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IN THIS ISSUE:

Guanidinium Compounds

Medicine in USSR

University of Minnesota Medical Bulletin

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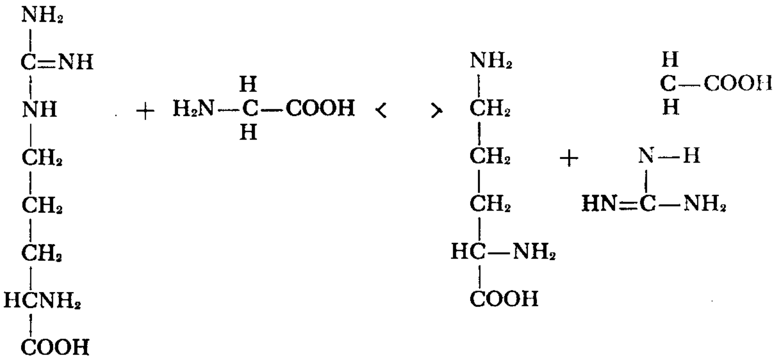
Staff Meeting Report

Guanidinium Compounds and Diuresis*

John F. Van Pilsum, Ph.D.†

This investigation represents an attempt to determine whether or not the enzyme transamidinase, or the compounds involved in its reaction, plays a role in kidney function. Transamidinase catalyzes the transfer of the amidine group from arginine to the amino group of glycine with the formation of guanidinoacetic acid and ornithine. Guanidinoacetic acid is then methylated in the liver to form creatine. At the time this study was begun, transamidinase activity had been found only in the mammalian kidney;[1] now, however, it is known to occur also in the pancreas.[2]



Arginine — Glycine — Orinthine — Guanidinoacetic acid

The reasons for thinking that this reaction might affect kidney transport of ions across the tubule were as follows:

(a) Transamidinase is a sulfhydryl enzyme; it is inhibited *in vtro* by parachloromercuribenzoate, and this inhibition can be reversed by cysteine, glutathione, or British anti-Lewisite.[1]

(b) The diuretic action of mercurials has long been known, yet their mode of action is not completely understood. Kleinzeller *et al.*,[3]

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*This report was given at the Staff Meeting of the University of Minnesota Hospitals on November 14, 1958.

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after investigating the effect of mercurial compounds in kidney slices, suggested that these compounds change the permeability of basal membrane of renal tubular cells, thus increasing the passive movement of Na^+ ion, Cl^- ion, and water back into the cells, resulting in a decreased reabsorption of salt and water. They also suggested that the state of the sulfhydryl groups of proteins in the membrane of renal tubular cells is a determinant of cell permeability to Na^+ and perhaps to water.[3] On the basis of these findings it was decided in this study to administer an organic mercurial to animals and to measure subsequent changes in kidney transamidinase activity and general kidney functon.

Method

Adult male albino rats were chosen as the experimental animals. It was necessary to force-feed the rats for two reasons: (a) Rats fed a diet *ad libitum* scatter their food, thus contaminating the urine to be collected; (b) Any changes in appetite and food consumption produced by the drugs used would also change the urine composition.

The rats were housed in cages over a funnel, and urine was collected over toluene, the feces being prevented from entering the urine by a glass-wool barrier in the mouth of the funnel. The urine was collected every 24 hours and analyzed for arginine, guanidinoacetic acid, creatine, creatinine, sodium, potassium, chloride, and nitrogen. The guanidinium compounds were measured by previously reported methods,[4] chloride by the potassium chromate method, nitrogen by micro-Kjeldahl analysis, and sodium and potassium by flame photometry. Kidney transamidinase was measured by incubating a kidney homogenate with a mixture of arginine and glycine and measuring guanidinoacetic acid formation.[1]

The diet contained vitamin-free casein, 20 Gm.; cornstarch, 56 Gm.; corn oil, 20 Gm.; choline chloride, 0.1 Gm.; salt mixture No. 2, 4 Gm.; dl methionine, 0.25 Gm.; and Upjohn Zymadrops,® 0.12 ml/Gm of diet. These ingredients were blended with water in a Waring blendor, and the resultant slurry made up to a total volume of 200 ml. The animals were started on the diet with a volume of 5 ml. twice a day, increasing over a period of five days to 10 ml. twice a day, with access to water *ad libitum.* The animals' weight did not change during the experiment.

Results

The first observation was that force-fed rats excreted creatine in their urine for about two weeks. Normally, no creatine is present, and this creatinuria of force-feeding is not understood. Insertion of the catheter into the stomach of rats did not induce creatinuria. Rats fed fox chow *ad libitum* and given their water by stomach tube did not exhibit creatinuria. Doubling the normal water intake by force-feeding also did not produce creatinuria, nor did changing from fox chow to the synthetic diet *ad libitum.* At any rate, an equilibration period of two weeks on metabolic experiments using force-feeding is recommended.

After the rats were observed to excrete no further creatine in their urine, a dose of Mercurhydrin® (calculated from the human dose) was given intramuscularly. The urine was collected daily for five days and analyzed. When no change in urinary composition was observed the dose was doubled and the urine collected and analyzed for the next five-day period. Six weeks later an effective dose was arrived at—approximately 30 times the human dosage (on the basis of dose per kilo body weight).

The results were as follows: On the first day following the injection of 0.08 ml. of Mercurhydrin, a 27 per cent decrease in creatinine excretion was observed, with a return to a normal value the second day. Creatine appeared in the urine the first day and remained for at least five days after the injection. Arginine increased to 170 per cent of the normal value the first day and gradually returned to normal in the five-day period. Guanidinoacetic acid levels in the urine remained constant. Potassium and sodium excretion increased 50 per cent and 25 per cent respectively the first day and returned to normal on the second day. These results were essentially repeated with the same group of rats given a second dose of 0.08 ml.

