylcholine

Without stimulation, record the volume of saliva (if any) produced in 1 min. Utilizing a 26-guage needle inject 0.5 ml of the acetylcholine (0.02 mg/ml) solution into the carotid artery on the ipsilateral side of the salivary gland used. After 10 s, record the volume of saliva produced during the next minute. Compare the saliva secretory rates before and after acetylcholine injection.

Effect of Atropine on Salivary Gland Secretion

Next inject 1 ml of 0.1% atropine into the femoral vein and wait 10-15 min. Again, inject 0.5 ml of acetylcholine into the artery and record the saliva flow as noted above. Compare the saliva flow to acetylcholine stimulation before and after atropine. Now stimulate the chorda tympani nerve. What differences are noted in the volume and consistency of the saliva formed? What is the mechanism of action of atropine?

Effect of Intravascular Saliva on Blood Pressure

Inject the 2 ml of saliva that was collected earlier into the femoral vein of a dog and record the arterial blood pressure change. The change in blood pressure must result from a chemical substance in the saliva. What might this chemical substance be and what might be its mode of action?

DISCUSSION AND RESULTS

This experiment is a modification of a time-honored laboratory exercise (3) for the physiology student. Shown in Table 1 are typical results obtained in our laboratory with dog saliva and plasma. The student should be asked to correlate the data he obtained with the current concept of salivary formation and flow (1,2).

TABLE 1. Osmotic Concentration and Electrolyte Composition of Saliva at Various Flow Rates

Flow Rate, ml/min	Osmolarity, mosmol/l	Na^+, meq/l	K^+, meq/l	pH
0.2 (basal)	122	28	17.0	7. 5
0.8	238	94	16.1	7. 6
1.8	254	100	15.4	8. 0
3.0	280	121	13.3	8. 5
Plasma	293	134	2.9	7.35

We have found this laboratory exercise extremely beneficial for the undergraduate student, dental student, and nursing student. This exercise will help the student to accomplish the following objectives:

1. Demonstrates to the student the physiology of the salivary gland.
2. Gives an understanding of the parasympathetic control of the salivary gland.
3. Demonstrates the influence of varying salivary flow rates on $[Na^+]$, $[K^+]$, osmolarity, and pH.
4. Demonstrates that salivary secretion is an active process as can be denoted from salivary duct pressure exceeding systolic blood pressure.
5. Gives an understanding of the scientific method and investigation.

The individual experimental manipulations and questions can be easily modified to accomplish each teacher's own objectives for the laboratory exercise.

REFERENCES

1. Davenport, H.W. *Physiology of the Digestive Tract.* Chicago, IL: Year Book, 1977, p. 91-101.
2. Mountcastle, V.B. (Editor). *Medical Physiology.* St. Louis, MO: Mosby, 1980, Vol. II, p. 1289-1293.
3. Sherrington, C.S. *Mammalian Physiology a Course of Practical Exercises.* New York: Clarendon, 1919, p. 74-80.

INTERNATIONAL BRAIN RESEARCH ORGANIZATION

ANNUAL PRIZE IN THE NEUROSCIENCES

The Drs C. & F. Demuth Swiss Medical Research Foundation announces the creation of a yearly *International Award of SFr. 15.000 for young investigators in the Neurosciences.*

For 1982, applications are invited from Experimental Neuro-oncologists, particularly those interested in primary tumors of the central nervous system. Candidates from all nationalities, not older than 35 years, should submit (i) their curriculum vitae including a list of publications, (ii) a resume of current and projected work (a single-sentence heading followed by 2 or 3 typewritten pages), (iii) reprints of their 3 most important articles, and (iv) names and addresses of two referees acquainted with their work.

The jury consists of Professors G. Baumgartner (Zurich), J.J. Dreifuss (Geneva), A. Pletscher (Basle), and H. Van der Loos (Lausanne).

The 1982 award will be presented at the opening of the First World Congress of the International Brain Research Organization (IBRO) "The Brain in Health and Disease" (March 31-April 6, 1982) to be held in Lausanne, Switzerland.

Applications should be sent before December 15, 1981 to Professor H. Van der Loos, President of the Swiss Chapter of IBRO, Institute of Anatomy, University of Lausanne, Rue du Bugnon, 1011 Lausanne, Switzerland.

Letters to the Editor

To The Editor:

We have completed several computer programs written in BASIC for use with microcomputers such as the Apple II. The subject matter and applicability of each are listed below. We will be happy to copy these programs onto disks compatible with the apple II microcomputer. Listings of each program are also available on request. To illustrate their use, please note Fig. 1 to 5 with their accompanying legends.

PERMEABILITY

This program was designed to help students to understand what factors influence how fast a cell changes its volume when it is placed in hyperosmotic and hypoosmotic environments.

Students will be able to choose the following values:

1. The osmolarity of impermeable solute in the medium.
2. The osmolarity of permeable solute in the medium.
3. The permeability of the cell membrane to water.
4. How permeable the cell membrane is to the permeable solute.
5. Students may start the experiment with a known osmolarity of permeable solute inside the cell.

The ordinate of each graph is the volume of the cell set as 100. The abscissa of each graph is time in arbitrary units. The length of each experiment is four units. When the experiment is ended, two values are projected on the graph. The left-hand value is the cell volume at the end of the experiment. The right-hand value is the volume of the cell if the experiment had achieved equilibrium. This option is introduced because equilibrium is not always achieved during the time plotted on the abscissa.

