CONTENTS

ARNO BENEDICT LUCKHARDT
1885 - 1957

Dr. Luckhardt was born in Chicago, on August 26, 1885. At the age of 12 he entered Conception College in Missouri. In 1903 he entered the University of Chicago from which he received the B. S. degree in 1906 and the Ph. D. degree in 1911. He received the M. D. degree from Rush Medical College in 1912. He was awarded the honorary degrees of Sc. D. by Northwestern University and L. L. D. by Conception College. His entire professional life was spent at the University of Chicago. He began as an assistant in bacteriology in 1908 and from 1909 until his retirement in 1950 he served in the department of physiology from assistant professor to William Beaumont Distinguished Service Professor.

He became a member of the American Physiological Society in 1911, was elected to Council in 1923, was secretary from 1931 to 1933, and served as president in 1933 and 1934. He served as president of the Federation in 1934 and served on the editorial board of Federation Proceedings. He visited Germany as a Rockefeller Fellow in 1924-25 and while there was elected to membership in the Kaiserliche Akademie der Naturforscher.

Arno Luckhardt was not only an eminent investigator but a dedicated teacher as well. His pupils were many and he was especially interested in his graduate students. Dr. Fenn in his account of the history of the third quarter century of the Society, cites a quote from Dr. Whitehead's reminiscences of the early days that exemplifies Luckhardt's concern for seeing that his graduate students got to meetings. Whitehead states, "I am writing in reply to your request for anecdotes from Society events. One of these related to the special trains which were arranged for by Dr. Arno Luckhardt, to provide cheap transportation to meetings from Chicago to various places where meetings were to be held. I can recall going on such 'specials', once to Washington, D. C., another time to Toronto, Canada. The accomodations were meager, consisting of day coach space and many times we rode on very old coaches of the Pennsylvania Railroad. At night the backs of the seats were removed and placed on the floor. The person would lie down on this hard seat back, cover himself with an overcoat, fold his coat to make a pillow and get whatever sleeping done he could by this means, which was often precious little. Many times when we attended meetings by getting such accomodations, we spent our own money for the trip. (No grant funds available). These 'special trains' became quite well-known by those living in the Chicago area and in regions west and north of there. They were known as the 'Luckhardt Specials.' Always, Dr. Luckhardt as well as Drs. Carlson, Tatum, Meek, Eyester, and many others were passengers on these trains. Many professors as well as students preferred to play bridge most of the night to resting (?) on the floor of the coaches."

Dr. Luckhardt published many researches on a great variety of themes: gastric motility, gastric and pancreatic secretion, parathyroid physiology, general and local anesthetics, visceral sensory nervous system, respiration. He is probably best remembered for his demonstration of the anesthetic properties of ethylene gas. He records the

fact that he inhaled an ethylene-oxygen mixture to the point of anesthesia some 700 to 800 times without any bad after effects. Luckhardt's discovery not only resulted directly in the introduction of a new and improved anesthetic; it also gave added impetus to the search for other new agents and new methods of administering them, and to the steps leading to the creation of a new specialty of anesthesiology. He was also first to show that animals can be maintained alive and in fair condition after complete parathyroidectomy by administering inorganic calcium salts to prevent and relieve parathyroid tetany.

Arno Luckhardt was a man of many interests. He was active in cultivating closer medical-dental relationships and for his efforts was honored by the American Dental Association by serving on its Council. His wide interests included the history of physiology. He accumulated one of the great historical collections of rare physiological books and papers. Among them are the records of William Beaumont's studies of digestion. His early education in Medieval Latin gave him the ability to read many classics of medicine in the original. He collaborated with James Henry Breasted in the interpretation of the Edwin Smith surgical papyrus, "the oldest scientific book in America and the oldest nucleus of really scientific medical knowledge in the world."

Physiology, education, medicine, surgery and dentistry were all enriched by his contributions.

REFERENCES

1. "Arno B. Luckhardt, Physiologist" by F. C. McLean, Science, vol. 127, p. 509, 7 March 1958.
2. "History of The American Physiological Society" by W. O. Fenn, American Physiological Society, Washington, D. C.

EXTRA-CORPOREAL TECHNOLOGY

The Eighth International Conference of Extra-Corporeal Technology is being held at the Roosevelt Hotel in New Orleans, La., July 16-18, 1970. For further information write Dr. Theodore Drapanas, Dept. of Surgery, Tulane Univ., New Orleans, La. or Dr. E. C. Berger, 287 East Sixth St., St. Paul, Minn. 55101.

DISCUSSION SESSIONS AT THE SPRING MEETING

The number of abstracts submitted to the Society for the Spring meetings exceeds the number of 10-minute presentations that can reasonably be scheduled. This disparity is growing. On the basis of the decision of the membership at the Business Meeting last Spring, oral presentations are limited to approximately 850. The total number of abstracts received was reduced to approximately 850 by eliminating every n^{th} paper from oral presentation. It seems clear that experimentation with new, more efficient methods of presentation of scientific reports is desirable in order to accomodate a greater number of reports.

Therefore, an additional alternative mode of presentation will be used this Spring as an experiment during the noon break in the regular sessions. Groups (coinciding with those listed in the back of the abstract issue of Federation Proceedings) will be scheduled for discussion meetings according to the scientific compatibility of the abstracts submitted. Authors who agree to participate will come to ROOM 11, CONVENTION HALL, at scheduled times with their slides. The schedule will be posted outside Room 11. In so far as possible, the subjects covered will be Endocrinology and Reproduction on Monday; Neurophysiology and Sensory on Tuesday; Cardiovascular and Blood on Wednesday; Transport, Muscle and Miscellaneous on Thursday; and finally Respiration and Environment on Friday. A Discussion Leader will be present to evoke and aid the discussion process. Since the usual 10 - minute talks will not have been given, the abstracts will serve as the basis for initial questions. If nothing else, this mechanism will allow people to know where they can meet authors of the excluded abstracts without having to search them out privately. Since the time of presentation is saved, it will be possible in this fashion to greatly increase the number of reports which can be handled per room-hour. If it is found to be a satisfactory method of sharing ideas and data, perhaps it can be used to replace some of the regular sessions for sub-areas where well-focused discussion groups could be identified. The likelihood of success of this mode of presentation would probably be increased by having a larger set of abstracts from which to choose compatible groups. Nonetheless, it is hoped the experiment using the otherwise randomly excluded presentations will allow the Society to evaluate this different kind of scientific meeting. Anyone with suggestions of how to improve the likelihood of success of this experiment please contact me.

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THE LABORATORY OF ENVIRONMENTAL PATHO-PHYSIOLOGY - 1969

D. B. DILL

Three years ago I described in The Physiologist the genesis of this laboratory which is under the administrative wing of the Desert Research Institute (DRI), University of Nevada System. I now propose to take stock relating in particular to the capabilities of outstanding high school students as manifested by their performance in a research laboratory. No claim is made for originality. William V. Consolazio while in the Cambridge Latin School came to work in the Harvard Fatigue Laboratory 41 years ago and his younger brother, Frank, a year later. I take great pride in their achievements. Bill is now Head of the Scientific Development Section of the National Science Foundation (NSF), and Frank is Chief, Bioenergetics Division, U.S. Army Medical Research and Nutrition Laboratory, Denver. Bill is a member of the American Society of Biological Chemists and Frank, of the American Institute of Nutrition. During a post-retirement period at Indiana University, I had another opportunity to observe the maturity and character of high school juniors brought together by an NSF Institute.

Seniors of the Boulder City High School selected in 1966 to work in this laboratory have borne out predictions of Principal McCormick and his faculty. Barneby is in West Point, and Leslie Startin, after two years as a Regents scholar with expenses paid at the University of California, Riverside, is spending a year at Göttingen. Leslie presented a paper at age 18 at a symposium in Albuquerque on "Physiological Systems in Semi-Arid Environments." The paper, "Body Composition of the Kangaroo Rat," was included in a publication by the University of New Mexico Press, 1969. Prior to this year, the highlight of her experiences was the summer of 1968, spent in the Institute of Arctic Biology, Fairbanks. Bob Parker, president of his high school senior class, was selected at the end of his first year at Ohio State as a member of a small group assigned to the field of educational research. Those selected were judged to be potential graduate students. Bob has been with us the past two summers; in 1968, he was one of two students who were research assistants in our 6-week study at the Barcroft Laboratory, White Mountain Research Station. The other assistant in that study was John Lynch, senior class president in 1967-68. John entered the University of California, Santa Barbara that fall and spends part time working in Horvath's Institute of Environmental Stress. Three students graduated last June; they were among the top four in scholarship. Sandra Miller is entering the University of Nevada, Las Vegas; Bob Greer, the University of Arizona; and Danny Morris, the University of Chicago. Danny joined us in 1966 on the basis of Principal McCormick's estimate of his potential. He has borne out that estimate by his scholastic record, his skill and intelligence manifested in the laboratory and his leadership. He won first prize in physics in the Southern Nevada Science Fair this year. He, too, was senior class president. He and Bob Greer were research assistants in our altitude study this past summer.

This school year seven students are working in the laboratory, about

two hours each school day and four hours Saturday forenoon. All are honor students interested in science. One is a freshman already skilled in electronics, two are sophomores, one a junior, and three seniors. One of the latter, Dianna Burk has won prizes in horsemanship and understands our burros. Another, David Freeland, has great dexterity with tools and is a ham radio operator. Dan Evans has a 4.00 grade point average, is senior class president, a leader in school activities and a gifted public speaker. Recently he was named a semifinalist in the 1969-1970 National Merit Scholarship program. He reported at the Davis meeting the study he is conducting of the natural environment of the kangaroo rat. With four transparencies to project and a few notes on 3 x 5 cards, he won warm applause from the audience, an impressive record for a 17-year old student. The University of California, Davis, put out a press release on his accomplishments.

My co-investigator, M. K. Yousef, and I are able to teach these students within a few weeks to be effective assistants. With their help in making observations, we have two papers in current numbers of the Journal of Applied Physiology on the burro and a third on "Hemo-concentration at Altitude." Since they had a major role in the latter study Parker and Lynch are joint authors. I consider it significant that not one of our 18 students, past and present smokes cigarettes. In fact, they tell me that only about 10% of their classmates smoke. It seems that the wheel has turned. A generation earlier parents were trying to persuade their children not to smoke cigarettes. Now these children are parents and they are under pressure from their children to quit smoking cigarettes.

We don't have funds enough to support senior scientists full-time. Yousef teaches at UNLV half time in the school year and is here the rest of his time. However, we find money enough to cover at least the expenses of a few visiting scientists who want to spend part of the summer in the desert. In 1967 Paul Robinson, Army Medical Laboratories, Edgewood, Maryland, Harry Frankel, Rutgers, Kay Burrus, Indiana University, and Gale Gehlren, Ball State were here each for several weeks. Robert Bullard of Indiana University, David Costill of Ball State University, and Klaus Klausen (leader in out altitude study) of the University of Copenhagen were here in 1968. This summer, Gary Packard of Colorado State University, Loren Myhre of Indiana University and Gale Gehlsen have been with us. Ralph Jung, USC School of Medicine, clinician and physiologist, was in charge of our 1969 altitude study. These scientists bring to bear on our projects fresh points of view. Their visits are mutually valuable. A colleague of mine of many years standing, F. G. Hall, had a leading part in our altitude and desert studies extending from 1935 to 1966. He played a major role in my life as a friend and as a collaborator up to the time of his death in February 1967.

The facilities described previously have been amplified by installation on the ground floor of a Forma Walk-in environmental room for animal studies. Also a shop has been built at one end of the ground floor and equipped with a desert cooler and electric heater. The former upstairs shop has been converted to a biological laboratory. We continue to enjoy excellent relations with the U.S. Bureau of Mines. We are their

non-paying guests. A "facility" essential to our program is the desert around us and another, that we appreciate utilizing, is the White Mountain Research Station about 300 miles distant. In between is Death Valley. I bought a corral, tack house and lean-to shelters located about one km from Boulder City. Ownership requires membership in the Horsemen's Association, so I am a dues-paying member. It would have been sticky business for DRI to have joined the Association. Our burro Mabel, was a member of a nearby wild herd; her captor sold her to DRI for $25. Maud, about the same age, from another herd was a gift. The tack house is well insulated. A desert cooler and an electric heater keep the temperature within tolerable limits for the 40 kangaroo rats held there in exercise and non-exercise cages as part of a longevity study. Two students share responsibility for animal care.

The University of Nevada System is a troika: UN Reno, UN Las Vegas, and DRI. Research grants from NSF, U. S. Public Health Service and Nevada Heart Association that support this laboratory are administered by the headquarters of DRI in Reno. Everyone I suppose has a cross to bear. Mine is that after three years I have not yet mastered the art of accounting and am still bewildered by monthly "Statements of Operation." Here at Boulder City we are 20 miles and 30 minutes from UNLV where we enjoy excellent relations with colleagues and administrators. I am one who enjoys life wherever he finds it: it has been a particularly happy life here in Boulder City. Besides gardening, my wife and I enjoy golf at a club ten miles distant in Henderson, and bowling. To quote the psalmist, "The lines have fallen unto me in pleasant places; yea, I have a goodly heritage."

OTOPHYSIOLOGY

An International Symposium on Otophysiology will be held at the Univ. of Michigan, Ann Arbor on September 17-19, 1970. For information write to Dr. Merle Lawrence, Kresge Hearing Research Institute, 1301 East Ann Street, Ann Arbor, Mich. 48104.

FOURTEENTH BOWDITCH LECTURE*

Blood-borne Signals
The Measuring and Modelling of Humoral Communication and Control

JOHN URQUHART
Professor of Physiology
University of Pittsburgh School of Medicine

Since Professor Bowditch's time, endocrinology has gone through two great transitions. The first was from non-existence to existence, and that occurred with the discovery of secretin by Bayliss and Starling in 1902. But even then the notion of internal secretions was already a half century old, having been introduced by Claude Bernard to describe the liver's internal secretion of sugar. Starling felt that the term internal secretion was inadequately descriptive and, in his Croonian lectures of 1905 (1), popularized Hardy's term "hormone" - after the Greek ὁρμᾶνειν to arouse or to excite (cf also p. 706 in ref. 2). In 1916, Schafer objected that a preferable term would have been hermone, after Hermes - the messenger, in order to avoid the etymological catastrophe of a hormone which exerts inhibitory actions (cf Chapter 1 in ref. 3). But the term hormone stuck, for both excitatory and inhibitory internal secretions, in keeping with the spreading anesthesia to the niceties of language.

In endocrinology, the first half of the 20th century was an era of discovery and description - description which was of technical necessity largely qualitative.

The second great transition in endocrinology was from the macroscopic to the microscopic - which I mean in the functional sense rather than structural.

The actions of a hormone pose fascinating biochemical questions - and the fascination of those biochemical questions has funneled the interest and attention of most of this generation of endocrinologists into the subcellular microcosm. These are interesting and necessary areas of investigation, but they have diverted attention from the more macroscopic aspects of endocrine physiology which have languished in a relatively descriptive and qualitative state. As my title suggests, I want to revive and pursue what is essentially the original theme in endocrinology (1) -- blood-borne signals which link the function of one organ with that of others.