Another group of rats was given 0.08 ml. Mercurhydrin after being force-fed the diet for only two weeks. This dose proved too great, for on the second day after the injection, complete renal failure occurred, and the rats died one day later. Evidently, the reason the rats in the first group had survived this same dose was that their tolerance had been built up through the gradual increases in dosage. At any rate, some data were obtained on the day following the injecion. (See Table 1.) Even though complete renal failure was produced (on the

TABLE 1

CHANGE OF URINARY COMPOSITION AFTER 0.08 ML. MERCURHYDRIN

	Milliequivalents or millimoles/kilo body wt/day							
	Creatinine	Creatine	Arginine	Guanidino-acetic acid	K^+	Na^+	Cl^-	N
Normal	0.30	0.0	0.02	0.02	1.3	1.5	1.2	43
First day	0.08	0.02	0.07	0.01	1.9	2.6	1.2	18

TABLE 2

CHANGE OF URINARY COMPOSITION AFTER 0.02 ML. MERCURHYDRIN

	Milliequivalents or millimoles/kilo body wt/day							
	Creatinine	Creatine	Arginine	Guanidino-acetic acid	K^+	Na^+	Cl^-	N
Normal	0.33	0.0	0.03	0.03	1.7	2.0	1.2	60
1 day	0.26	0.10	0.05	0.04	4.4	4.0	1.2	60
2 days	0.31	0.02	0.06	0.04	2.0	2.0	2.6	73
3 days	0.30	0.04	0.04	0.04	0.6	1.2	2.2	66
4 days	0.36	0.0	0.07	0.03	1.0	1.6	0.7	65
5 days	0.33	0.0	0.04	0.03	1.7	2.0	1.0	60

second day), creatine appeared in the urine, arginine increased about threefold, and K^+ and Na^+ increased 50 per cent and 70 per cent respectively, while chloride remained the same and creatine and total nitrogen decreased.

An effective single dose of Mercurhydrin was found to be 0.02 ml. for a 300 Gm. rat; the data obtained with this level are shown in Table 2. Creatinine excretion decreased 20 per cent the first day and returned to normal the second day. Creatine appeared in the urine for three days. During the first two days arginine increased 100 per cent, while total nitrogen increased 20 per cent Guanidinoacetic acid remained constant. Na^+ and K^+ increased 100 per cent and 160 per cent respectively, then decreased on the third and fourth days, with a return to normal on the fifth day. Neither chloride nor total nitrogen increased until the third day.

Three force-fed rats were used to determine the effect of Mercurhydrin in transamidinase activity. One was used as a control being given no drug; the other two were killed 12 and 24 hours respectively after the injection of 0.02 ml. Mercurhydrin, and their kidneys were removed for enzyme analysis. The results are shown in Table 3.

Similar urinary studies were done on rats given chlorothiazide (Diuril®), a new diuretic produced by Merck. Force-fed rats were given 17 mg. of Diuril, with the results shown in Table 4. There

TABLE 3

TRANSAMIDINASE ACTIVITY AFTER MERCURHYDRIN

	micromoles guanidinoacetic acid/Gm kidney/hr
Normal	7.0
10 Hours	12.0
24 Hours	15.0

TABLE 4

CHANGE OF URINARY COMPOSITION AFTER 17 MG. CHLOROTHIAZIDE

	Milliequivalents or millimoles/kilo body wt/day							
	Creatinine	Creatine	Arginine	Guanidino-acetic acid	K^+	Na^+	Cl^-	N
Normal	0.30	0	0.02	0.02	1.4	1.4	1.5	44
1 day	0.28	0	0.02	0.02	2.1	3.3	4.5	43
2 days	0.28	0	0.02	0.03	1.8	0.51	0.15	44
3 days	0.25	0	0.03	0.03	1.4	0.9	0.9	47
4 days	0.33	0	0.01	0.01	1.3	1.3	1.4	41
5 days	0.30	0	0.02	0.02	1.5	1.4	1.7	50

was no change in excretion of any of the guanidinium compounds, or of Nitrogen. K^+ excretion increased 50 per cent, Na^+ 65 per cent, and chloride 200 per cent the first day after administration of Diuril.

Discussion

The mechanisms of the diuresis produced by chlorothiazide and of that produced by the mercurial compound seem to be quite different. Cholorothiazide produced simultaneous sodium, potassium, and chloride diuresis (without any change in guanidinium compounds), and was two to three times more effective for sodium as for potassium. The mercurial produced a sodium and potassium diuresis that preceded the chloride diuresis, with a change in the guanidinium compounds, and was more effective for potassium than for sodium.

Since the mercurial compound produced a greater potassium than sodium diuresis and was accompanied by an increased excretion of arginine and creatine, one might be led to associate potassium diuresis with arginine or creatine. However, the force-feeding of diets supplemented with large amounts of creatine or arginine did not produce potassium diuresis, for the excess arginine and creatine were metabolized, and the urine showed no increases in either compound. Nor did the force-feeding of diets containing large amounts of potassuim chloride or bicarbonate increase the excretion of arginine or creatine.

This increased creatine and arginine excretion in mercury diuresis cannot be explained at present. It may be the result of cellular damage with the loss of arginine and creatine into the urine, but whether blood levels of these compounds increase under these conditions is not known. The fact that the proportionate increase of these compounds in the urine is much greater than that of the total nitrogen does perhaps suggest that creatine or creatine phosphate or arginine or arginine phosphate may affect the transport of other ions such as potassium.

Under the conditions of the experiments, transamidinase activity actually increased after injections of Mercurhydrin. From the limited data obtained so far, the mercurial compound does not appear to inhibit the enzyme's activity. Other investigators have shown that parachloromercuribenzoic acid, the classical sulfhydryl inhibitor, is not a diuretic. It appears, then, that kidney transamidinase has no role in kidney function.

Summary

1. The effect of an organic mercurial compound and of chlorothiazide upon urinary composition was determined in the force-fed rat.

2. The organic mercurial compound had a greater effect upon potassium excretion than on sodium excretion; chlorothiazide had a greater effect on sodium excretion than on potassium excretion.