The equations that form the basis of this program are those derived by Kedem and Katchalsky, using principles from irreversible thermodynamics (*Biochim. Biophys. Acta 27:* 229-246, 1958).

PERMEABILITY OPTION

In this program permeability of the cell membrane to water and solute is to be chosen at random. Students are given graphs of three experiments:

1. The cells are put into a medium containing only an impermeable solute whose concentration is chosen at random.
2. The experiment is repeated using a different concentration of impermeable solute again chosen at random.
3. In this experiment the cells are in an isosmotic medium of impermeable solute. Then a random concentration of permeable solute is added. Students try to deduce what membrane values were used and what concentration of permeable solute was added.

HCO_3 VERSUS pH

The purpose of this program is to visualize in graphic form changes in acid-base balance. The Henderson-Hasselbalch equation is solved and plotted with the HCO_3 concentration in milliequivalents per liter of plasma water on the ordinate and pH on the abscissa for a chosen P_{CO_2}. Included on each display is a plot of the plasma buffer line with a buffering capacity of 11 slykes. When one enters the three values pH, HCO_3, and P_{CO_2} obtained at different stages of a disorder in acid-base balance, it is possible to follow graphically the shifts which occur.

HCO_3 VERSUS P_{CO_2}

In this graphic display of the Henderson-Hasselbalch equation the log of HCO_3 is plotted on the ordinate. The log of the P_{CO_2} is plotted on the abscissa for different values of pH. The plasma buffer line is plotted over the range of values chosen. Shifts in acid-base balance may be displayed by plotting each set of values of HCO_3, P_{CO_2}, and pH during the course of the disturbance and/or during compensation.

How We Are Using These Programs

We use these programs to graph changes in acid-base balance in the anesthetized dog. A control sample of venous blood is obtained from the unanesthetized animal prior to phenobarbital anesthesia. After anesthesia, the femoral artery and vein are catheterized to obtain arterial and venous samples. Expired air is collected from a tracheal catheter into a Douglas bag and analyzed for expired CO_2. Blood samples are analyzed for pH, P_{CO_2}, and P_{O_2} and HCO_3 concentration is calculated. Ventilation rates are monitored and respiratory excretion of CO_2 is calculated.

Acid-base balance is perturbed by 1) hyperventilation by forced breathing, 2) hypercapnia breathing 5% CO_2, 3) infusion of $NaHCO_3$, and 4) infusion of HCl.

The laboratory is run as a demonstration, and the graphs are displayed on four 25-inch color TV sets mounted from the ceiling in the lecture room and slaved to the Apple II. Students follow the graphic display from procedure to procedure.

TITRATION

The program TITRATION is a display of the titration of weak acids or weak bases. It plots a graph. The ordinate is the number of milliequivalents of strong acid added to a chosen number of milliequivalents of conjugate base. The abscissa is pH.

The equation of Henderson-Hasselbalch is used to calculate the pH at each new value of weak acid formed when its conjugate base buffers the added strong acid.

$$pH = pK + \log \frac{\text{conjugate base}}{\text{(weak acid)}}$$

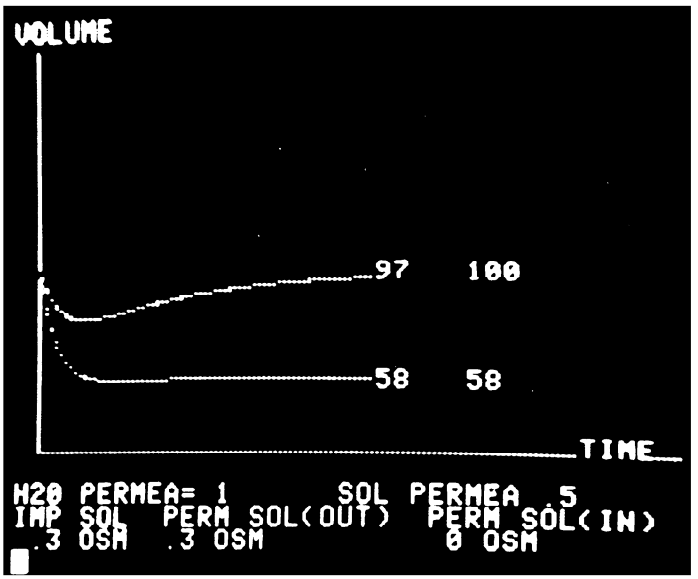

Fig. 1. *Lower Curve*: Simulation of the response of a cell at a given volume of 100 units when placed in an infinite volume of a solution made twice isosmotic with an impermeable solute. *Upper Curve*: Simulation of the response of a cell at a given volume of 100 units when placed in an infinite volume of a solution made twice isosmotic with equal osmoles of impermeable solute and permeable solute. *Objective:* 1) To illustrate that cells shrink and remain shrunken in a hyperosmotic solution of an impermeable solute. 2) To illustrate that cells shrink in a hyperosmotic medium, but then return to a volume determined by the osmolarity of the impermeable solute. Rate of volume change determined in part by permeability of solute.