These are problems in function perceived at the organ level, and they have to be attacked as such.

The experimental or measurement problem is threefold--first, it

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* Presented at Davis, California, August 28, 1969.

is to bring into view the function of an endocrine target organ; second, it is to gain experimental control over the concentration of the blood-borne signal in the target organ's arterial blood; the third problem is to be able to solve the first two without wrecking the target organ or crippling its response to the blood-borne signal. There is a conceptual or modelling problem as well, and that is to generalize about the dynamic relations which govern a target organ's response to a blood-borne signal.

In this lecture, I wish to focus your attention on two hormonally controlled processes - one is the secretion of cortisol by the adrenal cortex; the blood-borne signal which controls this process is the pituitary hormone, ACTH. The second hormonally controlled process is the production or secretion of glucose by the liver. Several blood-borne signals influence the hepatic production of glucose, some in one direction, some in the other. The adrenocortical secretion of cortisol and the hepatic production of glucose are two very different processes, and the two studies pose very different experimental problems. They are also at two different stages of scientific development. But both are alike in that the two processes are functions of one or more, albeit different, humoral substances. In their dissimilarity, they illustrate the power of a simple but general experimental and conceptual approach to hormone action which I propose to illustrate.

Of the two processes, the adrenocortical secretion of cortisol is both the simpler and much the more completely characterized, so I shall discuss it first. Our goal has been to model the dynamic action of ACTH on cortisol secretion. Such a model ought to accomplish two things. First, it should enable one to make hard-number predictions about the time course of cortisol secretion rate given information on the time course of ACTH concentration in arterial blood. In other words, a model should be capable of simulating that secretory function of the adrenal cortex. The second accomplishment of a model ought to be to relate the secretory dynamics of the intact gland to the biochemical mechanisms by which ACTH is believed to act on the synthesis and secretion of cortisol. So not only should a model simulate, it should also serve as the vehicle which relates or reconciles function perceived at the organ level with function perceived at the cellular and subcellular level. Since neither of these perceptions will be flawless, there will be not one but several, or perhaps many models - all of which simulate, but each one of which represents a different view about the underlying mechanisms of ACTH action.

The experimental support for this modelling effort is a set of observations on the time course of cortisol secretion rate that are associated with a variety of temporal patterns of change in ACTH concentration in adrenal arterial blood. We performed such studies on the canine adrenal (4-7). These were acute experiments, carried out with the dog under pentobarbital anesthesia. Blood from the dog's carotid artery was led through the pump and heater into the segment of abdominal aorta shown in figure 1. All the extra-adrenal arterial branches of this aortic segment were ligated, so that the pump controlled the blood flow through the left adrenal gland. It is an in situ perfusion. The adrenal receives

many small arteries rather than a single large one, so perfusion through a carefully dissected abdominal aorta insures uniform perfusion. Fortunately there is only one adrenal vein, so a catheter there (as shown in figure 1) permitted the collection of the entire venous effluent.

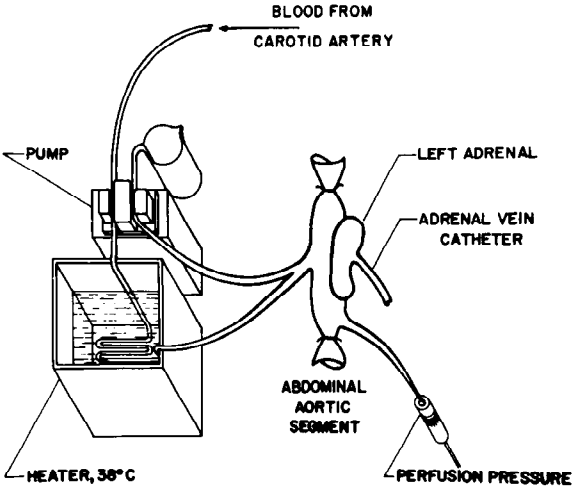


Fig.1. Schematic representation of the technique for perfusing the canine left adrenal gland in situ with heparinized arterial blood. The unlabelled beaker contains a solution of ACTH of known concentration in 0.9% bovine serum albumin in isotonic saline held at 0°. In some experiments the ACTH solution was pumped by a second pump; in either case, the flow of ACTH solution was 10% or less of the flow in the blood line. The figure shows the perfusion pressure being measured via a catheter in the left renal artery and the carotid blood-ACTH solution being pumped into the aortic segment via a catheter in the right renal artery. However, in all the experiments on time-dependent relations between ACTH concentration and cortisol secretion rate, the perfusate was pumped into the left renal artery catheter and the pressure was measured via the right; this change minimized the volume of the potential cul-de-sac between the point at which the perfusate entered the aortic segment and the segment's caudal limit. The combined volumes of the aortic segment and the perfusion tubing beyond the point of mixing between the blood and ACTH solution impose an artefactual dynamic lag on the desired dynamic changes in ACTH concentration in adrenal arterial blood. We estimated this lag by measuring the time course of Evans blue concentration in adrenal venous blood following stepwise changes in the rate of infusion of the dye into the perfusion line. The lag had an average time constant of 20 seconds, which we interpret as a negligible dynamic distortion in view of the much longer apparent time constants in the adrenocortical response to ACTH. From (4).

This perfusion technique was developed by J. G. Hilton and his colleagues in New York (8); I learned it from James O. Davis when I worked with him at the National Heart Institute. That association with him was very valuable to me. Jim Davis taught me how to conduct technically complex acute experiments.

Now in this preparation, our having experimental control over ACTH concentration in adrenal arterial blood depended on several factors. First, we removed the dog's pituitary at the beginning of the surgical procedure. By the time the experiments were begun, endogenous ACTH was reduced to negligible levels, as evidenced by very low rates of cortisol secretion. Thus, we could specify the absolute concentration of the hormone in adrenal arterial blood by independently controlling both the perfusate flow and the rate of infusion of solutions of known ACTH concentration. The local infusions of ACTH were usually at rates low enough to produce negligible increments in the systemic levels of ACTH. We assayed adrenal venous blood for cortisol by the double isotope dilution derivative method, (9; see also 4) which is specific and more than adequately sensitive.

With this preparation, we could vary ACTH concentration through one or another temporal pattern, while we measured cortisol secretion rate.

It is useful to begin with the steady state relation between ACTH concentration and cortisol secretion rate. The next figure (figure 2) shows that, with data from three experiments. We have plotted ACTH concentration on a linear scale rather than the conventional logarithmic one. That serves to emphasize that the coupling is most tight in the narrow concentration range between 0 and 10 μU/ml, where the slope is steepest. The secretory minimum is less than 1 μg/min -characteristic of the very low but never zero secretory rates in the absence of ACTH. The secretory maximum is about 10 μg/min and that value is characteristic of measurements of adrenocortical secretion in the intact dog given large amounts of ACTH. The range of cortisol secretion by these perfused glands - an 8-10 μg/min range - conforms to range of the gland in the intact dog; these points of agreement between the perfused gland and the gland in the intact dog are good but not complete reassurance that we did not cripple the gland in preparing it for perfusion. More complete reassurance would come if we had information about where some of these intermediate points (i.e., cortisol secretion rates associated with ACTH concentrations between 1 and 10 μU/ml) fall in the gland of the intact dog, but for technical reasons these measurements are not yet possible.

The slope of the ACTH concentration - cortisol secretion rate relation between 1 and 10 μU ACTH/ml is blood flow-dependent, although the maximum rate of secretion is independent of blood flow (4). In our studies on the dynamic relations between ACTH concentration and cortisol secretion rate, adrenal blood flow was held constant. I want now to turn to those studies on the dynamics of ACTH action.

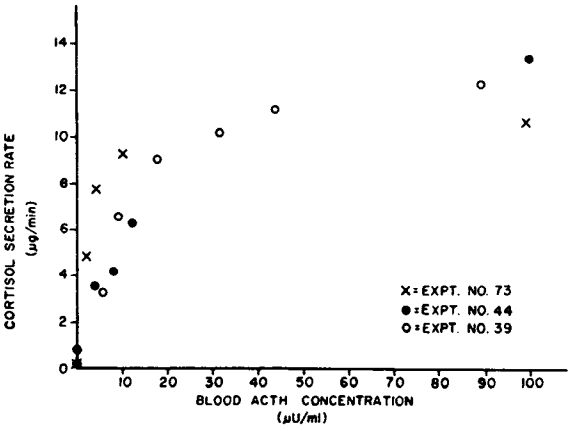


Fig.2. Steady-state relations between cortisol secretion and ACTH concentration in three experiments. From (6).

The next figure (figure 3) shows the effect of small stepwise increases and decreases in ACTH concentration in adrenal arterial blood. Note the ACTH concentration changes between 0 and 2 µU/ml - well within the steepest portion of the relation between ACTH concentration and cortisol secretion rate. After the first increase in ACTH concentration, cortisol secretion rate increased after about a 2 minute delay, rose steeply to a peak in about 10 minutes, then gradually settled back to an intermediate level of secretion which it held throughout the latter half hour of the response. Then at 60 minutes, we reduced the ACTH concentration in stepwise fashion back down to zero. After about a 2 minute delay cortisol output fell very rapidly, and settled down to its original level within only about 10 minutes. A second stepwise increase in ACTH at 100 minutes yielded up a virtual repeat of the first response. The fact that the second response resembled the first is good reassurance that the overshoot is a legitimate dynamic property of the gland and not simply the artefact of a dying preparation whose responsivity to ACTH was waning.

I did a lot of blundering around before I was willing to sample cortisol secretion rate so often over so long a period of time. At first I monitored only the first 15 or 20 minutes of the response to a stepwise increase in ACTH concentration; if just that much of either response in figure 3 is plotted out on a wide scale, it would look very convincingly like a nice smooth rise to a steady state, missing altogether the surprising overshoot, which rather cries out for some biochemical explanation. More of that later.

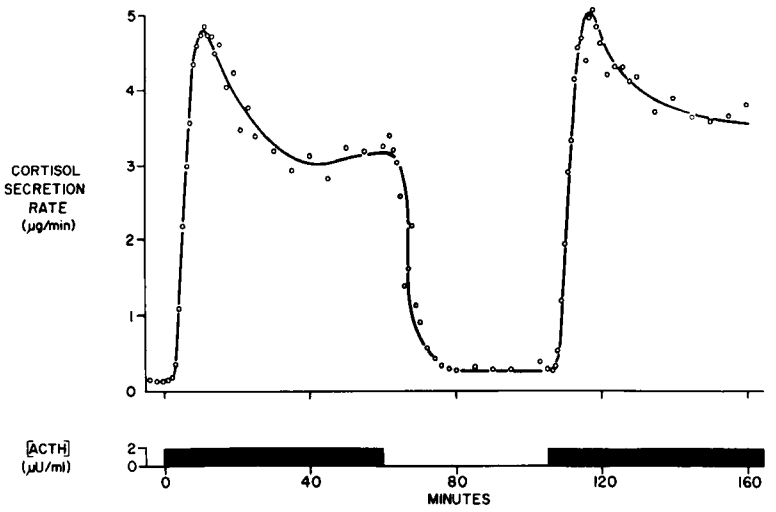


Fig.3. Time course of cortisol secretion rate following stepwise changes in ACTH concentration. From (5).

For now I want to use these data to make an important general point about physiological dynamics. There are two temporal patterns of ACTH concentration change shown in figure 3 - a stepwise increase and a stepwise decrease. There is a secretory response to each change - a rise with overshoot after the increase - a simple exponential decay after the decrease. Note that neither response could be predicted from the other. Cortisol output falls after the stepwise decrease more rapidly than it falls from the peak of the overshoot - and if you knew only the exponential decline after a stepwise decrease in ACTH concentration, there is nothing in it to suggest that the overshoot would take place on the occasion of an ACTH increase. Clearly, each of these two patterns of change in ACTH concentration served to illuminate different features of the dynamics of ACTH action. It follows that still other patterns of change in ACTH concentration might illuminate other, as yet unsuspected dynamic features. How many other possible temporal patterns might ACTH concentration be made to follow? Well, we have already seen two, so that leaves two less than . . . infinity. But we want to arrive at a dynamic model which will predict responses not only to these two rather contrived patterns of change but to all the others as well. How many of an infinite number of input patterns must we look at and which ones ought we to choose?

At issue is the abstract question of whether the dynamics of ACTH action can be treated as linear, with a few simple qualifications, or must be regarded as fundamentally nonlinear. The linear treatment of

such systems finds surprisingly widespread misapplication to just such problems as this one. Linear dynamics have great appeal because of an elegant and seemingly powerful set of mathematics with which to describe them. Let me illustrate an example linear system graphically, for it will reveal the fundamental assumptions in linearity. The left half of figure 4 shows the response of an example linear system to a pulse-like stimulus. The heavy smooth line in the upper left shows the response - an empirical observation. Its particular shape is irrelevant. It could be much more complicated, with oscillations and so forth, but whatever the response shape, the points I want to make will hold. Having made the observation on the system's response to this particular pattern of input - a pulse - we want to generalize about its response to all other possible temporal patterns of input. To do that, we quantize the response into discrete values as shown by the blocks--each of which has the same width as the input pulse and a height which takes the average value of the smooth curve in that interval. These blocks and the input pulse can be made arbitrarily narrow to improve the approximation, but this one with four blocks will illustrate.

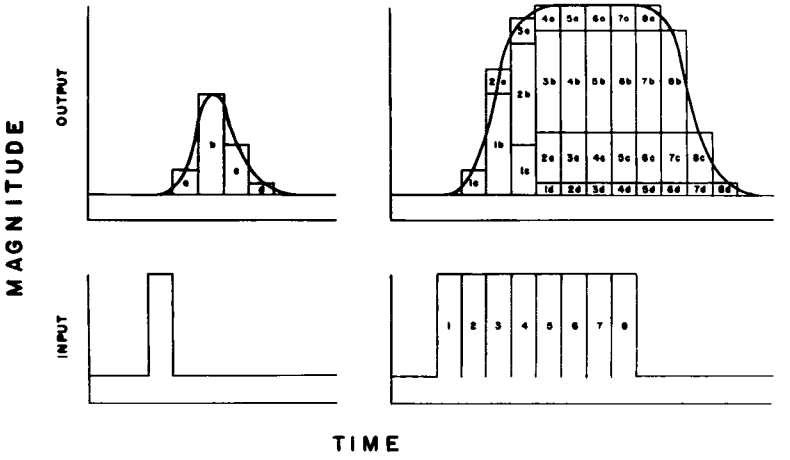


Fig.4. Temporal input-output relations in an example linear system. The figure is discussed in the text. From (10).

The essential points are two: 1. Any temporal pattern of stimulus can be approximated by a train of pulses of different heights. 2. The response to that train of pulses is a train of corresponding pulse responses. The right half of figure 4 illustrates. It shows a step function treated as a train of equal height pulses, numbered 1 through 8. Above is the train of pulse responses. The numbers match stimulus pulse and response. Each pulse response, lettered a through d, is identically the same as all others. Each new one comes along and plays out as if nothing else were going on, and merely superimposes itself on whatever response

happens to be left over from past pulses.