3. Injections of an organic mercurial compound resulted in a great increase of arginine and creatine in the urine. Chlorothiazide, administered orally, produced no change in the guanidinium compounds excreted in the urine.

4. Injections of an organic mercurial compound did not inhibit the kidney transamidinase activity *in vitro*.

References

1. Van Pilsum, J. F.; Berman, D. A.; and Wolin, E. A.: Assay and Some Properties of Kidney Transamidinase, Proc. Soc. Exper. Biol. & Med. 95:96, 1957.
2. Walker, J. A.: Role for Pancreas in Biosynthesis of Creatine, Proc. Soc. Exper. Biol. & Med. 98:7, 1958.
3. Kleinzeller, A. and Cort, J. A.: The Mechanism of Action of Mercurial Preparations on Transport Processes and the Role of Thiol Groups in the Cell Membrane of Renal Tubular Cells, Biochem. J. 67:15, 1957.
4. Van Pilsum, J. F.; Martin, R. P.; Kito, E.; and Hess, J.: Determination of Creatine, Creatinine, Arginine, Guanidinoacetic Acid, Guanidine, and Methylguanidine in Biological Fluids, J. Biol. Chem. 222:225, 1956.

Staff Meeting Report

Impressions of Physiology and Medicine In the USSR in 1958*

Frank Morrell, M.D.†

In the summer of 1957, the Soviet Academy of Science, in co-operation with the International Society of Electroencephalography and Clinical Neurophysiology, issued invitations for an international colloquium on the electroencephalography of so-called higher nervous activity. The meeting took place in October, 1958, in Moscow, USSR. The list of participants included scientists from many nations. Three people from the United States contributed papers to the symposium — H. W. Magoun, M. A. Brazier, and myself. In addition, there were three other Americans who participated in the discussions: Drs. Robert Galambos, Janice Stevens, and Lenore Morrell. Fourteen of the participants came from Western Europe or the Western Hemisphere, one from China, one from Japan, one from India, two from Czechoslovakia, two from Poland, one from Rumania, one from Hungary; the rest were from various centers throughout the Soviet Union. The cost of our stay within the Soviet Union was borne by the Soviet Academy of Science.

Before discussing our experiences, I should point out that since the occasion for this visit was a scientific meeting, and since virtually all our time was taken up by this meeting and the tours that followed, our view of the Soviet Union was very limited. In no sense is this a political report, for we had neither the time nor the qualifications to make an analysis of political or economic conditions. At best our information on these matters is anecdotal and limited to the scientific community.

One further bit of background information is necessary to place our experiences in proper context. The subject of the colloquium involved a relatively new branch of neurophysiology, although the problem under consideration was an old one. Broadly conceived it was the neural basis of learning, a subject to which much attention has been

*This report was given at the Staff Meeting of the University of Minnesota Hospitals on November 21, 1958.

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paid by Soviet as well as western scientists. More narrowly conceived, the subject was the physiological basis of the conditioned reflex.

One need hardly stress the fact that since the time of Pavlov, a large – perhaps the largest – segment of Soviet physiology has been concerned with the experimental study of conditioning. American and European physiologists, however, have largely concerned themselves with the more elemental functions of the nervous system, making little or no attempt to relate them to mechanisms of learning. Psychologists, on the other hand, have devoted considerable attention to problems of learning but have approached the field from the standpoint of input-output correlations and, with some exceptions, have ignored the neural events taking place within the organism.

Strangely enough, despite the fact that conditioning was the province of *physiology* in the USSR, both the Pavlovian and the Western psychological schools have, in common, placed main emphasis on input-output correlations. Both schools have devoted considerable *theoretical* attention to events in the central nervous system, but apart from mutilation by various ablations, no *experimental* attention was given to intrinsic brain processes. Although the development of electroencephalography in 1929 and of other electrophysiological methods in the early 1930's provided the technical means for investigation of central neural events, these techniques were largely unassimilated by either the Pavlovians or the schools of experimental psychology. Electroencephalographers themselves, however, made observations as early as 1935 which suggested that electrophysiological methods might fruitfully be applied to the investigation of problems of learning (Durup and Fessard,[1] and review in Morrell and Jasper[2]). But, in general, electrophysiology developed as a special branch of neurophysiology among European and American scientists who were not concerned with the questions of "higher nervous activity" and, to an extent limited by the war, among non-Pavlovian Russian investigators.

In the early 1950's systematic use of electrophysiologic methods in the study of learning mechanisms was begun. Increasing numbers of articles appeared from laboratories all over the world, in particular from Japan, Canada, the United States, and France. In 1955 the first international conference was convened in Marseilles. The published proceedings of that meeting stimulated further work and gave rise to special symposia at the International Congress of Physiology in Brussels, 1956, and at the International Congress of Neurological Sciences in Brussels, 1957. Interest in this new branch of neurophysiology has continued to grow, as evidenced by the fact that the Josiah

Macy Foundation has inaugurated a series of five yearly conferences on this subject and also by the plans for special symposia to be held at the June meeting of the American EEG Society and at the forthcoming International Physiological Congress in Buenos Aires. Another colloquium will take place in Pisa, Italy, three years from now. Thus the Moscow colloquium provided an opportunity to bring the exciting new data derived from the techniques of electrophysiology to the country that was the home of the conditioned reflex, and to share experiences with those scientists working directly in the Pavlovian tradition. This sharing bore fruit in a number of observations which I shall mention later.

There was also some relevant history in scientific events that occurred in the Soviet Union a few years ago. In about 1946 a series of scientific controversies took place in the Soviet Union (the best known perhaps is that in genetics), which resulted in decisions to purge Soviet science of the influence of so-called foreign bourgeois ideologies. In physiology this tendency was epitomized by a conference on Pavlovian physiology held in 1950 in which Academician K. M. Bykov emerged as the ideological leader of Soviet physiology. Severe criticism was leveled at such individuals as L. A. Orbeli, P. K. Anokhin, and I. S. Beritov for attempting to revise Pavlov's theories in the light of discoveries of foreign scientists. Those individuals who quoted foreign scientists widely in their published works were criticized as "cosmopolitans." The resolutions of the 1950 sessions directed the training of Soviet physiologists away from the techniques and ideas of foreign schools and toward a re-emphasis on the older Pavlovian methodology, and especially toward the application of this methodology to practical problems of medicine.