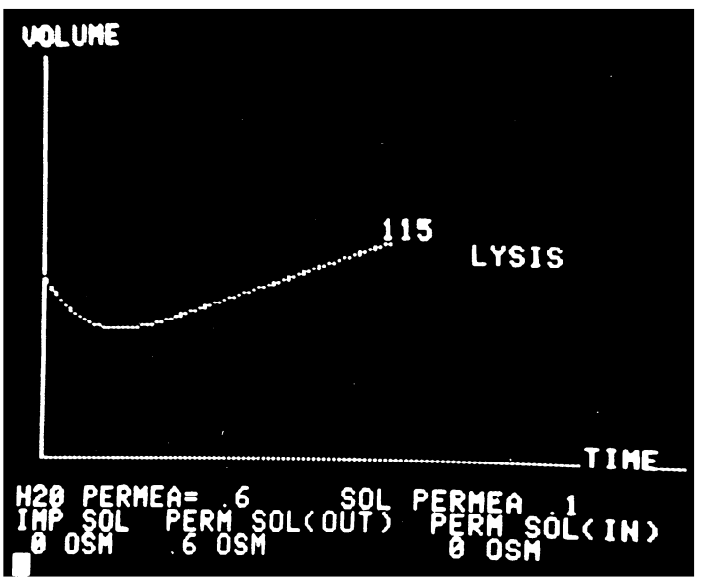

Fig. 2. Simulation of the response of a cell at a given volume of 100 units when resuspended in an infinite volume of a solution of permeable solute at an osmolarity twice isosmotic. *Objective*: To demonstrate that the final volume which the cell achieves is determined by the osmolarity of the impermeable solute in the solution. Note that its value is 0 and lysis is the final equilibrium value. The value of 115 units occurred at the end of the run, not at equilibrium. Time to equilibrium was slow because membrane permeability to solute was low.

The user is given the following options:

1. Range of pH values on abscissa.

   He may choose the range of pH values he wants to plot on the abscissa. He chooses the highest value and the lowest value.

Warning: If the results exceed this limit, the program will abort. If this happens enter RUN 5 or start again.

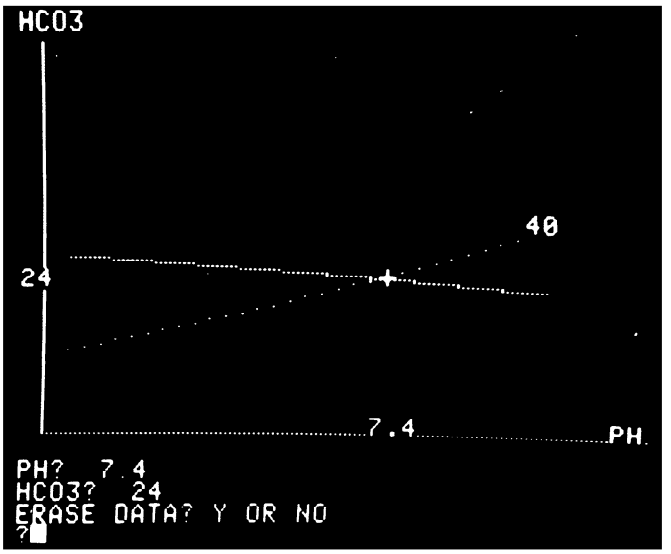

Fig. 3. Solution of the Henderson-Hasselbalch equation for a P_{CO_2} equal to 40 mmHg. Extracellular buffer line defined at 11 slykes. *Objective*: To establish the major components for a graphic analysis of disorders in acid-base balance. Normal plasma values are used.

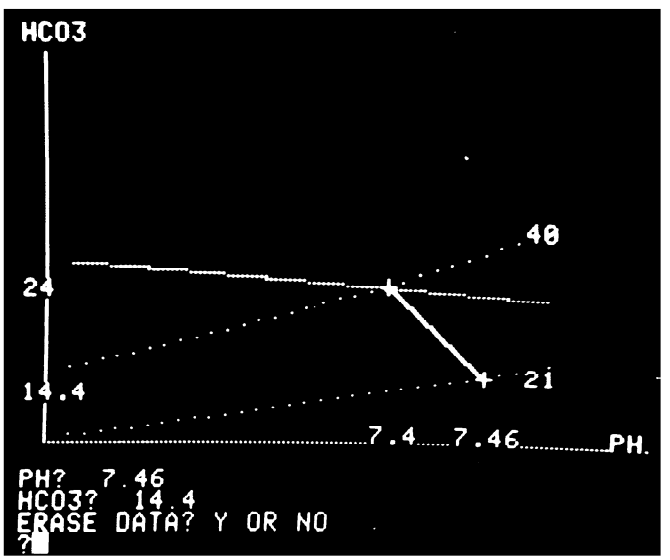

Fig. 4. Simulation of metabolic acidosis with overcompensation by hyperventilation. *Objective*: 1) Note normal values. 2) Note reduction in plasma HCO_3 concentration. 3) Note decrease in P_{CO_2}. 4) Note resultant from normal values which shows path of compensation.

2. Range of milliequivalents of acid to be added.

   Choice of the minimum and maximum number of milliequivalents of strong acid to be buffered. The maximal amount of buffer titrated is set at 1 meq more than the maximal amount of strong acid added. This procedure is chosen to avoid complete titration, since the Henderson-Hasselbalch equation does not apply under these circumstances.
3. Choice of the p*K* for the buffer pair of interest.
4. Several titration curves may be superimposed on the same graph.
5. A pointer that can be moved on the graph may be used with the two paddles.