This maneuver is called convolution, and is one of many fundamentally equivalent ways of describing linear dynamics. I think it is the clearest way to illustrate the implications of linearity, because it is stripped of all mathematics, which are uninformative to some people ... and seductive to others. (N. B. For the lecture, I used a colored slide to illustrate these points; the pulse response was approximated by twelve rather than four blocks and each pulse and pulse response was of a different color. Unfortunately, it was not possible to reproduce these figures here.)

A steady state is reached in the last interval of the first pulse response. That steady-state is composed of the sum of 4 blocks, each one from a different pulse response. An important point to note is the symmetry of the upgoing and downgoing responses. It takes 4 intervals to rise to a steady level - and it takes 4 intervals to fall to a steady level when the input was shut off. If you turn the downgoing response upside down, it exactly superimposes itself on the upgoing part of the response. In other words, the response to the downgoing step is predictable from the response to the upgoing step--quite different from what we observed with the adrenal cortex where the rising cortisol secretion after a stepwise rise in ACTH was altogether different in shape than the falling cortisol secretion after a stepwise drop in ACTH. So the dynamic asymmetry observed with the adrenal response to rising and falling concentrations of ACTH indicates that linear dynamic theory is fundamentally inapplicable. In one sense that is too bad because linear theory is so simple to apply. The only experimental data you would need is the adrenal's pulse response; to stimulate the gland's response to any other input pattern all you need is a big pair of scissors, reams of colored paper and a basketball court on which to lay out all the pieces. On the other hand, that ease of generalization which linear systems allow really means that they have rather dull and unexciting dynamics, and pose very little experimental challenge.

But we face a major challenge with a nonlinear process like the action of ACTH on the adrenal cortex. We want to be able to simulate the gland's dynamic responses to ACTH, but convolution with the gland's pulse response is inapplicable. Also, we are at a loss as to which temporal patterns of ACTH concentration to choose in testing the gland's dynamics. With nonlinear systems, there are no a priori ground rules and so we depended upon intuition and luck in choosing a relatively few in the hope that they would most starkly illuminate the dynamics of ACTH action on cortisol secretion. I am indebted to Arthur Iberall for much guidance in this, and for most of the little I know about dynamic systems. I count him as one of my teachers.

What I propose to show you now is how we proceeded to apply different temporal patterns of change in ACTH concentration to the perfused adrenal -which ones we chose and what they showed. For the time being, accept them as anecdotes - when the ACTH changes so and so, cortisol secretion rate varies such and such. But as the experimental data roll by, remember that there is only one set of mechanisms coupling ACTH to cortisol

synthesis and secretion, and with each new dynamic test we reveal something new about than one set of mechanisms.

Figure 5 shows the response to more stepwise changes in ACTH concentrations. At zero time, ACTH concentration was increased from 0 to 1 μU/ml; there was a big overshoot in cortisol secretion rate; then with a subsequent rise from 1 to 2 μU/ml, there was less overshoot in the response. Then I dropped the ACTH concentration from 2 down to 1 μU/ml; in so doing I was looking to see whether there might be some undershoot after the stepwise drop. There is very little - but it is not symmetrical with the overshoots.

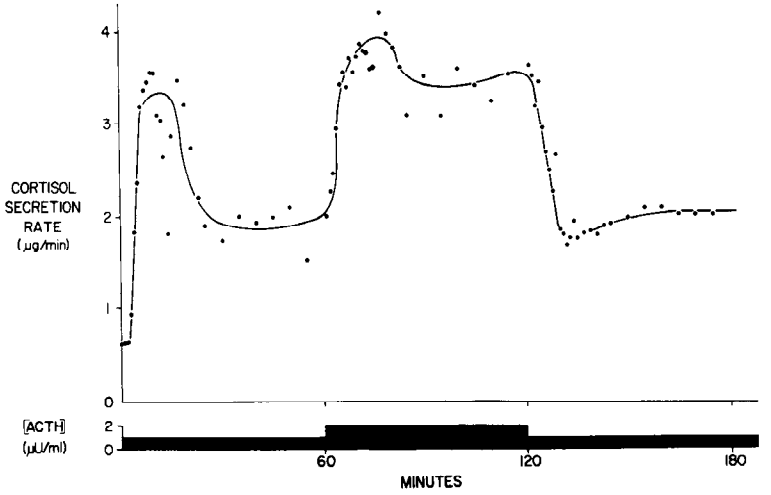


Fig.5. Time course of cortisol secretion rate following stepwise changes in ACTH concentration. At zero time, ACTH concentration was elevated stepwise from 0 to 1 μU/ml. From (5).

Figure 6 shows a staircase input pattern, with 2 μU/ml stepwise jumps every 40 minutes. Ernst Knobil calls this adrenal treppe. Here I was looking to see how many overshoots we could get before hitting the secretory maximum. You can see a clear-cut one in response to the first step, another in response to the second step, and then it becomes vague as we were getting up into the upper third of the gland's operating range.

Figure 7 shows a brief interruption in ACTH stimulation - a downgoing pulse, 5 minutes wide. Zero time was the 60th minute of stimulation at this ACTH level. Here I was looking to see whether the rapid rise in ACTH back to its original level would trigger a big overshoot - but it didn't; cortisol secretion started to fall, then as the ACTH came

back up, it turned the corner and rose smoothly and rapidly back to its original level without overshoot. In figure 3, you will note that there was a 40 minute interval separating a stepwise drop and subsequent stepwise increase in ACTH concentration, and there we saw overshoot when the ACTH was re-elevated. Thus, we can note that after ACTH falls, it requires more than 5 minutes but less than 40 minutes to restore the conditions necessary for the overshoot.

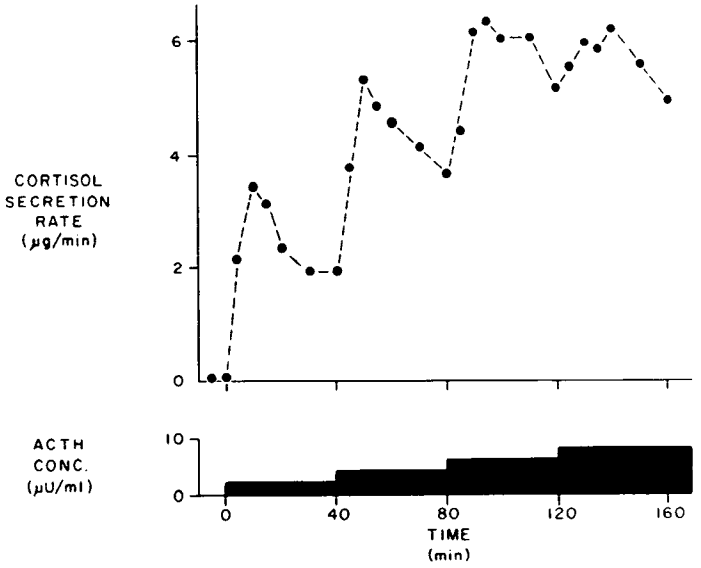


Fig. 6. Time course of cortisol secretion rate following stepwise changes in ACTH concentration. From (6).

Figure 8 shifts our attention to larger magnitude stepwise increases in ACTH concentration. In these two experiments ACTH concentrations was increased at zero time from 0 to 30 or 70 μU/ml; these increases ran cortisol secretion rate from minimum to near maximum levels. With these large increases in ACTH concentration, there was little or no overshoot; instead, cortisol secretion rate increases up to its steady state level and stays there. And it takes only about 10 minutes to reach that steady level.

Figure 9 compares the relative time courses of a declining cortisol secretion rate after small, and after large stepwise decreases in ACTH concentration. The ordinate scale for the low level decrease - from 2 μU/ml to 0 is on the right, and the dashed line shows the gland's response to that change: cortisol secretion fell exponentially with a half time of about 2-1/2 minutes. The ordinate scale for the large decrease from a

high level - from 30 μU/ml to 0 - is on the left. The solid line shows the response to that change. It follows a reverse sigmoid curve and takes about 25 minutes to get down to a steady level. The time course of the one decline is not predictable from the other.

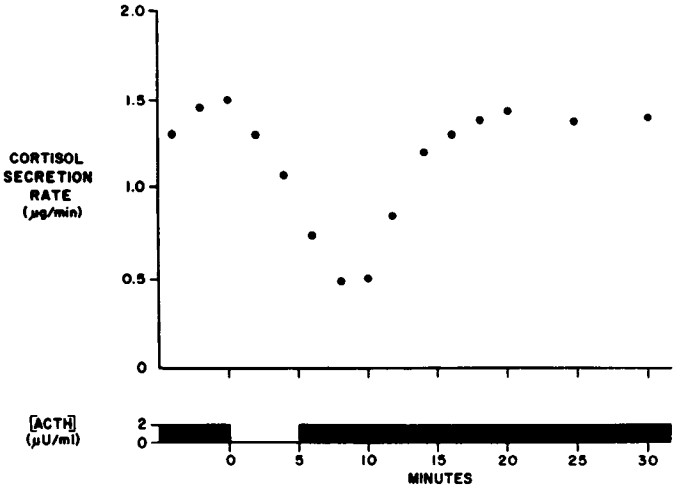


Fig.7. Time course of cortisol secretion rate following stepwise changes in ACTH concentration. Zero time corresponds to the 60th minute of stimulation at 2 μU ACTH/ml blood. From (6) and table 3 in (5).

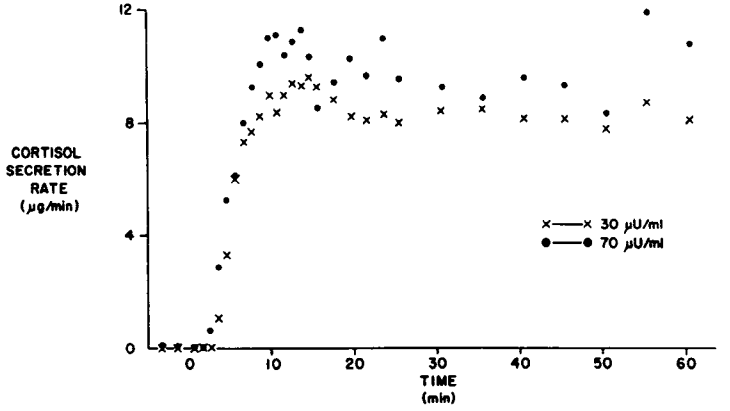


Fig.8. Time course of cortisol secretion rate in two experiments. At zero time ACTH concentration was increased stepwise from 0 to 30 (x) or to 70 (·) μU/ml and held at one of these concentrations throughout the remaining 60 minute measurement interval. From (5).

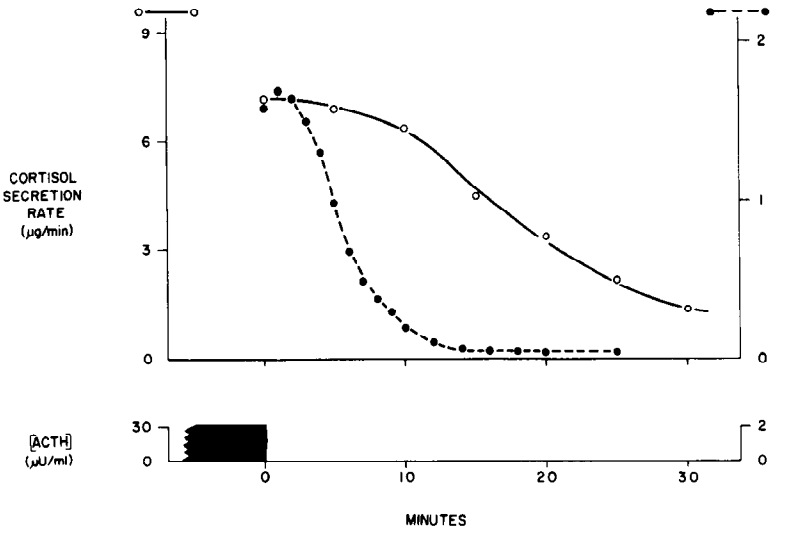


Fig.9. Time course in cortisol secretion rate following a stepwise reductions in ACTH concentration. Zero time corresponds to the 30th minute (30 µU/ml) or the 60th minute (2 µU/ml) of ACTH stimulation. The open symbols describe the time course of cortisol secretion rate after the drop from a nominal concentration of 30 µU/ml; the closed symbols, from 2 µU/ml. The 30 µU/ml concentration is termed nominal for the following reason. It required an infusion of ACTH at a rate of 0.21 mU/min at the 7 ml/min perfusion flow to produce an ACTH concentration of 30 µU/ml. However when ACTH is infused at that rate into a systemic vein the resulting concentration of ACTH in systemic blood is high enough so that cortisol secretion rate increases to 5-6 µg/min, i.e., an ACTH concentration of 5-10 µU/ml. When ACTH is infused at 0.21 mU/min into the adrenal perfusion line it may be that the adrenal binds or otherwise extracts some of the infused ACTH, but such measurements have not been made. The worst case would obtain if the adrenal neither bound nor extracted any of the infused ACTH; if that were so, the figure should show ACTH concentration at 35-40 µU/ml at zero time, falling stepwise at zero time to 5-10 µU/ml - the presumed systemic level. Thereafter, the ACTH concentration in both systemic and adrenal arterial blood would be expected to fall from 5-10 µU/ml to zero with a 6 minute time constant (11). Thus, the uncertainty about the time course of ACTH concentration complicates the interpretation of this experiment - i.e., the difference in the rate of decline in cortisol secretion rate from a high and from a low initial rate is overestimated by this experiment; however the difference is too large to be accounted for by even the worst-case differences in time course of ACTH concentration.

As you can see, the challenge is growing to tie all these responses to a single set of underlying mechanisms.

Thus far the test signals have all involved rapid changes in either direction--both small and large, with a lot of attention centered around the overshoot in the gland's response.

Now I want to turn to another kind of test signal - the sine wave. We did a number of studies at different frequencies with a ± 40% swing in either direction around a 2 μU/ml mean concentration. Figure 10 shows two cycles of data at a period of fifty minutes. Zero time corresponds to the 60th minute of sinusoidal stimulation at one cycle per 50 minutes. This was a big gland, with a secretory maximum of 16.9 μg/min, so the mean cortisol secretion rate is not out of line. The two ordinate scales are related on the assumption that mean cortisol secretion rate is linearly related to mean ACTH concentration. (Figure 2 supports the assumption of a linear relation of cortisol secretion rate to ACTH concentration within the ACTH concentration range of 1-8 μU/ml.) Cortisol secretion rate follows an approximately sinusoidal pattern, and lags only a small fraction of a cycle behind the ACTH signal.

