August Krogh: 1874–1949

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AUGUST KROGH was born in Grena, a small town in Jutland, where his father owned a brewery. His mother took care of his early education, and he went to school rather late. He became a Master of Science in zoology in 1899 and received his Ph.D. in zoology from the University of Copenhagen in 1903.

After 1899 he worked as assistant at the Physiological Institute under Christian Bohr, still known to us in physiology for his fundamental discovery in respiration, the "Bohr Effect," and in recent years known to us more generally through his distinguished son, Niels Bohr. It was natural that Krogh's thesis dealt with a respiratory problem, "On the Skin and Pulmonary Respiration of the Frog." It was published in the *Skandinavisches Archiv f. Physiologie,* and has proved a permanent addition to our knowledge.

At that time Christian Bohr was the chief champion of the theory that gases, especially oxygen, were secreted by the lung epithelium into the blood. Krogh accepted this theory, but he and Bohr agreed it was based on inconclusive evidence. In 1905, using methods of analysis developed mainly for work in insect physiology, he determined to search for more decisive evidence through studies of the tension of O_2 and CO_2 in the blood and in the alveolar air. This work was continued until 1910, much of it in collaboration with his wife, Marie Krogh, whom he married in 1905 while she was a medical student. The results led steadily away from the secretory theory and to convincing evidence that gas transport depended upon simple diffusion.

In 1908 he became lecturer in physiology at the University of Copenhagen and in 1910 was given a small laboratory of his own. This he named The Laboratory of Zoophysiology, changing from the original designation, Animal Physiology, in order to reduce attention from the antivivisectionists. The laboratory received in 1910 was occupied by Krogh and his pupils until 1928, when he moved into the beautiful new building which was given to the University of Copenhagen by the Rockefeller Foundation principally because of his accomplishments in physiology and in the fundamental understanding of medical problems.

Krogh's finest work was done in the original laboratory, although until his death he was steadily active with his own hands and at any time might have again been found in the midst of epoch-making discoveries. He had an abiding love for experimental work, which asserted itself wherever he was.

The first laboratory was in part of a solid block of Danish houses at Ny Vestergade 11. The quarters had been the university laboratory of bacteriology. Structurally, they offered exactly the same possibilities for efficiency and comfort as would be supplied by a large American house in the center of a heavily populated block in any of our large cities.

Krogh and his family lived on the two upper floors, thus having a proximity to the laboratory he felt most important. Indeed, I remember he told me in 1926 he would not move into the new quarters which were being built unless they included a place to live. This feeling did not arise from motives of comfort or economy. It was the expression of his total immersion in the affairs of the laboratory and his unwillingness not to be able to go and come at any time.

The laboratory was very small. No one, the Professor included, had a room to himself. Paul B. Rehberg, Krogh's assistant during my year in Copenhagen, did that winter occupy a small room alone, but the door was never shut, and at any time it was clear someone might go in with him.

In 1926–1927 A. N. Richards, Edward D. Churchill, and I occupied a room together. There was a large table in the center and old-style laboratory desks were on one side, together with a sink supplying cold water. Hot water was heated over an old coal stove in one corner, where a kettle was always in place. If we wanted more hot water or wanted it in a hurry a gas ring was available. We washed our own glassware and at one time I had a lot of it. I cannot remember we suffered from this!

In this room and two other small ones adjoining it, Krogh initiated, and to a large degree carried out, his observations upon the capillaries, for which he received the Nobel Prize in 1920. This work had somewhat the same sort of impetus as his first researches on gas transport. He was examining the diffusion of oxygen out of blood and into muscle. Gradually he became aware that, given the capillary area apparently available at rest, it was impossible to obtain the amounts of oxygen used by the muscle at work. In explanation he thought that capillaries in working muscle not only dilated but that vessels, closed during rest, became patent, so that the capillary surface for gas exchange was enormously increased and the muscle was enabled to work in an environment wholly suited to activity. The many investigations through which this first demonstration led Krogh and his pupils do not require comment. In the main, they were summarized in his Silliman Lectures at Yale in 1922 and published in his monograph, "The Anatomy and Physiology of the Capillaries."

The man himself was modest and informal. He possessed the simple directness of thought and approach that accompany absolute honesty. I remember how each morning about ten he drifted noiselessly downstairs in his old carpet slippers and entered the laboratory. He came to each of us in turn, always shook hands, and then at once began to talk of our work, which was never out of his mind. He had questions for us and suggestions as to progress and he was delighted if we came forward with posers for him. The experiments in progress were more or less integrated, but each worker owned his problem, and, although Krogh usually suggested the research, he never allowed his name to appear on the paper unless he had actually taken part in the work. The list of his publications is formidable, extending through 48 years of almost unbroken activity. He abhorred "directors" of laboratories, believing that a man responsible for a laboratory had the privilege of acting as a sort of enzyme to help produce results but had no place as the principal figure in the task.