Apparently the ensuing eight years saw a marked decline in the output and creativity of Soviet physiology (this was the opinion of many Soviet scientists with whom we talked) and resulted in the somewhat ludicrous picture of large numbers of scientists who were working on higher nervous activity with little or no knowledge of the lower nervous activity from which the higher is derived. Many Soviet scientists considered the October colloquium to be a revolutionary turning point in the history of Russian physiology. Significantly, many of those individuals who were severely criticized in the 1950 sessions were leaders of the discussions in October, 1958.

One example may serve to illustrate how important the Russians felt this conference to be. When the sessions opened, only two laboratories in the world were doing unicellular microelectrode analyses of conditioning: the laboratory of Jasper in Montreal and our own at Minnesota. At the end of the conference a visit to Leningrad had been arranged so that a period of four days intervened before we returned to Moscow to visit laboratories in that city. When we finally did return, we were shown four separate laboratories in which rooms had already been set aside for microelectrode studies, and Jasper and I were requested to advise on the kind of equipment to be purchased. Interest in our work was most evident among younger scientists who were in general extremely cordial and widely read in world literature.

This does not imply, however, that the benefits of the colloquium were all in one direction. We discovered, for example, that *our* ignorance of one of the fundamental findings of the Pavlovian school had greatly hindered the experimental analysis of certain processes in the reticular activating system. In the course of discussions, both Moruzzi and Magoun, the co-discoverers of the reticular activating system, pointed out that their original analysis of the mechanism of sleep had failed to consider the Pavlovian discovery of internal inhibition. They had assumed that sleep occurred when the influence of the reticular activating system excited by sensory input was withdrawn from the cortex. Thus sleep was considered as a negative neural event, as that which resulted from loss or decrease of unspecific sensory inflow. Only recently have neurophysiologists demonstrated that the central nervous system has an efferent control over its own input. Higher levels of the nervous system can exert a positive inhibitory downstream effect to exclude environmental stimuli which are of no significance to the animal. These new studies actually confirm and provide more detail for an observation made by Pavlov himself many years ago. It was clear from our discussions that a more detailed knowledge of the contributions of the Pavlovian school on the part of Western scientists would have markedly facilitated the investigations of the efferent control of sensation.

The Organization of Physiology

In the USSR, physiology is broadly conceived and includes the subdisciplines of biophysics, biochemistry, cellular and comparative physiology, embryology, genetics, pathology, pharmacology, neurology, and to some extent psychology. Despite this breadth of conception, in a practical sense Soviet physiology in the past few years has been very largely directed toward a detailed extension of Pavlovian ideas and experimental techniques. To some extent this may be due to the nature of scientific organization in the USSR. The direction and financing of all scientific research is organized through the Academy of Sci-

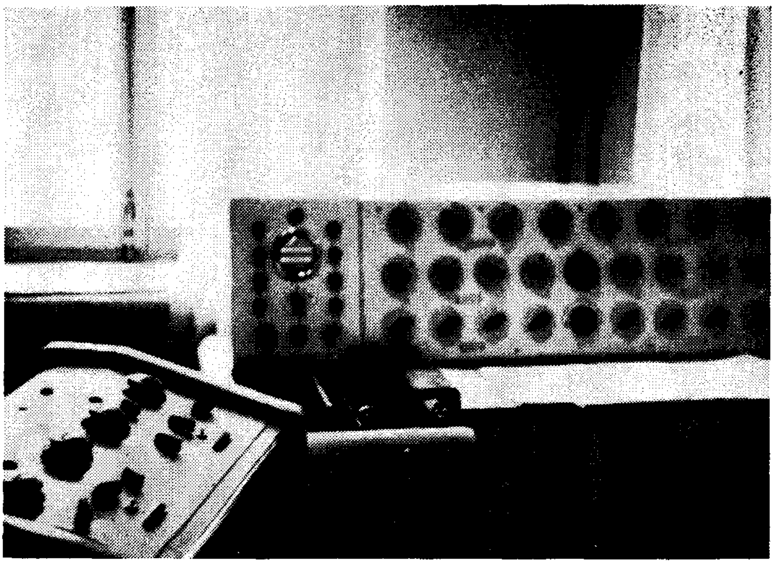

Figure 1. A Russian EEG machine and frequency analyzer

ences and the Academy of Medical Sciences of the Soviet Union. These bodies pass upon all research plans and allocate money to the various institutes. The institutes themselves are tremendous organizations with a highly centralized directorate. For example, Professor K. M. Bykov in Leningrad is director of five separate institutes, each of them containing many laboratories. He is in charge of the general direction of and financial disbursement for more than six hundred scientific workers. If one compares this with what is perhaps the largest single laboratory in the United States, that of Professor Magoun in Los Angeles, which has a total of 30 scientific workers, one may gain some idea of the extent to which centralization of scientific management in the USSR has gone.