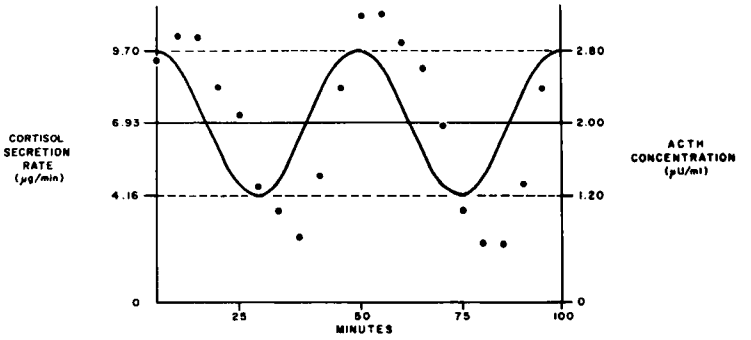


Fig.10. Time course of cortisol secretion rate (points) during sinusoidal variations in ACTH concentration (line) at 0.02 cycles per min. Zero time corresponds to the 60th minute of sinusoidal stimulation. The two ordinate scales are related on the assumption that the increment in cortisol secretion rate above the residual value, at ACTH = 0, is linearly related to ACTH concentration in the range from 0 to at least 3 μU ACTH/ml. The mean increment of the 20 cortisol secretion rates, above the residual secretion rate of 0.14 μg/min, was 6.93 μg/min, giving an expected incremental gain for this gland of 3.47 μg/min/μU/ml. The dashed lines show the upper and lower bounds of cortisol secretion rate expected in the steady state, but the observed values ran respectively higher and lower, indicating a small degree of resonance at this frequency. The maximum cortisol secretion rate by this gland was 16.9 μg/min.

Figure 11 shows 3 cycles at a twenty minute period. Again, zero time is the 60th minute of sinusoidal stimulation; despite that, the first cycle of data is rather erratic, but the last two are reasonably well behaved. In them, cortisol secretion rate lags about 90^{0} - a quarter cycle - behind the ACTH signal. The amplitude of the last two waves are in keeping with the expected steady state relation.

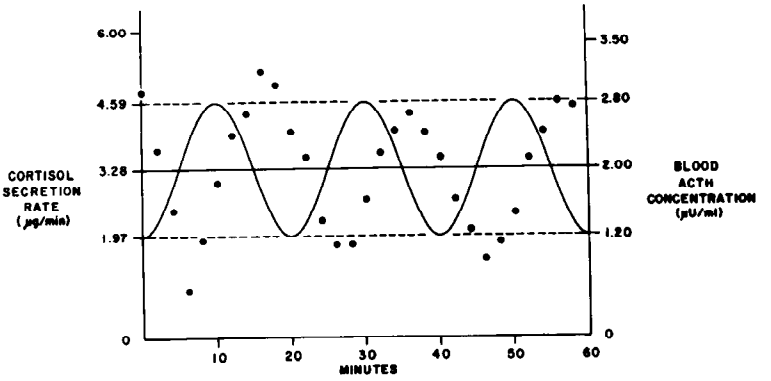


Fig.11. Time course of cortisol secretion rate (points) during sinusoidal variations in ACTH concentration (line) at 0.05 cycles per minute. Zero time corresponds to the 60th minute of sinusoidal stimulation. The two ordinate scales are related as discussed for figure 10. The residual secretion rate at ACTH = 0 was 0.06 µg/min. The maximum secretion rate by this gland was 10.9 µg/min. The data in this figure and in figure 12 are from the same gland.

Figure 12 shows 3 cycles at a ten minute period. It is a surprising result because the usual relation between ACTH and cortisol secretion rate is inverted at this frequency. There is a half cycle of lag, so that cortisol secretion falls as ACTH is rising and vice versa.

Figure 13 - and the last of this snowstorm of dynamic anecdotes - shows data at one cycle per five minutes. Here the gland is unable to follow a signal of such high frequency. One cycle per five minutes is high, of course, only in relation to adrenal dynamics. Don't try to sing it. Cortisol secretion rate merely hovers about a steady mean for the 15 minute test interval.

We emerge from this set of studies with the information that the gland's sinusoidal response begins to break up as frequency increases into the vicinity of one cycle per ten minutes. You can see, I think, that the information yield per cortisol measurement is a good deal lower in these frequency response tests than in the step tests. Nevertheless, we gained some useful information, plus the satisfaction of seeing the high degree of reliability in the coupling between ACTH concentration and cortisol secretion.

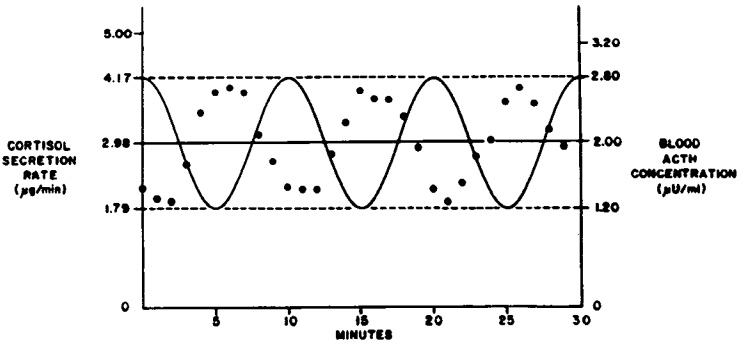


Fig.12. Time course of cortisol secretion rate (points) during sinusoidal variations in ACTH concentration (line) at 0.10 cycles per minute. Zero time corresponds to the 60th minute of sinusoidal stimulation. The two ordinate scales are related as discussed for figure 10. The data in this figure and in figure 11 are from the same gland.

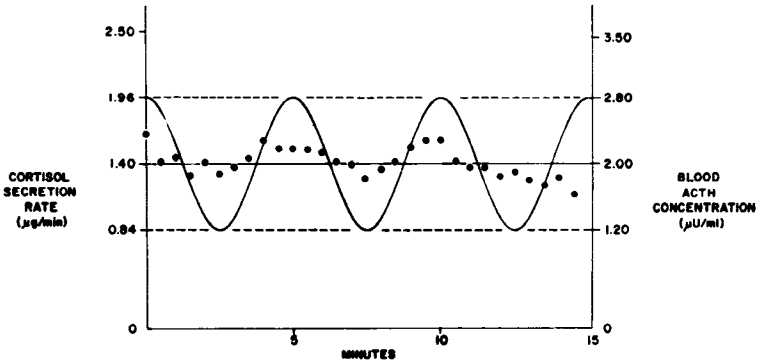


Fig.13. Time course of cortisol secretion rate (points) during sinusoidal variations in ACTH concentration (line) at 0.2 cycles per minute. Zero time corresponds to the 60th minute of sinusoidal stimulation. The two ordinate scales are related as discussed for figure 10. The residual secretion rate at ACTH = 0 was 0.29 μg/min. The secretory maximum of this gland was 11.8 μg/min.

What is that coupling? It is some set of biochemical mechanisms by which a polypeptide hormone flowing in at the arterial side of the gland makes steroid hormones appear on the venous side. You might think of it as the Rube Goldberg device inside the gland. That's only a half crazy way of looking at it, because there is a fundamental lesson in modelling to be learned from a Rube Goldberg device. The lesson is that the dynamics of a complex and non-linear chain of causality emerge from the equations of change for each step or link in the chain. And for practical purposes, the dynamics emerge from the equations of change just of the relatively slow or rate limiting steps. It was my engineering colleague in this work, C. C. Li, who saw how to apply this same point of view to the adrenal and thus opened up a very useful approach to modelling the dynamics of ACTH action.

I want to turn now to consider the modelling of ACTH action. Figure 14 shows one of the current views about how ACTH might act. Direct your attention first to the biosynthetic pathway, proceeding from cholesterol to cortisol. We shall talk about the big arrows later. In the unstimulated gland, cholesterol is present in abundance (12), but only small quantities of the other compounds are present within adrenocortical tissue (13). Cortisol is present in only small quantities also, but when the gland is stimulated by ACTH the quantity of cortisol rises (13). At any one time in the gland - whether it is stimulated or not - there is only enough cortisol to account for less than one minute of secretion (13). It means that the dynamics of cortisol secretion must therefore be the dynamics of cortisol synthesis and the dynamics of the linkage of ACTH to these steps.

We ought to look, then, to what, in a loose sense, we could call the equations of change of this pathway. Those equations arise from the principle of the conservation of mass. For example, the rate of change of the quantity of 11-deoxycortisol is equal to the rate at which it is produced from its precursor, 17 α-hydroxyprogesterone, minus the rate at which it is converted to its product, cortisol. This is called a conservation equation, and the rates of gain and of loss are governed by the kinetics of these enzymatic reactions, which are believed to be unidirectional. So a set of conservation equations, in this view, becomes the central core of the model.

Neither ACTH, nor cyclic 3', 5' AMP, which appears to mediate ACTH action, is a steroid precursor. That is a trivially obvious biochemical point but it is an important functional point because it means that the action of ACTH is expressed by changes in the rate parameters of one or more of the conservation equations.

Therein lies the basis for translating a conventionally stated hypothesis about the mechanism of action of ACTH into the terms of a dynamic model. The hypothesis shown by the heavy arrows in figure 14 will illustrate that translation.

This scheme is a hypothesis put forth by Koritz and Hall several years ago (14). They showed in vitro that pregnenolone could inhibit cholesterol hydroxylation. They also pointed out that pregnenolone is

formed from cholesterol within mitochondria and that pregnenolone must pass out of the mitochondrion before it can be converted to either of the next compounds in the pathway. So they suggested that perhaps ACTH, or some mediator, might act on the mitochondrial membrane to permit pregnenolone to pass out of the mitochondrion, thus lowering intramitochondrial levels of pregnenolone, relieving the inhibition on cholesterol hydroxylation, and allowing steroidogenesis to proceed at increased rates. It has a Rube Goldberg ring to it - and maybe even an element of humor - except to those who are intimately involved in working out the chain of causality that links ACTH to cortisol secretion. If we translate this idea of Koritz and Hall's into dynamic terms, does it serve to account for the dynamics of ACTH action on cortisol secretion?

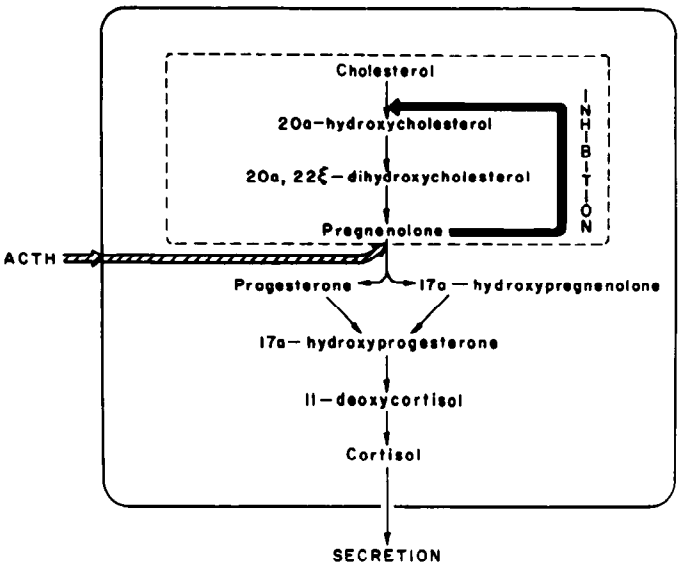
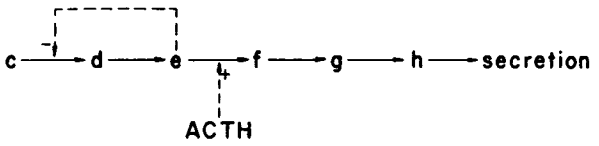


Fig.14. A schematic version of one hypothesis for the regulation of steroidogenesis by ACTH (14). The dashed line corresponds to the mitochondrial membrane. For simplicity, the intramitochondrial localization of the 11-deoxycortisol → cortisol step is not shown; correspondingly, that fact is not considered in the original hypothesis whose dynamic modelling is under discussion here.

The answer is yes (15). What does that affirmative answer mean? It means several things. First, it means that we were able to make up in our heads a group of kinetic parameters for a set of conservation equations (fig. 15; N. B. I did not show the equations in the lecture because, unless one is willing to discourse at some length about equations, there is nothing to be gained by merely flashing them on a screen.), such that the equation set could simulate the dynamic responses we had observed experimentally. So we have fulfilled the goal of simulation.

Second, the resulting set of equations is consistent with the verbal statement of the Koritz-Hall hypothesis. That, in turn, means that the Koritz-Hall hypothesis, together with a large number of assumptions about the enzymatic rate parameters, gives sufficient accounting for the dynamics of ACTH action on cortisol secretion. That does not prove the validity of the hypothesis, because other hypotheses, together with different assumptions about the rate parameters, will also simulate (cf. 16). But it is not completely trivial to have achieved the simulation from the Koritz-Hall hypothesis, because there are some hypotheses which cannot account for the gland's dynamics no matter what physically realistic assumptions one makes about the parameters.



$$\dot{a} = 0.5(I) - 0.59(a)$$
$$\dot{b} = 0.08(e) - (b)$$
$$\dot{d} = \phi(b) - 0.79(d)$$
$$\dot{e} = 0.79(d) - 0.0049(e) - 0.017(a)(e)$$
$$\dot{f} = 0.0049(e) + 0.017(a)(e) - \frac{8.6(f)}{6.5 + (f)}$$
$$\dot{g} = \frac{8.6(f)}{6.5 + (f)} - g$$
$$\dot{h} = g - h$$
$$h = \text{cortisol secretion rate in } \mu g/min$$
$$\phi(b) = 8.59\ \epsilon^{-0.3b}$$
$$I = \text{ACTH concentration in } \mu U/ml$$

Fig. 15. (upper) An even more schematic version of the hypothesis shown in figure 14. (lower) The equations of the model. The variables d through h are linked together in the equation structure in precursor-product relations just as in the schematic pathway shown above. The variable, 'b', mediates the inhibitory action of 'e' on the c→d rate parameter. The variable 'a', mediates the action of 'ACTH' (I, in the equations) on the e→f rate parameter, which is taken as a lumped enzyme rate parameter and membrane diffusivity parameter. For further discussion see reference 15.

I think it is fair to state that one of the criteria for accepting a hypothesis about the mechanism of ACTH action on steroidogenesis is the demonstration that the hypothesis provides a basis for simulating the dynamics of ACTH action, a basis which must be both physically realistic and compatible with available information. The assumptions that have to be made in order to achieve the simulation logically become the assumptions of the hypothesis, and so tests of the assumptions become tests of the hypothesis. Aside from the simulation, that is the scientific

value of the frankly speculative modelling.

Figure 16 shows the simulation provided by the Koritz-Hall hypothesis. The smooth line is the model's behavior. The dashed lines are ± one standard error around the mean of seven adrenal responses to a stepwise increase in ACTH concentration. The model's response to a stepwise decrease in its input decays with the same half-time seen in the experimental data. Figure 17 shows the model's response to a large stepwise increase in input corresponding to 30 μU ACTH/ml. The points are a set of experimental observations. The two ordinate scales, which differ slightly, were adjusted so that the two curves would superimpose, but the scaling difference is within the range of the gland to gland variation.