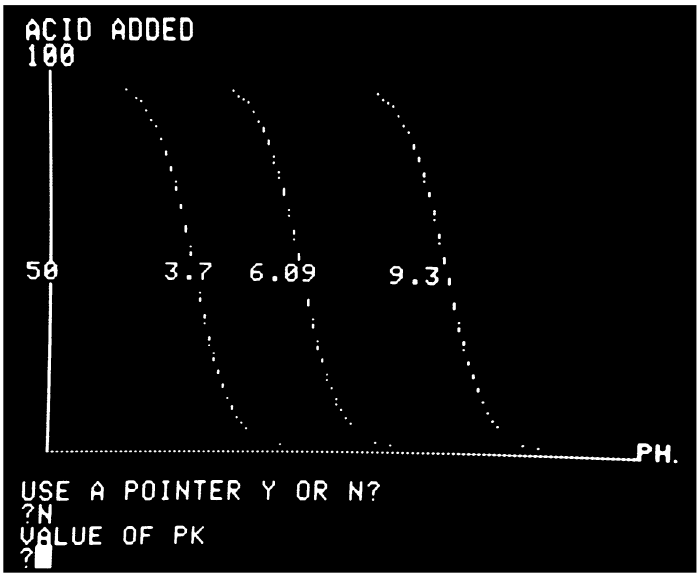

Fig. 5. Titration curves for three buffer systems. *Objective:* 1) To emphasize significance of p*K* of different buffer systems. 2) To emphasize the values of ratios of buffer pairs at a given pH. 3) To correlate with the status of fixed acids, bicarbonate, and ammonium in the urine.

How We Are Using This Program

This program is used during our lecture series on acid-base for freshman medical students. We use it as a visual aid to make the following points:

1. To refresh everyone's memory about the shape of the titration curve, the significance of p*K*, and the two moieties at each end of the curve.
2. By putting the pointer at selected pH values, to emphasize the ratios of selected buffer pairs that exist at the chosen pH. We use this technique to reinforce the following points:
   a) The significance of the HCO_3/CO_2 ratio as a buffer at pH 7.4
   b) The significance of the $HPO_4^{2-}/H_2PO_4^-$ ratio as a component of titratable acid excreted by the kidney and the reestablishment of buffer reserve
   c) The significance of the NH_3/NH_4^+ ratio as a trap for H^+ during acidification of the urine and the reestablishment of buffer reserve

(We compare ratios at pH 7.4 and at pH 4.5.)

To The Editor:

This letter is an offer to share a collection of teaching simulations that I have written to run on Apple II microcomputers. After up to two years of use by myself and by others the programs have recently been revised to improve operation in the hands of students. Most of the routines show responses to disturbances in graphic form. It is now possible to pause during the computations, to examine charts of numerical values of the variables, to change parameters, or to restart the program. At the end of the plot the graph may be saved on paper for use in student notebooks.

The programs are called by a series of menus which appear on the screen when the power is turned on. They fall in the general categories of electrophysiology, cardiovascular physiology, and compartmental analysis. The most useful one is the simulation of the Hodgkin and Huxley equations in which calculated voltage and conductances are plotted in response to two stimuli using parameters chosen by the operator. This program and several included variations have been very popular lecture demonstrations and helpful in self-study exercises for unraveling the ionic bases of the excitation process. There is also a simulation of ventricular excitation based on the four-current model of Beeler and Reuter.

One cardiovascular model accepts the physical parameters of the vessels and heart and rapidly displays a table of the blood volume distribution, ventricular outputs, and arterial and venous pressures for the systemic and pulmonic circuits. Another plots a graph of ventricular ejection and aortic pressure for different heart rates, stroke volumes, aortic compliance, and peripheral resistance according to the classic windkessel model. The three limb leads can be displayed for a QRS loop of any chosen electrical axes. There also are variations of several models by Dr. Thomas Coleman which illustrate the hemodynamic interaction between the heart and body fluids for a number of disturbances, such as renal stenosis with and without the baroreceptor reflex.

The compartmental kinetics models include a simple glucose tolerance test, published by Stolwijk and Hardy, and a pharmacokinetics demonstration of plasma concentration following chosen doses, and absorption and elimination rates. Miscellaneous routines dynamically show statistical distributions of the means of samples of different sizes and the effects of first-order damping on the shapes of physiological wave forms.

These programs will run on a standard-configuration Apple II with Applesoft BASIC or an Apple II+ and having one disk drive and 48K of RAM memory. The programs have been compressed by removing all remark statements in order to shorten loading and execution time and to save disk space. The disk of compacted programs and an instructor's manual may be obtained from me for my personal costs of duplication which are $5.00. Fully documented programs are on two diskettes and listed in a 175-page manual. This latter package may be obtained for my out-of-pocket costs of $10.

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Book Reviews

Comparative Physiology and Evolution of Vision in Invertebrates. Handbook of Sensory Physiology, vol. VII/6B. H. Autrum, Ed. New York: Springer, 1981. 629 pp., illus., index, $159.00.

The *Handbook of Sensory Physiology*, (VII/A, B, and C) is a three-volume series, all devoted to vision of invertebrate animals and edited by H. Autrum. These volumes cover in a comprehensive way the kinds of research that have been in progress on invertebrate eyes and vision. Volume VII/B, *Comparative Physiology and Evolution of Vision in Invertebrates,* is entitled *Invertebrate Visual Centers and Behavior.* This volume consists of four diverse but related chapters: "Neuroarchitectures Serving Compound Eyes of Crustacea and Insects" by N.J. Strausfeld and D.R. Nässel; "Neural Principles in the Peripheral Visual System" by S.B. Laughlin; "Polarization Sensitivity" by T.H. Waterman; and "Optics of Vision in Invertebrates" by M.F. Land. In these chapters new problems are raised, and some old questions are examined in light of new research, particularly with regard to the optical systems that evolved in the development of the eye of invertebrates.