Each of the institutes under Bykov's direction contained laboratories divided into special study areas. (For example, the Pavlovian Institute of Physiology has laboratories devoting special attention to the auditory system, another one to the visual system, another to conditioned reflexes in general, another to endocrine problems, another to neurotrophic influences, another to circulatory problems, and some devoted to brain biochemistry and to the physiology of digestion.) It was apparently difficult for scientists working in one of these groups to deal with problems that crossed the boundaries of investigations

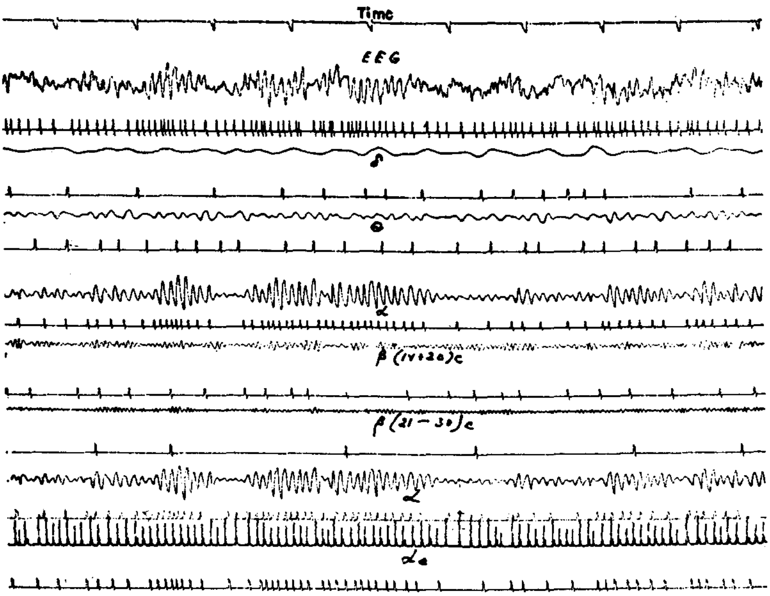

Figure 2. Example of a tracing from the machine in Figure 1. Explanation in text

carried out by other laboratories. Within those limits, however, each laboratory was supposedly permitted to determine its own research program. Of course, the degree to which the plans could be carried out depends upon the support provided by the director. There was no recourse to other sources of funds or facilities.

Facts such as these, of course, do not provide a complete picture of the scientific community, and our personal visits to the laboratories were more illuminating in this respect. While much Soviet work seemed morbidly monolithic, there were, we discovered, oases where highly creative and novel studies were under way. In Leningrad, for example, we came upon the laboratory of V. Kowjevnikoff. Although the main task of his laboratory was the study of auditory physiology, Kowjevnikoff and his wife had developed a program in cybernetics, a subject not held in high repute in the USSR. These two investigators had applied information theory to the development of computing machines and EEG analyzers which were as good as or better than anything we had seen in the West. Figure 1 shows a Soviet electroencephalograph and beside it, the frequency analyzer developed by Kowjevnikoff. Figure 2 is a tracing from that machine, in which the EEG record is broken down into its frequency components. These then are separately analyzed and integrated to determine the total amount of energy in each frequency band. The simultaneous write-out of each of the component frequencies permits an analysis of the time relationships among them, as well as the phase characteristics at each instant in time. This particular kind of data is lost in the conventional frequency analyzers used in our own country.

Kowjevnikoff spoke excellent English and seemed completely free and uninhibited in his discussions with us. He was critical of the director of the institute and pointed out that one of the defects of Soviet scientific organization was that such directors maintained their positions as long as they lived. There is no compulsory retirement, and therefore positions of authority tend to be held by people no longer familiar with newer work and newer ideas in the field of science.

Another interesting excursion was the trip to Koltushi, which was Pavlov's old laboratory, situated twenty miles outside Leningrad. The work at Koltushi is mainly concerned with evolutionary physiology and particularly the evolutionary development of the conditioned reflex. We saw many fascinating experiments involving a variety of animals all the way from conditioned fish to conditioned gorillas. An interesting exchange took place during this excursion reminiscent of a story told by Chauncey Leake, who visited the laboratory two years before. We were shown some reports of biochemical changes in the brains of rats as estimated after fixation by dropping in liquid oxygen. Special attention was devoted to ammonia concentrations. These were determined by a method involving a 2 per cent error of estimation, we were told. When asked about the standard error of a quoted average, Professor Solovieff replied, with a mock scowl, "There is no error!" When then asked, "How about standard deviation?", he again flashed, "There is no deviation!" Everyone laughed, and we spent considerable time discussing the significance of biological variation.

Some of the laboratories doing behavioral studies in animals had elaborately programmed equipment in which all measurements and the timing of all stimuli were automatic. But in many other laboratories the equipment and experimental chambers seemed exactly as they had been in the days of Pavlov.

In many ways the laboratories of Leningrad epitomized what we saw of Soviet physiology, which is characterized by: (1) tremendous centralization of control and of financing; (2) excellent and extensive facilities, plentiful money, a great number of scientific workers, all resulting nevertheless in what seemed to us a generally poor output of scientific work; and (3) isolated areas of brilliance and creativity.

It was refreshing to return to Moscow where many of the laboratories were not restricted to work with conditioned reflexes. In general, these laboratories had better equipment, although a great deal of it was of foreign manufacture, and were run by physiologists who seemed perceptive, alert, and capable. Individual investigators spent a great deal of time showing us their experiments in detail and demonstrating their laboratory facilities, and discussing practical implications of their work. Most spoke English, and therefore interpreters were rarely required. The group was split up so that only a few individuals went to each laboratory at any given time. I myself had the opportunity of spending a full day actually performing an experiment in the physiological laboratory of Professor V. S. Rusinov, an experiment involving the effect of polarizing currents on brain potentials. This, of course, permitted a much more detailed observation of techniques and of equipment, which were of top quality, as well as an opportunity to get to know the younger scientific workers.

A discussion I had with one of these younger scientists during the experiment illustrates the danger of making glib assessments of scientific qualifications on the basis of limited conversation. On observing the prolonged aftereffect of a DC polarization, I asked Dr. A. A. Sokolova how she might explain this persistent effect. She answered, "I explain it as Vedensky did as the inertia of the central nervous process." "But," I said, "that is simply using another word to describe what we saw. What do you think is the *mechanism?*" When pushed in this manner she rather shyly and hesitantly explained her view in fairly adequate electrochemical terms. I asked, "Why did you first quote Vedensky, rather than giving me your own, more up-to-date explanation?" She replied, "That is the way we are generally taught to answer."