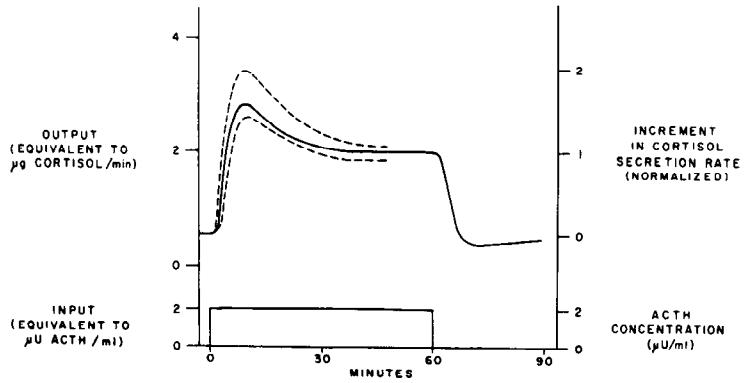


Fig.16. Simulation provided by the equation set shown in figure 15. The solid line in the upper portion of the figure is the model's output; the dashed lines are ± 1 standard error about the average of data on the responses of seven adrenal glands to a stepwise increase in ACTH concentration from 0 to 2 μU/ml. The original data are in table 2 of reference 5. Before computing the average, each set of data was normalized to the mean of the increment in cortisol secretion rate, above the residual value, at 50, 55 and 60 minutes after the stepwise increase in ACTH concentration. Then the set of seven normalized increments in cortisol secretion rate were averaged, and the standard error of the mean at each point in time was computed. The dashed lines represent smooth curves connecting respectively, all the upper and all the lower limits of those standard errors. From (15).

So we end up with a dynamic model which simulates the action of ACTH on cortisol secretion by the intact gland. The model may or may not be faithful to the underlying mechanisms of action of ACTH. Regardless of the ultimate validity of the mechanistic detail in the model, we can simulate the glucocorticoid secretory function of the adrenal.

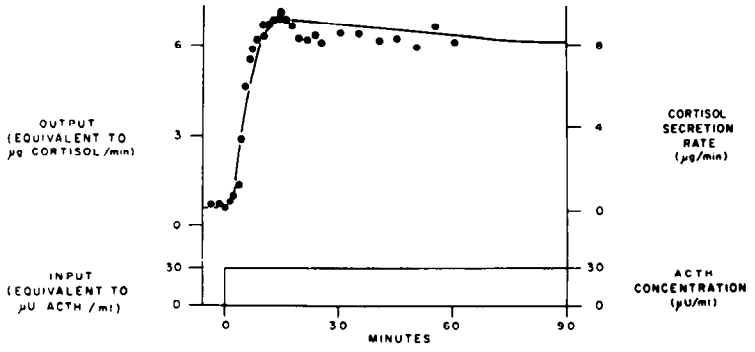


Fig.17. Comparison of the simulation provided by the model (smooth curve) and a set of experimental observations (points) after a stepwise increase in input or ACTH concentration of 30 μU/ml. The two ordinate scales are adjusted to align the initial and final values of the two variables. The experimental data are the same as those in figure 8. From (15).

Now there is a modelling problem at a higher level of organization. The adrenal cortex is only one gland in a neuroendocrine control system whose function is a topic of much interest. The adrenal model is an essential piece of the modelling of that system of hypothalamus, pituitary, adrenal, liver, and so forth. Eugene Yates has pioneered in endocrinology in assuming the responsibility of first putting together (17) and then continuing to update (18, 19) the modelling of a major neuroendocrine system. A good part of the rationale for the work I have discussed is to be found in his modelling. That is not our only point of contact, however, for Gene Yates initiated me into physiological research and continues to show me what science is about.

Now at this point, I would like to make a few comments about the communications aspects of the action of ACTH on cortisol secretion. It draws our attention to the statistical uncertainty in the relation between ACTH concentration and cortisol secretion. You see that uncertainty in figure 18, where ACTH was being held steady at 2 μU/ml. The mean secretion rate is 4.23 μg/min and, on the assumption of Gaussian variation, you see the calculated standard deviation, which is a little over 10% of that mean. The standard deviation includes uncertainty from two sources - one is the cortisol measurement and the other is the gland itself. Now the statistics of the cortisol measurement are such that it has a coefficient of variation of 1.8% of the mean, a low value which reflects the skill of Amy Maxwell who did all of the cortisol measurements. In this run of data, the estimated measurement error, expressed as a standard deviation, is 0.08 μg/min. The residual error

of 0.37 µg/min is thus an approximation of the uncertainty in the gland's secretory function. The dashed lines show ± 2 standard deviations, in other words, a 95% confidence interval. The width of that 95% confidence interval is about 1.5 ug/min, which is an appreciable fraction of the possible range of cortisol secretion rate, between minimum and maximum.

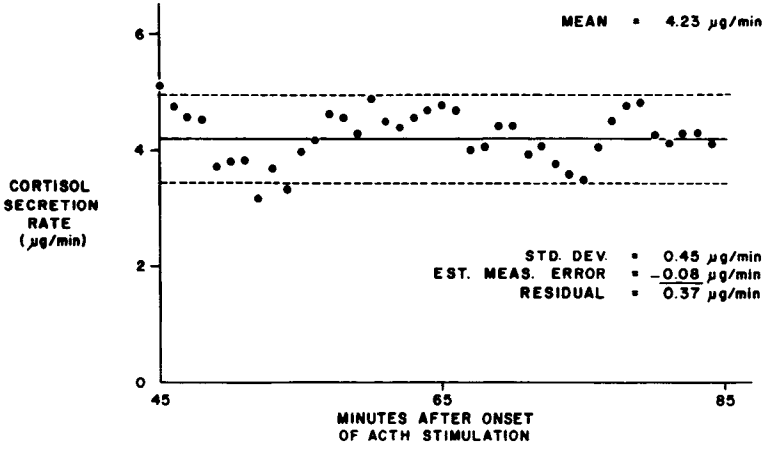


Fig.18. Time course of cortisol secretion rate from the 45th and 85th minute of stimulation of the gland at a constant ACTH concentration of 2 µU/ml. The computations are described in the text. The dashed lines show plus and minus 2 times 0.37 µg/min about the mean value of 4.23 µg/min. The estimated measurement error is 1.8% of the mean (see text).

If you were an observer, sitting in the adrenal vein, trying to read the strength of the ACTH signal from instantaneous cortisol secretion rate, you could obviously make only a relatively coarse distinction, but how coarse? Figure 19 shows a measure of that coarseness. Here we have set ACTH concentration to run cortisol secretion at four different levels across its range, 1, 2, 4, and 200 µU/ml, and have measured the statistical fluctuations, in steady state cortisol secretion rate, in the same manner as in the previous figure. The heavy solid lines are mean rates of secretion and the shaded areas are the 95% confidence intervals. These measurements provide an initial basis for a communications view of the adrenal response to ACTH. There is room for about 8 of these 95% confidence intervals between the secretory minimum and maximum. We can summarize the communicational view of the gland by saying that there are statistical uncertainties in the secretory response to ACTH, and that these uncertainties effectively map a continuous scale of ACTH concentration into about 8 statistically defined ranges of cortisol secretion. With that amount of uncertainty, it is unrealistic to make any finer distinction in the instantaneous rate of cortisol secretion than one of eight possible values. If you view the gland as a signal

converter, you can say that it converts with an accuracy of about 3 bits. That is a jarringly technological way to talk about a gland, but it serves to remind us that blood-borne signals are received and interpreted with neither absolute certainty nor absolute uncertainty, but something in between.

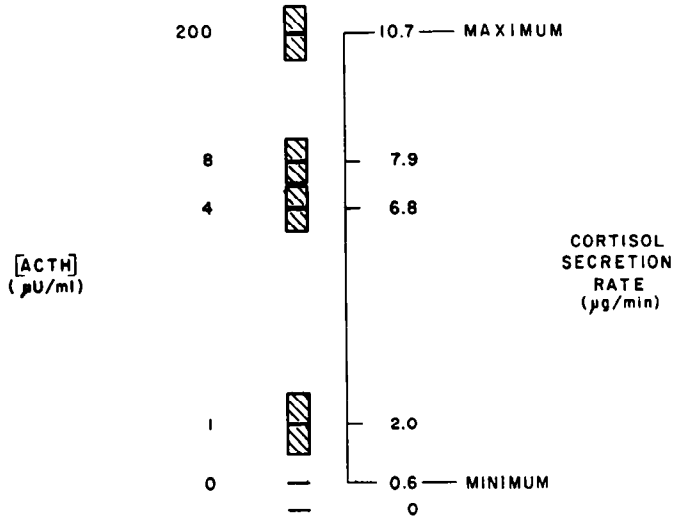


Fig.19. Relation of the statistical uncertainty in the steady state rate of cortisol secretion to ACTH concentration. The heavy horizontal lines, and the corresponding number on the scale of cortisol secretion rate are the mean of seven cortisol secretion rate measurements made every 4 minutes after the 45th minute of constant ACTH stimulation at the concentration shown to the left. The cross-hatched areas show plus and minus two times the residual standard deviation computed as shown in figure 18. From (7).

I would like to turn your attention now to a different problem involving blood-borne signals - namely, control of the hepatic production of glucose.

Suppose we look at it as shown in figure 20. The analogy with the adrenal cortex is clear, but it is complicated by virtue of more than one major blood-borne signal being involved in the control of glucose production.

Let us begin with the following question, which is a logical starting place: what effect does glucose itself have on hepatic glucose production? It is classical teaching (cf. 20) that the liver produces glucose when the blood glucose concentration is low and that, as glucose concentration rises, hepatic production falls, finally to zero, and then production be-

comes, in a sense, negative as the liver takes up glucose, storing it as glycogen. The inference is usually drawn that glucose has a direct inhibitory effect on the hepatic production of glucose, although there are other blood-borne signals, such as glucagon and cortisol, that are known to influence hepatic glucose production as well.

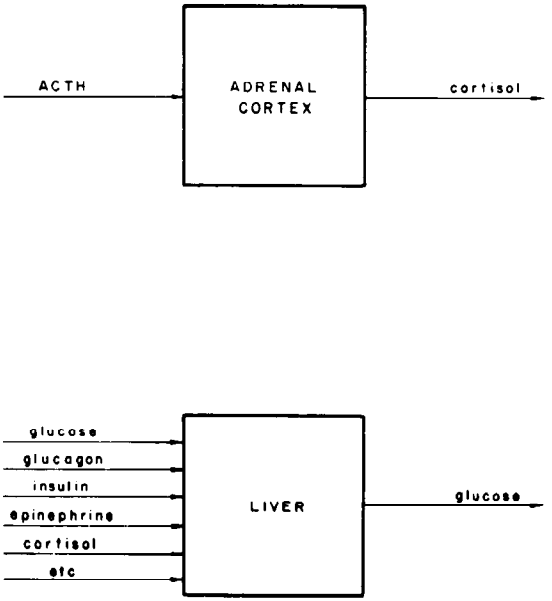


Fig.20. Black-box views of the adrenocortical secretion of cortisol and the hepatic production of glucose.

To study the actions of blood-borne signals on the liver poses a major technical problem because the liver is so big. For example, if you contrive to double glucose concentration in portal venous blood, you very rapidly have large glucose changes in systemic blood, and then you can no longer distinguish direct effects of the glucose on the liver from indirect, systemically mediated, effects on the liver. In loading the liver with glucose, you cannot escape loading the whole animal. On the other hand, if you excise the liver and perfuse it extracorporeally, it does not do to have a recirculating perfusate if the goal is to work out the dynamic relations between the various blood-borne signals shown in figure 20 and hepatic glucose production. The reason for that statement is that in such experiments one has control over the blood-borne signals only at the instant the perfusion begins. Thereafter, the liver removes some things and adds others to the recirculating blood - all in a fundamentally uncontrolled way. That would seem to leave us

with only one alternative and that is a one-pass perfusion - but to do that with arterial blood and to stay within the same animal species is prohibitively expensive. It requires about a dozen animals' blood volumes for every hour of perfusion.

Ernst Knobil aroused my interest in the general area of metabolism but in particular the liver's role in glucose homeostasis. We were once on opposite sides of the lectern when I was a medical student. For some years we have been on the same side of the lectern but I continue to learn from him. This problem of studying the hepatic production of glucose seemed unapproachable until a compromise solution dawned on me. That compromise was to connect the liver of a very small animal to the circulation of a much larger animal. The reductio ad absurdum is a mouse liver perfused by an elephant, but it illustrates the logic of the experimental design. No possible rate of glucose production or uptake by the mouse liver would perturb the elephant's glucose homeostasis, and it would require negligible quantities of hormone added locally to the mouse liver's blood supply for testing over physiological ranges of hormone concentration.

Instead of mice and elephants, we used small dogs and large dogs, with an 8 or 10 to 1 size ratio. The dog is one species in which there is a very large size range among adults. A great advantage of the dog is the absence of major blood groups, so that blood can be exchanged acutely with very infrequent immune reactions (21).

Figure 21 shows the preparation schematically. An arterial line connects directly to the hepatic artery; the portal vein receives arterial blood also, but the pressure is reduced. These vascular connections are made, one at a time, while the liver is in situ, so that the organ is never deprived of blood flow. A peristaltic pump returns hepatic venous blood to a systemic vein in the big dog. The liver is excised and floated in freshly drawn canine ascites. That makes the liver almost weightless so that its own mass does not interfere with the low pressure portal flow in dependent portions of the organ. Most of the livers have come from weaned pups but we used very small adults whenever they are available. Charles Pearson did the surgery in all but the first few experiments. In our adrenal work, he did all the hypophysectomies and then assisted me with the adrenal isolation; now I assist him with the livers. He also drew all these figures.

We can control the local addition of test substances to the hepatic blood, but we have no control over the composition of arterial blood coming to the small liver from the big dog. Therefore, the stability of the big animal is critical. All the dogs were fasted overnight. In many of the experiments the donor was conscious, with indwelling arterial and venous catheters placed some days before, under general anesthesia. Then for four days previous to the experiment, the big dog was treated with reserpine (2.5 mg per day given intramuscularly) in the attempt to minimize catecholamine transients during the experiment. In addition, reserpine provided sedation. However, in the experiments described here, we anesthetized the big dog with dial-urethane, because of its long action and constancy of depth during the four to six hour duration of the experiments, and placed the arterial and venous catheters acutely. The dogs were heparinized.