Let me indicate briefly what each chapter covers. In chapter 1 Strausfeld and Nässel summarize the basic principles of nerve cell organization. The emphasis is on the optic lobes in a crustacean (the crayfish) and in an insect (the fly) as model systems. Their concern is about structural organization in relation to function.

In chapter 2 Laughlin considers the principles that relate to the cellular structures that assimilate and process optical information from the environment; i.e., the adaptation of structure to function. The barnacle ocelli and the locust ocellus are presented as examples of systems where definitive measurements reveal that single receptors have complex membrane properties and that there are regions of the cell membrane that function for different aspects in the process.

In chapter 3 Waterman discusses polarized-light sensitivity. A large number of animals not previously thought to be sensitive to polarized light are indicated. Included in the discussion of polarized-light sensitivity are examples from arthropods, molluscs, and vertebrate photoreceptors as well as to extraocular photoreception. There is considerable interest in polarization sensitivity, and broad implications are indicated surrounding questions of direction finding, visual contrast enhancement, navigation, and homing. Although the specific mechanisms involved in all these behavioral responses are not completely know, Waterman gives a very comprehensive treatment of polarized-light sensitivity.

The most interesting to this reviewer was chapter 4 by Land, which deals with optical systems and vision. It indicates the enormous diversity of the various kinds of eyes that evolved among the invertebrates: their optics and photoreceptors. The review develops a picture of optimal strategies for adaptive development of vision from detailed observations of structure of invertebrate eyes together with the principles of physical optics.

Stages in transforming visual data from receptors to information and then to information for reaction are outlined. However, much of the definitive research in biological methods for transforming visual information remains to be done.

On the whole this is an exciting volume, for it not only indicates the direction of the research but can also serve as a teaching and research tool. The text is well written and profusely illustrated with photographs of the organisms (including electron micrographs) and drawings, tables, and graphs. These are very helpful in following the discussion in the text. There is an authors' index to publications as well as to species and to subjects.

The price of this and the other two volumes in this series are prohibitive for students and most researchers. It is unfortunate that these chapters cannot be reproduced in paperback and sold as individual monographs. Nevertheless, this volume, and the other two (VII/A and VII/C), should be in libraries, for it is an invaluable source of information to all interested in vision, optics, and photobehavior of invertebrates and their relationship to the eyes and vision of vertebrates.

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Epilepsy: A Window to Brain Mechanisms. J.S. Lockard and A.A. Ward Jr., Eds. New York: Raven, 1980. 296 pp., illus., index, $29.50.

One perquisite of academic life is the opportunity to visit the laboratory of a colleague. In these days of diminishing budgets and funding, this option, while still available, is often difficult to use as costs of travel have increased. This small and information-packed volume by Drs. Lockard and Ward takes us on an informative and challenging visit to the laboratories of the Regional Epilepsy Center of the Department of Neurological Surgery at the University of Washington. We "see" Departmental laboratories whose work is associated with the ongoing and incisive look at epilepsy as a paradigm for the study of the complexities of cerebreal function.

As Herbert Jasper points out in his preface, Dr. Ward and his colleagues' approach to the study of epilepsy is in the grand tradition of the evaluation of brain function established by J. Hughlings Jackson. In his initial overview of the subject, Dr. Ward points out that many of the questions to be asked in biology are posed by the clinical conundrums of disease. Answers can be obtained by the application of the techniques to be found in the physiological laboratory. As thse techniques are often many and varied, the "multidisciplinary" approach may often provide more comprehensive and complete responses to the inquiries made to the system.

A visit to this laboratory carries us through an evaluation of a primate model for epilepsy (J.S. Lockard), a cellular look at the epileptic neuron (Wyler and Ward), and the application of operant conditioning to the activity of the central nervous system (Wyler). We observe studies of membrane phenomena (Schwartzkroin), a comparison of the normal and abnormal activity of the neuron (Calvin), and evaluation of injury (Loese and Howe). There is an evaluation of pathological anatomy (Westrum and Harris) and a look at pharmacological interactions with the disease, both as thereapeutic endeavors and as probes for the understanding of functional elements in neuronal activity in a series of chapters by Levy, Wilensky, and Ojemann. The behavioral complexities of the brain are not ignored. Model systems are explored by Lockard and the human disease by Drill and Ojemann.

One of the particular strengths of this volume is the capacity for the reader to see the relationship between laboratory studies of brain function, the normal human condition, and the mechanisms of disease. The importance of basic understanding to the solutions of difficult clinical problems of human disability is particularly emphasized in a volume of this type.

One can come away from reading *Epilepsy* with a number of useful concepts. As an overview to an understanding of the relationship of disease to physiological processes the book is particularly useful. It is clearly a document which supports the need for vigorous basic and clinical investigation. It is a fascinating review of the life work of a laboratory director and his colleagues. It can be strongly recommended.

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Captopril and Hypertension. Topics in Cardiovascular Disease. D.B. Case, E.H. Sonnenblick, and J.H. Laragh, Eds. New York: Plenum, 1980. 236 pp., illus., index, $23.50.

This monograph consists of a series of 15 chapters divided into three parts: the first is related to some aspects of humoral and physiological mechanisms in hypertension; the second deals with the analysis of the angiotensin-converting enzymes in terms of exploring the most relevant characteristics of an enzyme used to develop appropriate inhibitors; and finally, the third part presents some results from the clinical use of such inhibitors. This collection of manuscripts is made of transcripts of the conferences presented at a symposium entitled "Pathogenesis of Hypertension," held at the Henry Chauncy Conference Center, in Princeton, NJ.