The Teaching of Physiology

A visit to the new and grotesquely ornate Moscow University permitted some discussion of the teaching program in physiology. The university includes a huge central building which contains classrooms and a central tower and large quarters for students and faculty in the wings. Several other large buildings, scattered on the grounds, are mainly for the use of the natural sciences. The humanities are housed in a separate and older university area near the center of Moscow. The new university is on a high hill overlooking the Moscow River and providing a magnificent view of the entire city. Architecturally it is baroque and massive but otherwise conventional in general arrangement. The teaching facilities, classrooms, and laboratories are large, airy, well lighted, and well appointed. Equipment was similar to that seen in most physiology laboratories in this country.

Professor Ch. S. Kostayants, head of the department of physiology, received us cordially and provided us with tea and caviar. He seemed a dynamic, knowledgeable individual who had traveled widely outside the Soviet Union. He demonstrated the laboratories and teaching facilities and pointed out some especially interesting teaching demonstrations he had developed over the years. These included the suspending of an isolated frog heart in physiological saline solution to demonstrate the effect of various drugs on the cardiac musculature, and the electrical recording of the slow oscillation of paramecia by means of microelectrodes inserted directly into the infusorium. Kostayants explained that his department taught only university students, since medical students now have a separate school independent of the university. Matriculation in the department of physiology is by competitive examination, and we were told that facilities are available only for those students at the top of the list.

Students electing to enter the faculty of biology spend two years in general studies, during which time basic sciences are emphasized but considerable attention is also paid to history and literature. They then select the field of biology in which they wish to specialize. Students who elect to enter physiology are faced with an initial five-year program. The first year is spent mainly in learning methods and research techniques; for example, two months are spent on nerve muscle preparations, two months on animal operative technique, two months with electronic equipment technique, etc. The next two years are devoted to a research project, either one devised by the individual student or a part of a larger project. In the last year students are required to present a thesis based upon original work which, however, does not lead to a degree but rather, along with passing a stiff competitive examination, permits the student to become an "aspirant" for the degree of Candidate. Two to three more years of specialized work are required for this degree, after which the student is qualified to teach at a university or a medical school or, very often, in the lower schools. The doctorate is seldom given, and it requires about ten years more of research work, the publication of many papers, and a second thesis. We saw and talked with many of the students, almost all of whom spoke English well. Many were women, and many were non-Russian in nationality. Chinese and Indian students were noticeably prominent.

Although the main purpose of the department of physiology was the teaching of university students, a considerable amount of research work was also being carried on. In the research laboratories we saw a good deal of new equipment, mostly of foreign manufacture. We were told that until recently the use of modern techniques had been hampered by lack of adequate equipment. This was particularly true, we noticed, in the field of stereotaxic surgery. We were also told that industry had recently made great efforts to develop biological instruments, but that these were just beginning to be produced in quantity and were available to only a few institutions. We did see, however, some Soviet-made oscilloscopes, amplifiers, and recording cameras which were of excellent quality. In one room we saw what appeared to be an entire corps of engineers setting up a new piece of equipment, and we were allowed freely to examine the circuits and components.

Our general impression was that the training program in physiology was broad, comprehensive, and solidly based. It was more highly structured with a more rigid curriculum than would be found in most Western training centers. There seemed little opportunity for student initiative, at least in the early stages of training. The academic hierarchy is apparently quite strict with clear-cut demarcations and great deference paid to professors.

The Neurosurgical Institute

On one occasion, alone and without an interpreter, I went to the Burdenko Neurosurgical Institute in Moscow. My visit was unannounced, but at my request I was promptly taken to see the director of the electroencephalography laboratory. He received me with some surprise and embarrassment because he had planned an electrocorticogram for that morning and explained that he would not have very much time to spend with me. I indicated that I would be most anxious to see the electrocorticogram, and so we went together to the operating theater.

The institute is a large one with 350 beds, 14 full-time neurosurgeons, 30 assistant neurosurgeons, and 100 research workers. There were five operating theaters, all of them spotlessly clean and containing fairly conventional equipment. The operation we observed was for the removal of a meningioma in a 58-year-old woman who had had symptoms of seizures. To my observation the surgery seemed technically of a high order. (The corticogram was performed for research purposes only and had nothing to do with the clinical requirements of the situation.) The cordial neurosurgeon explained that in general, neurosurgery was very conservative in the Soviet Union. "For example," he pointed out with a smile, "We do not do excisions for relief of focal epilepsy." Since this was just such an operation, I asked for further explanation. He pointed out that neurosurgeons are in the habit of removing any abnormal tissue such as a tumor or post-traumatic scar, but that even if the electrocorticogram shows epileptiform activity in surrounding tissues that tissue is not removed. The underlying assumption is that such tissue will gradually return to normal once the inciting cause has been removed. The electroencephalographer pointed out that there was considerable dispute over this matter within the Soviet Union, and that in general, the treatment of epilepsy, both medical and surgical, was far behind that in western countries. He said that most patients with seizures are institutionalized or are treated by psychiatrists with relatively little attention to medication. However, the Academy of Medical Sciences had recognized the gross deficiency in this field and had requested that much more research be devoted to the problem of epilepsy. I was informed that medical therapy of most neurological diseases was on a relatively low level, and this was ascribed to a generally low level in pharmacology. For example, the most generally used analeptic was caffeine, and I was told that such drugs as Amphetamine and Metrazol were not generally available in the USSR.