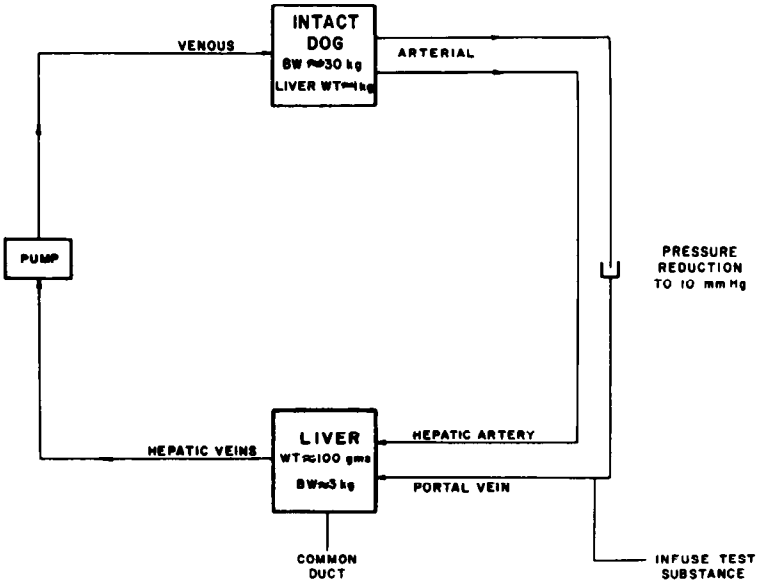


Fig.21. Experimental scheme for liver perfusion. Hepatic venous blood was collected via a catheter in a segment of inferior vena cava excised along with the perfused liver. The tip of that catheter was positioned far enough below the perfused liver so that the vena caval segment hovered on the point of collapse. Hepatic venous blood fell into an open cylinder from which the pump returned the blood to the intact dog. The pump was under servo control to hold constant the level of blood in the cylinder. The intact dog was positioned on a level higher than the perfused liver to overcome the resistive pressure drop in the hepatic arterial catheter, so that hepatic arterial pressure was approximately equal to the intact dog's arterial pressure. A catheter in the common duct permitted the collection of bile, which flowed, in technically satisfactory experiments, at the rate of 0.5 - 2.0 cc/hour. The lymphatic drainage of the liver was not cannulated but was occluded by the various ligatures placed during excision of the liver. Probably as a consequence, the soft tissues of the porta hepatis were always edematous at the end of the perfusion; the liver parenchyma was not swollen in technically satisfactory experiments, but was of normal consistency and of uniform, though somewhat more bright red color than normal probably because of its perfusion with fully oxygenated blood through the portal system. The ascites in which the livers were floated was freshly drawn from a dog with a thoracic inferior vena caval constriction (22).

It has taken a good deal of experience to achieve technically satisfactory perfusions. Figure 22 shows the gradual improvement in hepatic blood flows from pathologically low levels up to the physiological range of 0.8 to 1.2 cc/gm/min. The two arrows show points at which we made major technical improvements. The time off for teaching set us back, but only temporarily.

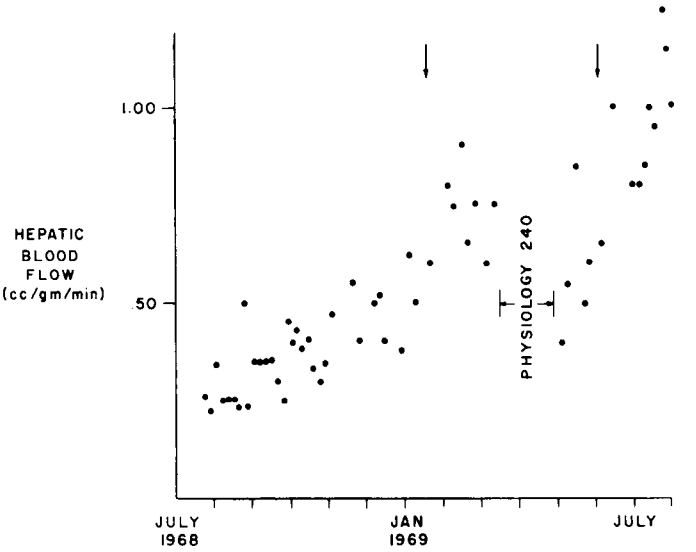


Fig.22. Influence of time (and experience) on the blood flow through the perfused livers. Hepatic blood flow was measured from timed collections of the venous effluent from the liver in a graduated cylinder.

Figure 23 defines the experimental question. In this experiment, we have the liver being perfused by an overnight fasted large dog under dial-urethane anesthesia. The liver came from a very small adult, which had also been fasted overnight. Glucose production is a little over 10 mg/min at a time when the plasma glucose concentration was 125 mg% and immunoreactive insulin concentration in plasma was 1-2 mμg/ml. At the point indicated by the up arrow, we began to infuse glucose intravenously into the big dog. Glucose production by the perfused liver fell precipitously and then hovered around the zero point. At the down arrow, the glucose infusion was turned off; glucose production increased somewhat after the infusion ended, as glucose concentration fell. Insulin concentration rose during the glucose infusion, as expected; its rise lags somewhat behind the change in hepatic glucose production. This experiment repeats the classical findings of Soskin and Levine (20). Clearly, one or more blood-borne signals emanating from the big dog brought about this rapid drop in glucose production.

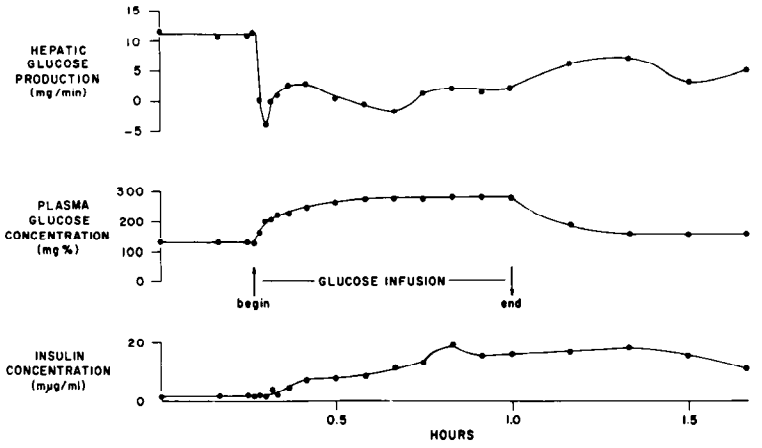


Fig.23. Time course of hepatic glucose production by a perfused liver and glucose and insulin concentrations in the blood of the intact dog. Glucose was infused intravenously into the intact dog at 10 mg/Kg body weight/min. Glucose production in this and all subsequent figures is the result of the calculation of a glucose balance across the liver, and is equal to the rate at which glucose appears in hepatic venous blood (the product of hepatic venous blood flow and hepatic venous blood glucose concentration) minus the rate at which glucose is presented to the liver in hepatic arterial and portal venous blood (the product of hepatic venous blood flow and the systemic arterial blood glucose concentration in the intact dog). Glucose was measured by the glucose oxidase method in this experiment, but by an automated version of the ferricyanide method in the experiments shown in subsequent figures.

This result raises the obvious question: what is the direct effect of glucose on the hepatic production of glucose? The next figure (fig. 24) shows data from three experiments in which glucose was infused locally into the portal vein of the perfused liver. The time course of the locally induced change in glucose concentration was made to match the time course of the systemic glucose concentration change in figure 23. Glucose reduced the production of glucose to below zero, that is, each liver halted net production of glucose and began taking up glucose. Presumably it was stored as glycogen, but we have not yet documented that point, for we lack a satisfactory way to biopsy the liver without starting up an uncontrollable blood leak. A blood leak throws uncertainty into the balance calculation because we cannot know the proportion of pre- and post sinusoidal blood in the leak.

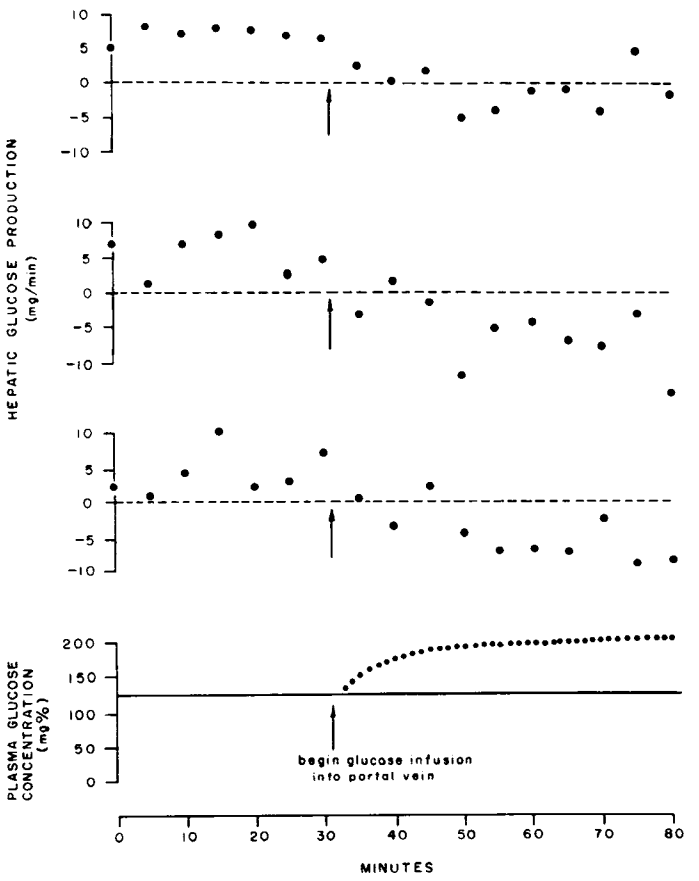


Fig.24. Time course of hepatic glucose production by three different perfused livers in response to an increase in glucose concentration in hepatic blood. From above downwards, the systemic plasma glucose concentrations before the addition of glucose into the portal venous supply were, respectively, 134, 108 and 122 mg%. In each experiment the rate of glucose infusion was under computer control, to increment the glucose concentration in the plasma of hepatic blood (dotted line) according to the time function $80(1-e^{-t/12}$ min) mg%, the final infusion rates being 43 mg/min. Note that glucose penetrates canine red cells very slowly (24) so that the glucose infusion is calculated on the basis of hepatic plasma flow. During the time 50-80 min the concentrations of glucose in systemic plasma (solid line) changed by + 13, + 2, and -4 mg%, respectively in the three experiments from above downwards. The graphical plot of plasma glucose concentration represents the mean of the three experiments, the solid line being the systemic value and the dashed line being the hepatic value. The concentrations of immunoreactive insulin in systemic plasma were 6 mμg/ml in each of the three experiments prior to the glucose infusion, and increased by less than 1 mμg/ml during the glucose infusion.

The results shown in figure 24 are confirmatory of a long suspected, but much debated effect. (See reference 23 for a convincing demonstration of this effect in the perfused rat liver, plus a survey of the history of this problem.) But beyond confirming the point, the data in figure 24 enable us to reckon the strength of this direct effect of glucose on hepatic glucose production. The local rise in hepatic blood glucose concentration effected a mean drop in glucose production of 11.1 mg/min (from a mean of +5.7 mg/min during 0 -30 minutes to a mean of -5.4 mg/min during 50-80 min, when the concentration was nearly steady. One measure of the strength of this autoregulatory response can be had by relating the 11.1 mg/min drop in net glucose production to the 43 mg/min mean rate at which glucose was being added to portal venous blood from 50-80 min: the autoregulatory response is 26% of the imposed glucose load. Another way of looking at this autoregulatory response is to estimate the plasma glucose concentration at which glucose production is reduced to zero. If the inverse relation between plasma glucose concentration and hepatic glucose production is linear, within the 100-200 mg% range, the concentration that just halts net production would be approximately 160 mg%, and the slope of the assumedly linear relation would be - 0.14 mg/min/mg% increase in plasma glucose concentration. These two parameters are useful figures to know in interpreting responses of the intact animal but they are certain to be influenced - perhaps nonlinearly - by at least some of the blood-borne signals shown in the lower half of figure 20.

An important question which I unfortunately cannot answer with certainty at present is whether the liver's response to glucose infusion into the big dog, as in figure 23, exceeds the response predictable alone from the glucose effect, shown in figure 24. It will take further experimentation to settle that point with certainty. (In the lecture, I erroneously reported that there was a large difference, because due to a now corrected technical error, I had underestimated the strength of the direct effect of glucose on the liver.)

One major difference between this perfused liver preparation and the in situ liver is that here arterial blood is supplied to the portal vein. In particular the contribution of the pancreas is minimized, since the concentrations of both glucagon and insulin are bound to be lower in systemic than in portal venous blood. It is therefore of interest to see how the pancreas might influence the hepatic production of glucose. One approach would be to draw portal venous blood from the big dog to supply the perfused liver, but rather than inflict the necessary surgery on the big dog, whose metabolic stability is such a critical matter in this experimental design, we elected instead to introduce a pancreas from a second small dog in series with the liver. The perfusion scheme is shown in figure 25. My student, Richard Bergman, has worked out an elegant approach to perfusing the pancreas, and he reported some of the dynamics of its insulin secretory responses at this meeting (25). It is his preparation that we used here. The second portion of the duodenum is included in the preparation, since its separation from the head of the pancreas jeopardizes important blood supply to the gland.

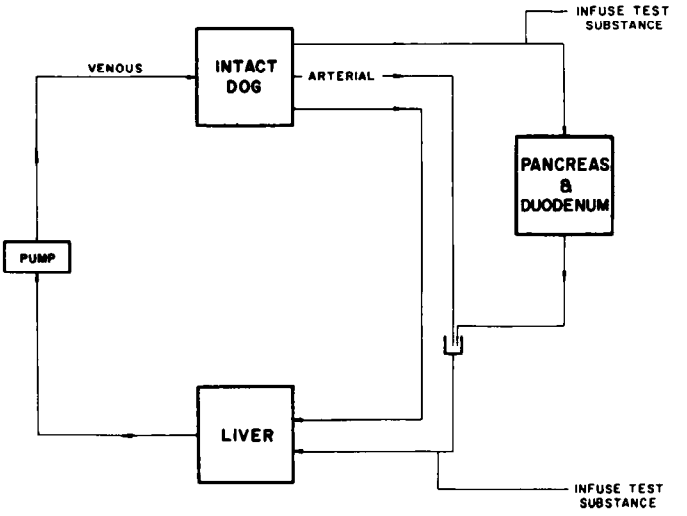


Fig.25. Experimental scheme for combined liver and pancreas/duodenum perfusion. The liver and the pancreas/duodenum come from different dogs. The venous effluent from the pancreas/duodenum may be added to the portal venous blood, as shown, or returned directly to the intact dog. The technique for perfusing the pancreas and duodenum is that of Bergman (25). Briefly, arterial blood is conveyed to the pancreas and duodenum via a catheter in the coeliac artery, all of whose branches save the splenic and the pancreatico-duodenal have been ligated. The splenic is ligated distal to the last pancreatic branch. Pancreatic venous effluent is collected via a catheter in the portal vein, all of whose extra-pancreatic tributaries are ligated. After these catheters have been placed, the pancreas, together with the portion of the duodenum which abuts the head of the pancreas, are excised and placed in a container filled with canine ascites. The container is placed on a vertical level higher than the portal venous supply of the perfused liver, so that pancreatic venous pressure is near atmospheric.