The first section intends to analyze some important humoral and physiological mechanisms underlying the production of hypertension. It is introduced with a chapter entitled "Blood Pressure Homeostasis," in which R.A. Vukovitch and J.R. Knill made a very brief summary of classical concepts on the circulatory systems, as can be found in most books on physiology.

In the second chapter, E.L. Bravo, H.P. Dustan, and R.C. Tarazi analyze some of the characteristics of hypertension induced by long-term oral administration of an electrolyte-active steroid, metyrapone, which is used without reducing renal mass or increasing salt intake. Their hemodynamic findings relate to reciprocal changes of cardiac output and total peripheral resistence and to the manner in which the development of this hypertension is altered by the administration of β-adrenergic blocking agents (acebutolol) or central α-agonists (clonidine) or by changes in sodium intake. The findings have led the authors to postulate that these electrolyte-active steroids induce hypertension by altering the membrane properties of vascular smooth muscle.

E.E. Muirhead presents a comprehensive review on the more recent advances on the functions of the renal medulla, which could be conceptualized as an important endocrine antihypertensive organ. In this chapter the nature of antihypertensive action of polar and neutral renomedullary lipids is examined. It is suggested that these medullary antihypertensive endocrine mechanisms act in close relationship with the renin-angiotensin system.

The influence of the sympathetic system on renin release is analyzed in chapter 4 by W.S. Peart, who attempts to define the specific alterations occurring in tetraplegic subjects and in patients suffering from Shy-Drager syndronme. The circadian rhythm of plasma renin activity, cortisol, and aldosterone as well as chronic changes in plama renin activity induced by sodium deprivation, volume changes, or by angiotensin are also examined. This analysis disclosed that the above-mentioned neurological alterations produced peculiar patterns whose complexity does not allow a complete morphological systematic study of the manner in which renin release is affected.

In chapter 5, N. K. Hollenberg offers a very interesting survey on the manner in which angiotensin plays a major role as a determinant of the renal perfusion and function. Such a concept is mainly supported through a critical comparison of the philogenetic development of both the renin-angiotensin system and nephron structure from fish to primitive mammals. The concept that glomerular dynamics can be regulated not only by changes in the vascular tone of the afferent and efferent arterioles but also by the stimulation of contractile elements contained in the glomerular mesangium opens a new dimension for the role that the renin-antiotensin system plays in several physiological and pathological situations. The section discussing the aspects of the physiopathology of hypertension includes a chapter in which J. N. Cohn analyzes the influence of changes in systemic vascular resistance which respect to the left ventricular function and also the mechanism that underlies the beneficial aspects of peripheral vasodilators in patients with cardiac insufficiency.

The second part of the book is comprised of five chapters devoted to the analysis of the angiotensin-converting enzyme. The most relevant biochemical properties and immunobiological characteristics are well analyzed by R. L. Soffer and E. H. Sonnenblick (chapter 7). D. W. Cushman et al. outline in chapter 8 the major criteria used to develop the synthesis of potential converting enzyme inhibitors.

These chapters are followed by a well-written and comprehensive review by B. Rubin et al. of the effect captopril exerts on blood pressure in different physiological and pathological models. This section is very valuable inasmuch as it contains information on the duration of the converting enzyme inhibitors which blocking the effects of exogenous angiotensin I in normal animals of when given to animals with renovascular or genetic hypertension. These pharmacological features are completed in the following chapter (chapter 10) by a complete analysis of the toxicologic effects of captopril in animals. In this part of the monograph an attempt has been made to establish a line of comparison between experimental and clincal medicine: the chapter on toxicology is followed by a prelimnary report on the results that H.R. Brunner et al. have obtained in patients with different types of hypertension treated in a long-and short-term fashion with these drugs.

Finally, part III of the book is composed of four chapters where the most clinically relevant aspects of the use of captopril are analyzed. The first of these chapters serves as an introduction in which J.H. Laragh outlines the importance of the volume and constrictor effects of the renin-angiotensin system, explaining the clinical effects of blocking the converting enzyme. This is followed by an analysis of actual results obtained by Laragh's group from high-, normal-, and low-renin hypertensive patients receiving SQ 20881 or saralasin. The notion that seems to dominate the experience of the author is that although the inhibition of converting enzymes may potentiate the kinin systems, and thereby explain some unexpected results, the effects of the drug can in general, be ascribed to the blockade of the biological actions of the renin-angiotensin system.

The validity of these concepts, however, is somewhat questionable. The results presented by Gavras et al. in chapter 14 show that the fall of blood pressure that follows the administration of Teprotide in patients with renovascular hypertension, chronic renal failure, primary aldosteronism and in some patients with essential hypertension submitted to high- and low-sodium diets or in upright, lying, or standing positions cannot always be predicted from the pretreatment levels of plasma renin activity. The authors conclude that the major difficulties in using Teprotide to evaluate renin-dependent situations are not presented by the appearance of "false negative" results, since no

high-renin patients were found to be resistant to Teprotide, but there are patients in whom the blood pressure falls in spite of the low preinjection levels of plasma renin activity ("false negatives").

Finally, in the last chapter, Case et al. analyze the clinical experience with blockade of the renin-angiotensin system by captopril in hypertensive patients, showing that the drug produces a significant decrease in blood pressure when given for a period of up to six months. It is also reported that in some cases with a less satisfactory response to captopril, significant falls in blood pressure were obtained after the administration of a diuretic. The presence of fever and rash and, more disturbing, reversible proteinuria was reported to exist in three patients.