Some General Comments

The entire group of western visitors was much impressed with the graciousness and hospitality with which we were received. Our hotel accommodations were palatial, our own room, for example, having a grand piano in part of the suite. We were allowed to go anywhere we pleased and to take pictures of anything we liked. We were assigned individual interpreters and could use them or not as we pleased. We were not aware of any reticence on the part of Soviet scientists, and indeed we were impressed by the free and sometimes violent discussions which took place at the scientific sessions. The younger scientists especially seemed quick with criticism of the older generation, although only in private conversations. There was a fine sense of humor in our dealings and we received the distinct impression that many of the Russians were as aware of the absurdity of some of their own political and organizational leaders as we were of some of ours. The sentiment was very widely expressed that we all had much to learn from one another, and that increased exchange would go a long way toward helping the development of science in all our countries and, perhaps, even toward making a peaceful world a little more likely. At the end of the colloquium, the staff of the Institute for Brain Research in Moscow voted that for a term of one year only English would be spoken in the laboratories of that institute. The broadcasts of the BBC were listened to by almost everyone to whom we spoke, and, in fact, we were told that this was one way they improved their English.

It was hard to form a coherent impression of the general standard of living from our limited contact. We did, however, visit some stores and found them generally devoid of anything but the barest necessities of life. Consumer goods were not plentiful, with two notable exceptions. These exceptions were books, which were plentiful, very cheap, sold on every street corner in many languages, and widely read, if we might judge this by the number of people surrounding the bookstalls; and excellent phonograph records, also relatively inexpensive. Other things, such as clothing, were extremely costly by our standards. Although the scientists with whom we worked were highly paid and obviously highly respected members of their society, the people we observed in the street seemed generally poorly dressed. We saw many children also poorly dressed, but clean, alert, and very interested in knowing all about America and other countries represented in our delegation. In fact, everywhere we went children surrounded us, many spoke English, even those ten years of age, and asked for souvenirs for which they were willing to exchange either trinkets or rubles worth many times the value of the object they wanted.

A summing up of such a varied experience can at best be a vague and schematic thing. In general, we were not tremendously impressed with the bulk of Soviet physiology, although we were very impressed with certain individual laboratories. We found their approach excessively monolithic but already in process of change. We felt that their research programs were hampered by an archaic academic system and an overly centralized organization. We found the teaching of students in general of high quality, although this may be a recent development, and we found the young scientists competent, widely read, and eager to learn. We all felt that much mutual benefit could be gained by further colloquia such as this and by further exchange of scholars and students. Many of the Soviet scientists openly expressed the thought that their own government by its policies of isolation and by its glorification of Soviet science as opposed to all foreign science, as well as by the imposition of certain political lines in biology, had hampered the full development of Russian physiology. All of those who expressed this feeling, however, seemed confident that this situation could not help but change for the better.

Acknowledgments

I should like to express my deep appreciation and gratitude to the following local foundations: Applebaum, Cohen, Coile, Tankenoff, and Hill, as well as to the Teagle Foundation and to the United States Public Health Service for making our trip to Russia possible.

References

1. Durup, G. and Fessard, A.: L'electroencéphalogramme de l'homme. Année psychol. 36:1-32, 1935.
2. Morrell, F. and Jasper, H. H.: Electrographic Studies of the Formation of Temporary Connections in the Brain. EEG Clin. Neurophysiol. 8:201-215, 1956.

Medical School Activities

Dr. Wesley W. Spink, Professor of Medicine, was one of 17 men invited from various medical centers to participate in a symposium on "The Biochemical Response to Physical Injury" held in Semmering, Austria, last September. The symposium was organized by the Council for International Organization of Medical Sciences of UNESCO with the assistance of the Wellcome Trust and the International Union of Biochemistry. Dr. Spink presented a paper on "Metabolic Factors Related to Bacterial Inflammation and Shock."

A paper presented by Mr. Alvin Shemesh, Head, Department of Medical Art and Photography, received an award as the most outstanding paper delivered at the Twenty-eighth Annual Meeting of the Biological Photographic Association in Washington, D.C., last August. The paper was entitled "Some Experiments in Color Radiography."

Among the papers presented recently by Dr. L. M. Schuman, Professor of Epidemiology, were the following: "Role of State Health Departments in Research," at the Annual Seminar of the Association of Business Management in Public Health, Lake Itasca, September 22; and "Veterinary Public Health," at the First National Institute on Veterinary Public Health Practices, University of Michigan, October 9. Dr. Schuman has received a grant from the National Institutes of Health for the current academic year for the Postgraduate Training Program in Epidemiology. As consultant to the National Cancer Institute, he attended a meeting on Leukemia Studies in Bethesda, Maryland, in September.

Dr. B. J. Kennedy, Associate Professor of Medicine, was guest lecturer at the Eleventh Annual Scientific Meeting of the Detroit Institute of Cancer Research October 29, speaking on "The Physiological Responses During Hormone Therapy of Breast Cancer."

At a meeting of the American Board of Dermatology in Detroit on October 16, Dr. Francis W. Lynch, Professor and Director, Dermatology, was elected President for the ensuing year. Among successful candidates in the examinations of the Board were Ramon Fusaro, Instructor, and James Tuura, Clinical Instructor, in the Division of Dermatology.

Along with two other American scientists, Dr. Frank Morrell, Assistant Professor, Psychiatry and Neurology, was invited by the Academy of Sciences of the USSR to attend an International Colloquium on Neurophysiology in Moscow, October 6-19. (For his report, see this BULLETIN, pp. 120-132.) Dr. Morrell also attended the International Seminar in Neurophysiology at Salpetrière in Paris and visited neurophysiological laboratories in England, France, Italy, Denmark, and Czechoslovakia, as well as the Soviet Union, returning to the University early in November.

MISS RUTH E. GROUT, Professor of Health Education in the School of Public Health, has been awarded the Cleveland Health Museum's Elisabeth S. Prentiss national award in health education for 1958. The award, "to Ruth E. Grout, M. P.H., Ph.D., Friendly Master-Teacher," was presented October 28.

A citation and an honorary fellowship in the American College of Dentists were presented to DR. WALLACE D. ARMSTRONG, Head, Physiological Chemistry, at the organization's annual convention held in Dallas in November.

In recognition of his "outstanding achievements in the fields of hospital administration, public health and in improving licensing laws," MR. RAY M. AMBERG, Director of the University Hospitals and President of the American Hospital Association, was honored at a dinner in St. Paul November 7. Hosts at the dinner were members of the Minnesota Hospital Association.