Figure 26 shows the influence of the pancreas on hepatic glucose production. First, we simply watched glucose production for a little over an hour. Then, when we switched the pancreatic venous drainage into the liver's blood supply, there was a rapid rise in glucose production. At the two hour mark, we increased the glucose concentration in the arterial supply of the pancreas. Thereupon, glucose production fell, but only to the original level of production, not to zero or below. It will be of great interest to learn how much larger a drop in glucose production occurs when both the pancreas and the liver see a rise in glucose concentration, than when only the liver or only the pancreas sees the rise. But that is an experiment yet to be done.

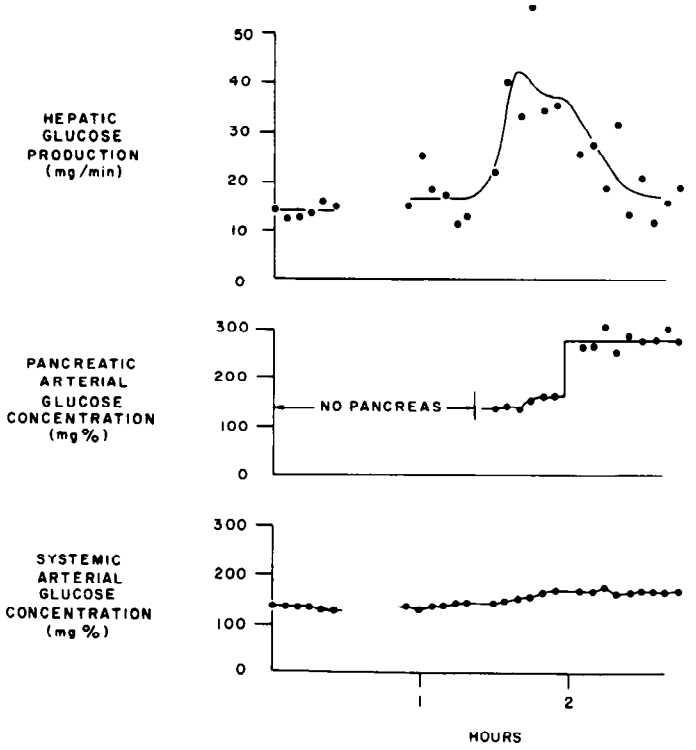


Fig.26. Some effects of the pancreas/duodenum preparation on hepatic glucose production. During the interval marked "No pancreas", the venous drainage from the pancreas/duodenum was returned directly to the intact dog. Thereafter the venous drainage was added to the perfused liver's portal supply. At 2 hours, we began the infusion of glucose into the arterial supply of the pancreas/duodenum preparation to produce the increase in pancreatic arterial glucose concentration as shown in the middle panel. Dial-urethane anesthesia.

Our working hypothesis is that the pancreatic secretion of glucagon is responsible for the large increase in glucose production when the pancreatic venous blood flows through the liver, as shown in figure 26, and that the drop in glucose production to control levels during pancreatic arterial hyperglycemia reflects a virtual cessation in glucagon secretion. The role of insulin is yet to be determined in this preparation. The liver's response to exogenous glucagon can be seen in figure 27. There is no pancreas in the perfusion, only a liver. Here we were probing across a four order of magnitude range to find the increments in glucagon concentration which are necessary to increase glucose production across the range seen in figure 26. From the data in figure 27,

you see first a small and then a large rise in glucose production at increments of 10^{-2} then 10^{-1} mμg/ml. These livers have only about 500 mg of glycogen after the overnight fast so it is unlikely that after the period of surgery and then the hour of documented glucose production shown here (figure 27), that much of the increased production can be glycogen breakdown. But we have not measured that directly, for the reasons I mentioned earlier. Shortly after the second hour, we switched glucagon off and glucose production fell quickly to its original value. Then we started a glucose infusion into the big dog. Then glucose production fell to zero and glucose uptake began. Between the third and fourth hour we were beginning to test the liver's response to glucagon but were hampered by a non-steady state, and then I made a stupid mistake that let a lot of air bubbles get into the perfusion line and we had to quit.

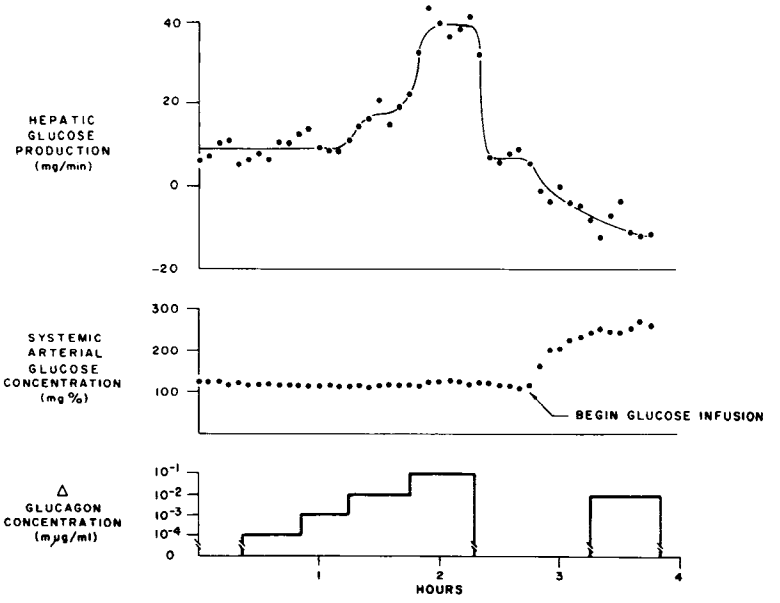


Fig.27. Influence of glucagon on hepatic glucose production. The increments in glucagon concentration were calculated by dividing the rate of glucagon infusion (into the portal supply) by total hepatic blood flow. At the time indicated by the arrow, a glucose infusion was begun into a systemic vein of the intact dog at a rate of 10 mg/Kg/min. Dial-urethane anesthesia.

We are obviously in the early stages of this work, and I have been more concerned with developing satisfactory technique and with gaining some feel for the time dependencies of glucose production than with testing specific hypotheses. Whatever the blood-borne signals are that inhibit glucose production and promote glucose uptake, and vice versa, we ought to be able to reproduce the responses of the liver in the intact animal by appropriate local changes in hepatic blood. We shall have achieved quantitative accounting when we can match local concentration changes with systemic concentration changes and produce identical hepatic responses. After we reach that point, we can go on to do dynamic testing as we did with ACTH and the adrenal. The interacting effects of the several blood-borne signals (figure 20) will be of great interest. But despite that inherent complexity, we ought to insist on one of the outcomes being a well-documented simulation that can make hard-number predictions. If achieved, it will be a crucial part of any model of metabolic regulation. And maybe, as in the adrenal work, there will also develop some new challenges to the biochemists, to use A. V. Hill's phrase (26).

Hill's scientific memoirs (27) drew my attention to three of St. Paul's admonitions to the Thessalonians (I, v, 21) which serve well here as a conclusion (see also Preface to ref. 2).

"Despise not prophesying-"

For prophesying, read modelling.

"Prove all things-"

No one will quibble with that, but we ought to note that what we set out to prove is very closely related to the prophesies or predictions that follow from current theory or modelling.

"Hold fast that which is true."

That needs no comment from me.

Acknowledgements

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CYBERNETICS CONGRESS

The Sixth International Cybernetics Congress will be held in Namur, Belgium, September 7-11, 1970. Those wishing to take part in the Congress or to obtain further information should write to the Secretariat of the International Cybernetics Association, Palais des Expositions, Place Andre Rÿckmans, Namur, Belgium.

BIOLOGY OF AGING

A summer course in the biology of aging will be given by the Department of Microbiology, Stanford University, July 6-17, 1970. Detailed information may be obtained from Dr. Gabe Maletta, National Institute of Child health and Human Development, NIH, Bethesda, Md. 20014.

NEWS ITEMS FROM MEMBERS
PAST 80 YEARS OF AGE

GEORGE WHIPPLE wrote:

"I am sending on to you a little publication, giving some information about the grand dinner that they gave me on the occasion of my ninetieth birthday."

Excerpts from the account in MEDICAL REVIEW, University of Rochester, Fall 1968, follow.

George Hoyt Whipple was ninety on the 28th day of August, and for that occasion were gathered at the Newport House a majority of the men with whom he founded the School of Medicine and Dentistry in the early 1920s.

Nathaniel Faxon was there, and so were Stanhope Bayne-Jones, George Corner, John Morton, and William McCann. Kept away by circumstances were Karl Wilson and Wallace Fenn ...

Wallace contributed the following:

This is the house that George built.
These are the students that George allowed
To enter the school so well endowed
To train in the house that George built.
These are the teachers of wisdom and wit
Taught by George to be worthy and fit
To teach the students who came to sit
Here in the house that George built.
This is the gym with volleyball court
And exercise items of every sort
That George declared there ought to be
To protect the students from dread TB
That threatened the house that George built.
This is the annex for A. E.C.
Added by George in such secrecy
For all the workers who have added their bit
To the fame of the house that George built.
This is the W wing indeed
Added by George for a growing need
For space in which new projects could fit
Somewhere in the house that George built.
Wing R was added to fill the void
And John Romano was there employed.
With his innate wisdom to find the point
Where human minds get out of joint.
Argue the matter how they wilt,
It's part of the house that George built.
So wing after wing the house expands
To meet the ever growing demands.
There was wing OO and double G

And a court filled in for the library
For education and patient care
That every function may have its share.
And all that's been added bit by bit
Yes, all that will ever be added to it
Will be part of the house that George built.
So this is the George, New Hampshire born
Who mastered the art of living long
And whose 90th birthday finds him still
Working away at his desk with will
In his brick-lined room still unadorned
With paint or plaster he so much scorned.
So, courage my friends and be of good cheer
For we can be sure that George is still here,
Watching his school grow year by year,
Guarding the house that George built.

D. E. JACKSON at 91 replied to Bruce Dill:

"I am deeply grateful for the lovely card which you have sent me. It reminds me that the past was a reality and not just a dream as it sometimes seems to some of us. I even recall a custom which at one time was much in vogue in this country, when teenagers often carried around with them small note books in which friends were asked to write verses or some statement by which the friend could be remembered. One of these verses ran as follows:

Tis sweet to be remembered,
Tis sad to be forgot
So dear friend let me whisper
To you forget me not.

Just now I am very busy working on a problem from which I venture to hope that something a little more valuable than usual may result. Yesterday I had five pictures (oils) put on display in the Art Exhibit of the American Society of Anesthesiologists in San Francisco. And at the Commencement last June the University of Cincinnati granted me the Honorary degree of Doctor of Science.

To many of the 'old timers' I think it will be cheering to learn that your committee does something more than simply note the sparrow's fall."

A. V. HILL writes as follows:

"I have just finished correcting the proofs of a book, FIRST AND LAST EXPERIMENTS ON MUSCLE MECHANICS (Cambridge University Press, Spring 1970). The first experiments were with Herbert Gasser in 1923-24, the last were in 1964-67 before I left London to come here. The principle adopted in writing about them was taken from a line of Horace's which, translated freely, runs 'What's to stop you from telling about your experiments with a laugh?' Jo Barcroft always told about his that way. But he came from Newry in Ireland where one of

the founders of the APS also was born - Newell Martin. My only connection with Ireland is five generations back. The rest of my genes came from Devon, Somerset, Gloucester, and S. Wales; but people can laugh there too.

You will be interested in this. The Royal Society has a project and a Committee, for scientific research in schools. A teacher at Gordonstown School in Scotland has asked for (and received) their blessing and support for experimental work on work rate, heart rate, energy expenditure, and fat loss in school activities. He has my blessing too! Gordonstown is the strenuous school where Prince Philip and his son Charles were. They will probably lose fat all right."

EDWARD A. BOYDEN writes:

"I am happily occupied in a stimulating department with the privilege of teaching and with NIH support for research. As an extra bonus I have had the good fortune to be a guest investigator, during parts of the last two summers, at the Institute of Diseases of the Chest in London. One outcome of this was the first wax reconstruction of the terminal air passages in the lung of a premature of 30 weeks - at which time it first becomes functional. Here "terminal bronchioles" branch into respiratory bronchioles and these into elaborate clusters of thin-walled saccules (no alveoli nor alveolar ducts present at this time). Lately, I have learned that bronchial arteries arise late, and pulmonary arteries of systemic origin, very early in embryonic development. Now I'm reconstructing and analyzing the gross physiological unit of the human lung - the pulmonary acinus.

My Irish setter is a very satisfactory and understanding companion - accompanying me to Medical School every day. Music and friends complete the setting."

GUSTAV ECKSTEIN'S colorful reply to Gene Landis was as follows:

"My view of the world? I can shrink that into a sentence: It is more unchanging than it momently appears, and physiology is as fresh to me as when I was young. I am grateful to it every day for the way it both widened and narrowed my view.

Yesterday I sent back page proofs of a book. You know that illusory satisfaction. It is a book aimed at the general reader but does draw on my long career as a teacher. Its title is THE BODY HAS A HEAD.

Since finishing that manuscript, more than half a year ago, I have returned to a book on Pavlov that I began before he died, when I visited with him and talked to him of it. Subsequently I went again to the Soviet Union, and have never let the subject alone. Now am at it exclusively and should be done with it not too far off. I came to know several who knew Pavlov well, ... two great men, particularly, Walter Cannon and Harvey Cushing;... When that book is finished, mischievous Nature willing, I shall bring together what I have jotted down about the daily life of an animal, really a class of animals, that I have watched and

grown fond of.

The Department of Physiology here has allowed me to stay, as has the Dean, never hinted that I should be in Barbados, and the Department of Psychiatry for half a dozen years has included me in as a listener and occasional talker. So, my body thrives, my head, I think, is not especially senile, though the senile rarely know."

W. R. HESS writes to Landis:

"Lieber Herr Prof. Landis:

Es hat mich sehr gefreut, von Ihnen eine Mitteilung zu erhalten. Seit mehr als vor 2 Jahren habe ich mich in der klimatisch begustigten Zone sudlich der Alpen niedergelassen und lebe hier mit der Welt und mir selbst im Grossen Ganzen zufrieden. --Gerne werde ich Ihnen im Verlauf der nachsten Wochen etwas zur Verfugung stellen, was fur den angegebene Zweck vieleicht Interesse hat. Heute nochte ich mur soviel sagen, dass ich wirklich 1881 geboren bin und zwar am 17, Marz.

Ich hoffe, dass es Ihnen immer gut geht, wobei inch mich noch sehr lebhaft an unser Zusammensein erinnere, als ich Ihr Gast war.

Mit vielen freundlichen Grussen: Ihr

(Signed) W. R. Hess"

BERNARDO A. HOUSSAY writes to Eugene Landis as follows:

"I was born on April 10, 1887, in Buenos Aires and my present private address is: Viamonte 2790--Buenos Aires. My laboratory place is: Institute de Biologia y Medicina Experimental - Obligado 2490 -- Buenos Aires , Argentina. I am still the Director of the laboratory.

Many thanks for your birthday greetings for 1969."