In summary, this monograph cannot be taken as a complete all-inclusive review on the effects of captopril and hypertension. However, the editors have succeeded in organizing the various papers in a way which offers the reader an interesting introduction to pertinent aspects of the physiopathology of hypertension that are relevant to the mechanisms of actions of the converting enzyme inibitors, general pharmacological actions of captopril, and the preliminary results obtained by different investigators in humans.

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The Renin-Angiotensin System. Advances in Experimental Medicine and Biology. New York: Plenum, 1980. 307 pp., illus., index, $37.00

This volume is part of *Advances in Experimental Medicine and Biology* a continuing series that has been devoted to the renin–angiotensin system. The several chapters written by different well-know authorities in this field corresponds to a series of lectures presented at the 14th Midwest Conference on Endocrinology and Metabolism, which was held at the University of Missouri at Columbia, MO, September 28-29, 1978. This conference dealt with many different aspects of the renin-angiotensin system including the biochemistry, anatomy, physiology, and comparative endocrinology of the several system component. It included also other areas related to angiotensin receptors, angiotensin-converting enzyme, the control of renin release, angiotensin and aldosterone secretion, and the role of the renin-angiotensin system in the central nervous system. The coverage of each of these topics is limited to the analyses of the recent findings made by each author in his own area of expertise, whereas the analyses of findings made by other investigators are generally restricted to specific subjects under discussion. The material presented by each author is interesting, objectively evaluated, and written in a very comprehensive fasion. Clinicians and basic scientists in the area of physiology and pharmacology who are unfamiliar with the functional characteristics of the renin-angiotensin system will find this book informative.

L.T. Skeggs present a brief review of the history of the renin-angiotensin system and the major findings made in his laboratories on the chemistry of angiotensin, renin substrate, renin, along with some actions related to the angiotensin-converting enzyme and inhibitors of the renin-angiotensin system. The physiological significance of inactive and active forms of renin is superficially covered; and an update on the present investigation of "renopressin" only occurs duing the discussion.

A comparative analysis on endocrinology of the renin-angiotensin system is covered by H. Nishimura, who has made a thoughtful analysis of the several biochemical and physiological aspects of the renin-angiotensin system in nonmammalian vertebrates. The several aspects in developmental significance of the juxtaglomerular apparatus, the biochemistry and biological actions of the different components of the renin-angiotensin system, and the role of hemodynamic factors in the control of renin release are well analyzed and placed in perspective.

The structure of the juxtaglomerular apparatus is analyzed by Dr. Barajas, who focused on is previously reported studies on the components of the juxtaglomerular apparatus as analyzed with serial sections of either light or electron microscopy. The functional theory that emerges from a three-dimensional reconstruction of the relationship of the distal tubule to the afferent and efferent arterioles and the innervation of the juxtaglomerular apparatus is also examined.

J.E. Zehr analyzed the work performed in his laboratory with respect to the influence of prostaglandins on renin release and the role played by the nervous system. A succinct review on molecular approaches to the study of angiotensin receptors by M.J. Peach and a short outline on the inhibitors of the angiotensin-converting enzyme by D.W. Cushman are included. The role of angiotensin II in the regulation of aldosterone biosynthesis by R.E. McCaa assesses the results of his laboratory on this subject, and I.A. Reid presents a well-balanced survey on interactions between the renin-angiotensin system and the brain.

In summary, most of the authors have succeeded in presenting a critical review of advances made in their own laboratories with respect to the data published by other investigators. The chapters written by Nishimura, Peach, and Reid have also succeeded in presenting in-depth reviews of the recent advances made in that field. It is unfortunate that publication of this material has taken almost three years.

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Vertebrates: Physiology, Readings from Scientific American. 263 pp., and Vertebrates: Adaptation, Readings from Scientific American. 256 pp. Introduction to each by N. K. Wessells. San Francisco, CA: Freeman, 1980. Illus., index, each book: hardback $19.95, paperback $9.95.

These two books were designed to be used together, although each can stand alone. The papers in both books are an introduction to the physiological and biological environment of vertebrate organisms – their adaptation for living in their environment with an overall picture of how this adaptation is integrated with the physiology of the body. The interested reader should first go through the series of papers on vertebrate physiology for an overview of the background material needed to grasp more fully the concepts presented in the volume on vertebrate adaptation.

Both volumes are a compilation of classic articles by some of the most prominent scientists in their fields, extracted from various issues of the *Scientific American.* These articles as selected present an overall picture of the evolutionary changes that have occurred in the structure and function of vertebrates and have resulted in their adaptation to living successfully in their particular environment.

Vertebrates: Physiology is divided into five sections: Vascular System Biology (5 papers), Gas Exchange and the Lungs (5 papers), Water Balance and Its Control (2 papers), Temperature Adaptations (4 papers), and Hormones and Internal Regulation (7 papers). *Vertebrates: Adaptation* has six sections: General Features (1 paper), The Body and Movement (7 papers), Special Structures (3 papers), Reproduction (3 papers), Orientation and Navigation (4 papers), and Vertebrates in Their Habitat (5 papers). In both volumes each section has an informative introduction that serves to orient the reader and consolidate the

material covered. In *Vertebrates: Physiology* there are survey articles such as "The Heart" by Carl J. Wiggers, "The Lung" by Julius H. Comroe, "The Thermostat of Vertebrate Animals" by Heller, Crawshaw, and Hammel, "Salt Glands" by Knut Schmidt-Nielsen, and "Adaptations to Cold" by Laurence Irving as well as articles concerning specific vertebrates as "The Physiology of the Giraffe" by James V. Warren, "The Diving Women of Korea and Japan" by Suk Ki Hong and Hermann Rahn, and "The Hormonal Control of Behavior in a Lizard" by David Crews. In *Vertebrates: Adaptation* survey articles include "Adaptation" by Richard C. Lewontin, "Paleonurology and the Evolution of Mind" by Harry J. Jerison, and "The Control of Walking" by Keir Pearson. Articles concerning specific forms include "The Head of the Sperm Whale" by Malcolm R. Clarke, "The Phalarope" by E. Otto Höhn, "The Mystery of Pigeon Homing" by William T. Keeton, "How Snakes Move" by Carl Gans, and "Kangaroos" by J.T. Dawson.