DR. JAMES MARVIN, Associate Professor, and DR. DONN G. MOSSER, Associate Professor and Director, Division of Radiation Therapy, addressed the Minneapolis District Dental Society in September on "Radiation Hazards of Dental Practice. Dr. Mosser and DR. MERLE LOKEN, Assistant Professor, Division of Radiation Therapy, presented a paper on "Relative Biological Efficiency of Various Types of Ionizing Radiation," at the International Congress of Radiation Research at Burlington, Vermont, last August.

In addition to having been elected an affiliate member of the Royal Society of Physicians, London, DR. JOHN J. BITTNER, Professor and Director, Division of Cancer Biology, addressed the Symposium on Viruses and Cancer of the Seventh International Cancer Congress in London last July. In September he spoke at the University of Michigan Medical Center's annual cancer retreat, and on October 3 he participated in the seventy-fifth anniversary observances of the University of North Dakota by talking on "Experimental Mammary Cancer in Mice with Reference to the Human Problem."

PROF. W. LANE WILLIAMS, formerly associate professor of anatomy, has assumed the chairmanship of the Anatomy Department, University of Mississippi Medical Center, Jackson, Miss. On January 1, DR. BERRY CAMPBELL, Professor of Anatomy, will take the position of Research Professor of Neurology at the College of the Medical Evangelists, Los Angeles.

An alumnus and former faculty member of the College of Medical Sciences, DR. ROY G. HOLLY, has been elected a Fellow of the American Association of Obstetricians and Gynecologists. In May he will become an Associate Examiner for the American Board of Obstetrics and Gynecology. Dr. Holly is now Professor and Chairman of the Department of Obstetrics and Gynecology at the University of Nebraska College of Medicine.

IN MEMORIAM

DR. SILAS C. ANDERSEN, '24,
Minneapolis, Minnesota

DR. IRVING J. GLASSBERG, '34,
Minneapolis, Minnesota

DR. FRANK LAWLER, '12,
Minneapolis, Minnesota

DR. DONALD R. READER, '38,
St. Paul, Minnesota

CAPTAIN ERNEST B. SWANSON, '56,
Truax Field, Madison, Wisconsin

DR. LEON A. WILLIAMS, '97,
Minneapolis, Minnesota

Faculty Publications

BRADLEY, S. G. and ANDERSON, D. L.: Taxonomic Implication of Actinophage Host-Range, Science 128:413, 1958.

BROZEK, J.; MORI, H.; and KEYS, A.: Estimation of Total Body Fat From Roentgenograms, Science 128:901, 1958.

BROZEK, J. and TAYLOR, H. L.: Psychological Effects of Maintenance on Survival Rations, Am. J. Psych. 71:517, 1958.

LICHSTEIN, H. C.: On the Specificity of Biotin in the Metabolism of Propionibacteria, Arch. Biochem. 77:378, 1958.

LYON, R. H.; LICHSTEIN, H. C.; and HALL, W. H.: Influence of Age on Metabolic Activity of *Mycobacterium tuberculosis*, Proc. Soc. Exp. Biol. & Med. 99:79, 1958.

SIMONSON, E.: Adaptation to Glare, Am. J. Ophthal. 46:353, 1958.

TAYLOR, H. L. and KEYS, A.: Criteria for Fitness and Comments on Negative Nitrogen Balance, Ann. New York Acad. Sc. 73:465, 1958.

TUNA, N. and FRANTZ, I. D., JR.: Fatty Acids and Atherosclerosis, U. of M. Med. Bulletin 29:479, 1958.

WILKINSON, C. F., JR.; EPSTEIN, F. H.; KEYS, A.; KINSELL, L. W.; POLLAK, O. J.; and STARE, F. J.: Panel Discussion on Lipid Metabolism in Cardiovascular Disease, J. Am. Geriatrics Soc. 6:451, 1958.

ZINNEMAN, HORACE H.; JOHNSON, JANET J.; and LYON, RICHARD H.: Proteins and Mucoproteins in Pleural Effusions, Am. Rev. Tuberc. 76:247, 1957.

ZINNEMAN, HORACE H. and ROTSTEIN, JEROME: A Study of Gamma Globulins in Dystrophia Myotonica, J. Lab. & Clin. Med. 47:907, 1956.

WEEKLY CONFERENCES OF GENERAL INTEREST

Physicians Welcome

Monday,	9:00 to 10:50 A.M.	OBSTETRICS AND GYNECOLOGY Old Nursery, Station 57 University Hospitals
	12:30 to 1:30 P.M.	PHYSIOLOGY- PHYSIOLOGICAL CHEMISTRY 214 Millard Hall
	4:00 to 6:00 P.M.	ANESTHESIOLOGY Classroom 100 Mayo Memorial
Tuesday,	12:30 to 1:20 P.M.	PATHOLOGY 104 Jackson Hall
Thursday,	11:30 A.M. to 12:30 P.M.	TUMOR Todd Amphitheater University Hospitals
Friday,	7:45 to 9:00 A.M.	PEDIATRICS McQuarrie Pediatric Library, 1450 Mayo Memorial
	8:00 to 10:00 A.M.	NEUROLOGY Station 50, University Hospitals
	9:00 to 10:00 A.M.	MEDICINE Todd Amphitheater, University Hospitals
	1:30 to 2:30 P.M.	DERMATOLOGY Eustis Amphitheater University Hospitals
Saturday,	7:45 to 9:00 A.M.	ORTHOPEDICS Powell Hall Amphitheater
	9:15 to 11:30 A.M.	SURGERY Todd Amphitheater, University Hospitals

For detailed information concerning all conferences, seminars, and ward rounds at University Hospitals, Ancker Hospital, Minneapolis General Hospitals, and the Minneapolis Veterans Administration Hospital, write to the Editor of the BULLETIN, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14, Minnesota.