Dr. GRAYSON P. McCOUCH writes as follows:

"How kind of you to add a personal note to the type-written one. I, too, have greatly enjoyed semi-retirement: about four days a week at the lab, with two younger colleagues working on special reflexes in the monkey. What with an increasing senile tremor and progressive loss of memory I am no longer pulling my weight in the boat. I have regretfully decided to quit when two papers are finished (perhaps by Christmas).

Then I plan to try to learn to play the cello (with a poorly controlled vibrata), perhaps to perpetrate attempts at oil painting, and certainly to ride my horse daily instead of twice a week. For all these plans rural Chester County is an admirable setting. My social activities are connected with Planned Parenthood and World Federalism. I hope to find more time for reading Spanish and French and for an occasional trip abroad.

It was refreshing to get a bit of news from you and to learn that all goes well with you in Upper Bucks County."

Dr. SAMUEL E. POND writes:

"I keep busy helping the under-dog, tutoring biology and physiology with the College of Basic Studies of the University here in the city's older school buildings. All of this is now part-time avocation: three days a week on administration, two days a week tutoring, some of the time with the family and friends, consulting, etc. There's little time for recreation.

I have seen remarkable changes - from making x-ray tubes at home, along with other tricks in early medical electronics with circuit breakers, transmitting medical lectures in 1910-11 by water-cooled telephone transmitters and flaming arcs, making the large baking ovens for the whole human body in Springfield, when we learned keeping the head out was a real trick to prevent scalding at the neck as we raised the oven temperature of over 400, for 20 minute bakes, to heal up charlie-horses, etc. football injuries and the like. Think of applying these early experiences, with poorly calculated risks, over into the string galvanometer, optical transmitters for muscle contraction waves, into the modern EKG and EEG stuff and the computer-related or inter-related lab-operating room-clinic. I still wonder why when we set up for CO_2 background and angioscopy, the brain surgeons got scared and went on with O_2 for fluoroscopy to locate the tumors with such poor radiation-contrast. From 1903 to 1969 is a long stretch in side-lines!"

EUGENE OPIE, age 96, replied to Hal Davis:

"I have received your letter and I am greatly pleased by it. In spite of deficiencies of sight which prevent me from reading or writing letters or numbers less than about one half inch across I go to the Rockefeller University about five times a week and enjoy the privilege."

Dr. WALTER C. ALVAREZ, busy at 85, supplied the following notes on his activities:

"In 1930, because of the big depression, I lost my physiologic laboratory and assistant. In 1948 I published the fourth edition of AN INTRODUCTION TO GASTROENTEROLOGY with a bibliography of some 2,720 items. It summarizes the world's literature on the motor functions of the digestive tract. I devoted my spare time to clinical research in migraine, little strokes and non-convulsive epilepsy.

I wrote books on MINDS THAT CAME BACK; LIVE AT PEACE WITH YOUR NERVES; PRACTICAL LEADS TO PUZZLING DIAGNOSES; INCURABLE PHYSICIAN; LITTLE STROKES; and a series of articles on migraine. I now am seeking publishers for two books on non-convulsive epilepsy. I have a number of ideas for more books.

CARLOS MONGE wrote as follows to Bruce Dill:

"It has been a great pleasure to receive your letter October 18 and greetings for my birthday - 85, 13th December. Your greeting gives me a great opportunity to have another bottle of wine on my anniversary, remembering you.

Did you know I published HIGH ALTITUDE DISEASES, Charles Thomas Pub., 1967, ADAPTATION TO HIGH ALTITUDE IN ADAPTATION OF FARM ANIMALS, Lea & Febiger, 1968, and MAN, CLIMATE AND CHANGES OF ALTITUDE IN MAN IN ADAPTATION, BIOSOCIAL BACKGROUND, Aldine Pub., 1969? I don't remember if I wrote to you on the subject. By the way, the last years ADAPTATION TO THE ENVIRONMENT is always on my Bureau's table. The purpose of the book under your guidance is simply wonderful.

Many, many thanks for your letter and greetings. My son is doing fine. He was appointed on High Altitude Committee as Chairman during the last International Congress of Physiology and later on, in a Symposium in Denver."

Dr. NORMAN M. KEITH states in a letter to Eugene Landis:

"I am still a great believer in the importance of physiology to medicine."

JESSE McCLENDON:

Jesse McClendon wrote Essex about his difficulties with the University of Minnesota Press that led to his resignation; he then joined the Hahnemann faculty. His book on GOITER AND CRETINISM was not published and his later efforts to find a publisher have failed. He then took up a study begun in 1919 of plants used for food or medicine by the Indians. He writes, "I despair of getting figures of these plants as I am blind in the left eye, stone deaf in the left ear. For ten years my left facial nerve has given jabbing pain. I am so crippled and my semicircular canals so deficient that I sometimes fall even when using crutches. I have premonitions of dying and having more than five years work thrown into the waste basket. Therefore I am trying to leave it in care of a Garden Club:

Women's Club for Plants for Peace
President: Atlantis Octavia Marshall
Artist: Lois Rapp
Photographer: Ann Carpenter
Temporary Officers:Non-Members:
Botanist: John H. McClendon
Secretary: J. F. McClendon
Progress Report: 1250 Native American Plants used by Indians as Food and Drugs

You may say 'What the hell has peace to do with it.' All I know is that except for Cinchona, gardening has nothing to do with war. Further-

more, I believe that these plants were discovered by women and children who were forced to eat plants when the men were ...hunting.

With fond recollections of and Christmas greetings to the Physiologists at Rochester, from your fellow physiologist."

Jesse McClendon

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INTERNATIONAL SOCIETY OF CARDIOLOGY

The Council on Epidemiology and Prevention, International Society of Cardiology announces its Third Ten Day International Teaching Seminar on Cardiovascular Epidemiology, August 23 - September 4, 1970, in the British Isles. Up to 25 student fellows can be accomodated. Nominees should be at the postdoctoral level, with some residency training or its equivalent, planning an academic or research career, and interested in cardiovascular epidemiology. Limited funds may be available to pay for room and board during the Seminar, and for transportation in an amount up to $200.00 per accepted fellow. Nominations should be submitted to: Jeremiah Stamler, M.D., Secretary, Council on Epidemiology and Prevention, International Society of Cardiology, Room LL 139, Chicago Civic Center, Chicago, Illinois 60602, USA.

INTERNATIONAL SYMPOSIUM ON MENTAL RETARDATION

The 1970 International Symposium on Mental Retardation will take place in London, March 14-25, 1970. For further information write to Dr. Margaret J. Giannini, Center for Mental Retardation, New York Medical College, 105 East 106 Street, New York, N.Y. 10029.

INTERNATIONAL DIABETES FEDERATION

The Seventh Congress of the International Diabetes Federation will be held in Buenos Aires, August 23-28, 1970. For further information write Dr. V. G. Foglia, Paraguay 2155. 7º piso, Buenos, Aires, Argentina.

COMMUNICATION ACTIVITIES OF PROFESSIONAL SOCIETIES

LOUISE H. MARSHALL

The field of technological and scientific information exchange is so vast and at the same time so easily fragmented into disciplinary, type of service, and individual preference components that national and even international perspectives are needed for a comprehensive view. Within the executive branch of the federal government, the Committee on Scientific and Technical Information (COSATI) has taken the lead in keeping abreast of what is going on. Among COSATI's many activities has been formulation of guidelines for information processing and provision of a forum for exchange of ideas and opinions on recommendations.

An opportunity for concerted action of nongovernmental interests in this broad field came through the Committee on Scientific and Technical Communication (SATCOM), organized in 1966 by the National Academy of Sciences and the National Academy of Engineering to study intensively the complex processes by which research results are communicated. Vehicles for communication that were included were journal publications of original research, reviews, surveys, abstracts, indexes, bibliographies, library services, preprints, meetings, and personal contact. The 3-year project was financed by the National Science Foundation.

From the beginning, SATCOM sought to engage the attention and involvement of the professional societies in its activities, because the Committee was convinced that the quality of any information exchange depends on the authoritative input of active scientists. This viewpoint was expressed when the chairman made clear they were talking about communication from brain to brain and not from brain to machine or machine to machine. The professional societies, which were established to provide more effective channels of communication for their members, have a crucial role to play "...because their membership includes the principal generators and users of scientific and technical information." SATCOM challenged the societies to accept greater responsibilities.

Two open meetings have been held by SATCOM to which were invited representatives of the major professional societies. The first meeting, in November 1967, was called to generate discussion and elicit suggestions from the societies. Called the SATCOM Correspondents' Conference, this meeting of about 300 persons had two working sessions, a dinner with topics assigned to each table, and a third working session of parallel discussion sections. The theme of one of the discussion sections was "Objectives for the information programs of scientific societies and other professional organizations - publications, meetings, reviews, and surveys." The second open meeting, held in July 1969, was organized by COSATI to provide a forum for discussion of SATCOM's recent report, Scientific and Technical Publication (1). The American Physiological Society was not represented at either meeting. For this reason, I want to summarize those of the fifty-five recommendations that are germane to our Society's objectives, with the purpose of highlighting our accomplishments, and to urge that we give some thought to our deficiencies.

SATCOM believes that the professional societies must redefine their activities to meet changing times. In general, present activities do not reflect the technology now available. Although the societies are uniquely able to collect, organize, and assure the quality of the information they distribute through their meetings and their primary distribution programs, they usually have not assumed any responsibility for abstracting and indexing services. Yet, they are in a position to determine continuity and progress in their disciplines.

The role of authoritative evaluation of the primary information was emphasized in the discussion and in the report. J. J. Baruch, president of Interuniversity Communications Council (EDUCOM), said the problem is not so much the information explosion as it is the pollution of information. Coping with the flood of information today is like trying to learn how to drink from a fire hose.

SATCOM's report proposes leadership at the national level through creation by the National Academy of Sciences-National Academy of Engineering of a Joint Commission of Scientific and Technical Communication to stimulate greater effort toward coordination among private organizations and to facilitate their interaction with government. Also at the national level, it urges management of public information programs by appropriate societies, federations of societies, or commercial organizations; increase in the scope of the 1961 page-charge policy statement to include the processing of information for access, consolidation, and special use; and government assistance and support of society efforts to achieve international cooperative agreements relative to scientific and technical communication.

At the society level, SATCOM urges greater effort;1) to meet the need for critical reviews and data compilations, and advocates funding of these efforts by sponsors of research and development; 2) to fulfill the information needs of the practitioner, including provision of access and awareness services; 3) to organize subdisciplinary groups with common information needs (need-groups), and to support the development of need-group services. The report suggests that societies experiment with publication of short-lag, brief-reports journals and with superjournals which reprint the most outstanding papers in a selected field; that they publish the "who, what, where" type of information that facilitates informal interpersonal communication; and that meeting sponsors explore means of enhancing the effectiveness of such gatherings. Among the specific recommendations made was provision of adequate time and facilities for informal interpersonal communication at meetings. In the area of research on information exchange, the report points to the responsibility of scientific and technical societies to ensure the participation of competent scientists, engineers, and practitioners in the guidance and evaluation of experiments with innovative information handling procedures.

How do the present activities of the American Physiological Society measure up against these recommendations? First, as a matter of perspective, the publication of original research reports in Society journals amounts to about 20% of the physiological literature in English

and about 12% of the world literature (2). Section editors have managed to check pollution of the physiological literature published in their pages by about 42%, the percentage of manuscripts received that rejected for publication in the Society's journals (3). An unknown number of these papers are eventually published elsewhere.

"Scientific and technical societies must develop, propose, and assist in implementing new and better ways to identify needs for critical reviews and data compilations and to further efficient preparation of them" (4). Both in Physiological Reviews and in the Handbooks, original findings have been repackaged for users. How critical is the evaluation of the original sources, and does it represent a consensus or an individual scientist's opinion? There is a need here for "some equivalent of the tradition of intelligent journalism by means of which people in other walks of intellectual life can be well informed without always having to rush off to original manuscripts" (5). A way should be found for continuous revision of the data in the Handbooks, rather than freezing information that at best is a year old before publication. In relation to interpersonal communication at meetings, the coffee-lounge discussion areas at the XXIV International Congress of Physiological Sciences, held in Washington in 1968, proved to be a highly successful means of enhancing meeting effectiveness. But we have nothing comparable at the annual Federation meetings.

The "who, what, where" type of information has been published for neurophysiologists and is free for the asking (6). Again in connection with the XXIV Congress, plans were discussed to make available such information for all of U.S. Physiology, but were dropped as not feasible.

Should SATCOM's recommendation for a joint commission be implemented, about 20 members broadly representative of the major scientific and technical communities and information handling organizations would comprise its membership. Is the American Physiological Society willing to let AIBS or FASEB speak for physiology? The Society has no formal grouping of scientists with a common interest in scientific communication, although there are many individuals among its membership who are conducting interesting and innovative experiments in several aspects of this broad area. In fact, the Society has no formal means of coordinating an input into the Nomenclature Committee of IUPS, nor of letting its members know what IUPS is accomplishing in this area.

I believe that a start toward involving physiologists in improving information exchange could be made with a cataloging of the ongoing activities, no matter how small, that are being carried out by its members. I believe a second approach could be made by exposing the membership to innovative ways of supplying information which is directly relevant to their needs. In some cases, the scientist is not able to identify his need because he has been using what he learned years before and is accustomed to, and does not know what is available. The scientist should be brought face to face with technological advances such as microfiche, ultramicrofiche, and electronic video recording.

The role of improved communications in more effective education

of physiologists should not be overlooked. The SATCOM report does not address itself to the influence of universities in shaping scientific and technical communications. Continuation of the Society's uncoordinated approach to communication problems means we are standing still in a field that is rapidly changing because of pressures from improved technology and the massiveness of information sources.

REFERENCES

1. Scientific and Technical Communication, A Synopsis. SATCOM, 2101 Constitution Ave., N.W., Washington, D.C. 20418, 30 pp., free; Scientific and Technical Communication, Pub. 1707, Printing and Publishing Office, NAS, 2101 Constitution Ave., N.W., Washington, D.C. 20418, pp. 330, $6.95.
2. Percentages are based on numbers of articles published in journals listed under Physiology by NLM and are underestimations because they exclude articles in general and other-discipline journals. Data from a Demand Search for the period October-December, 1968, kindly provided by Constantine J. Gillespie, Head, MEDLARS Management Section, NLM.
3. Average rejection rate in 1968 of AJP, JAP, and JN. Personal communication from Sara Leslie, Managing Editor.
4. Scientific Information Notes, 1(2): 1-3, 17-19, 1969.
5. No information on Information, Nature, 223: 11-12, 1969.
6. IBRO Survey of Research Facilities and Manpower in Brain Sciences in the United States. Committee on Brain Sciences, NRC, 2101 Constitution Ave., N.W., Washington, D.C. 20418, 314 pp., free.

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INTERNATIONAL ATOMIC ENERGY AGENCY SYMPOSIUM

A Symposium on Dynamic Studies with Radioisotopes in Clinical Medicine and Research will be held in Rotterdam, The Netherlands, August 31 - September 4, 1970. For further information write to Dr. T. Nagai, International Atomic Energy Agency, Karntnerring 11-13, 1010 Vienna, Austria.