As Dr. Wessell's prefaces (in both books) point out, the collection of papers are intended for supplemental reading for persons taking courses in introductory biology, comparative anatomy, and physiology.

I recommend these volumes highly to students and to those who wish to update and expand their knowledge of the details of the fascinating field of vertebrate adaptation. However, although the author has done an excellent job of presenting the material, it should be recognized that the papers were all published between 1957 and 1979 with many in the 1960's, thus precluding more recent findings and theory. This does not negate the value of the earlier papers but does necessitate the need for further examination of more recent literature. Similarly, the papers are those published only in *Scientific American;* others of importance and pertinence should be examined also, even for information supplemental to introductory courses. The prices are reasonale; the reading stimulating and revealing as in most *Scientific American* articles.

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Perinatal Pathology. Current Topics in Pathology, vol. 66., E. Grundmann and W.H. Kirsten, Eds. New York: Springer, 1979. 218 pp., illus., index, $52.80.

Perinatal Pathology, a recent volume of *Current Topics in Pathology* series, is of interest to those involved in the reproductive sciences, particularly reproductive pathology and immunology, perinatology, and obstetrics. The book contains seven chapters and 88 figures. The first chapter deals with "The Placenta and Low Birth Weight. In this chapter a number of factors, both fetal and maternal, contributing to low birth weight are reviewed. Included is a description of placental examination by relatively sophisticated technics, such as an angiography and transmission and scanning electron microscopy. The second chapter focuses on a poorly defined, somewhat loosely used term, "Placental Insufficiency." The author attempts to qualify morpholigc patterns based on maturation and circulatory disorders of the placenta with abnormal clinical outcome. Unfortunately, one is left still in search of a thread of continuity and substance within a plethora of divergent conditions.

The topic of maternal-fetal immunology includes chapters on "Interactions Between Maternal and Fetal/Neonatal Lymphocytes" and the "Transfer of Humoral Secretory and Cellular Immunity from Mother to Offspring." The latter section presents interesting comparative data on immune substance transfer during reproduction with the use of some well-constructed schematic diagrams. A thorough, practical, and concise chapter deals with the clinical, pathologic, and predictive aspects of "Single Umbilical Artery malformation with Congenital Malformations." A chapter on "C-Type Virus Expression in the Placenta" summarizes current knowledge in this area with theories of the relevance and significance. The last chapter devoted to "Transplacental Effects of Diethylstillbestrol" summarizes current knowledge on the effects of this condition in male and female offspring. Included are some practical points on diagnosis by culposcopy, cytology and tissue examination.

In summary *Perinatal Pathology,* which is devoted to subjects of timely interest, is well planned, informative, and of practical value. The figures are mostly quite useful; some are excellent. The references are extensive. At times the wording of the text is unclear, which may be due to difficulties with translation. All in all the book should be useful to anyone currently involved in reproductive biology.

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Lung Connective Tissue: Location, Metabolism, and Response to Injury. J. A. Pickrell, Ed.; R. Burrell, J.O. Hill, J.L. Mauderly, J.A. Pickrell, and R. Wolff, Contributors. Boca Raton, FL: CRC Press, 1981. 203 pp., illus., index, $59.95 US, $68.95 foreign.

Lung Connective Tissue: Location, Metabolism and Response to Injury is written as an encyclopedic review of the literature in which the contributions of various individuals and research groups are specifically acknowledged. The first portion of the book contains several chapters on the structure and metabolism of collagen, elastin, and proteoglycans, including studies on these components from lung and many other tissues. The middle portion contains chapters on the types of lung cells, cell interaction with the connective tissue matrix, immunologic mechanisms of lung injury, and the sequential changes occurring after pulmonary injury. The last portion of the book contains chapters on the alterations in connective tissue in pulmonary fibrosis, emphysema, chronic bronchitis and asthma, and neoplasia.

The editor (and major contributor), an investigator in the area of inhalation toxicology, draws heavily on his own work on lung collagen metabolism after radiation exposure. The chapters on collagen are the most extensive. The book is the first major review of the area since the reviews by R.G. Crystal and coworkers in 1975 and covers material through early 1979. Although references to abstracts in 1978 and 1979 are understandable, an editorial flaw is the quotation of many abstracts several years old. In places the information given is very dense and reading does not flow smoothly. On the other hand, in chapter 11, the editor attempts to summarize and synthesize various experimetnal facts about mesenchymal cells and connective tissue components with a speculative model for their interaction.

The book does not contain much pulmonary physiology in the usual sense. Rather it acknowledges the fact that research in pulmonary disease not only includes examination of pathology and physiological measurement of alterations in lung function but attempts to understand alterations in lung disease at the molecular level. The book will be useful to investigators in the area of lung disease at all levels. The extensive references at the end of each chapter provide access to the literature prior to 1979.

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