After 1910, when Krogh became independent in the Ny Vestergade laboratory, I have been able to count over twenty Americans who worked in the new laboratory, and of this number all except two became professors or heads of departments. With the possible exceptions of Sir Joseph Barcroft and Sir Thomas Lewis, I believe August Krogh dealt with more American students than any of his contemporaries. His personality and his influence were never lost to us, nor did he ever cease to be interested in what each of us was doing.

He spoke and wrote English almost perfectly. On his visits to my house I remember how assiduously he went through *The New Yorker,* never permitting a phrase to escape him. His sense of humor was keen, and he appreciated the American idiom. He read many American books and was devoted to Mark Twain, William Prescott, and Francis Parkman—the last two fed his interest in archaeology. During the last twenty years of his life Krogh came frequently to this country. As he entered our laboratories, all were conscious of his quiet friendliness, and of the readiness with which he listened to and examined the work being done. He had great sagacity and directness in planning experiments. He was an excellent technician and deviser of apparatus, but he was completely ruthless in making it as simple as possible. The beauty of mechanical things attracted him, but he considered refinements in apparatus unessential to the problem at hand to be expressions of weak intellect, and they never interested him.

From 1901 until about 1917, Krogh's investigations were largely in the field of respiration and gaseous metabolism, and students who went to him represented this aspect of physiology. His interest, however, was inclusive, and he never forgot the breathing and energy metabolism of insects, which had intrigued him at the beginning of his career and which, after he retired from his professorship in 1944, became his entire occupation in the small private laboratory he had constructed.

Krogh's absorption in physiology did not preclude other activities. He was a faithful and influential member of the university faculty and of the Danish Royal Society. In March, 1949, a bit before his final illness set in, he wrote me describing the sort of action which was characteristic of him, though unexpected in so quiet and contained a man.

> I caused a great stir in Denmark by resigning on Jan. 14th from our Roy. Soc. because I could not persuade them to go in actively to improve conditions of scientific work in this country. The whole of the Danish press commented favorably on this step and I feel sure that in the long run it will prove useful. At least it has shown the authorities that if they want to do something positive public opinion will be behind them.

In 1922, when in this country, he learned all he could about the production of insulin and on returning to Copenhagen he joined Hagedorn in the founding and construction of the Insulin Institute, which supplied and continues to supply the drug to Scandinavia and much of Europe, besides notably advancing research on diabetes.

The second world war was an incredible experience to him. He was a warm admirer of German science and had many German students. The intellectual descent of Germany into Nazism was to him impossible. When the Nazis took Denmark and Norway and attempted to impose an ignorant dictatorship upon these highly cultivated and free-thinking people, he joined his friends in constant, silent revolt. Had he been younger his participation would certainly have been active, and he would have suffered physically as did his associate Rehberg. In October, 1944, Krogh wrote:

> I don't think I have had a word from you after the terrible April 1940, but I have taken the opportunity to

write you at least once during a visit to Sweden. Now again I am here, and this time I shall have to stay until Denmark is liberated. About the middle of June I had an intimation of imminent danger and had to go ''underground,'' which in my case meant going about in North Zealand on my bicycle and staying for periods not too long with various friends and relatives. I am sorry to say that I had not really deserved this honour, having done very little towards the cause, and I fear it was only because I was considered ''prominent'' that I might be worth ''liquidating.'' I had arranged to spend the summer at a small and secluded limnological laboratory, when I received word from Stockholm that my son-in-law, Christer Wernstadt, was very seriously ill, and could I come. After deliberation with well-informed persons it was decided that I should apply for regular visas and try to come ''legally'' to Sweden, and this succeeded in such an incredibly short time that there is a strong suspicion that the German official in question knew of the danger and wished to be helpful. Anyway I arrived safely on July 9th.

In addition to the Nobel Prize, August Krogh received honorary degrees and memberships in scientific societies from many parts of the world. It is our pleasure that he was one of those given the doctorate at the Harvard Tercentenary in 1936, and thus, in addition to having had a hand in the training of eight full professors at Harvard, he appears upon the rolls of the university.

Those who knew him will never forget this man and those not so fortunate will ever gain inspiration from his clear-sighted and classically simple observations.

Technical Papers

A Limitation on the Ultracentrifuge Separation-Cell Technique[1]

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The ultracentrifuge separation cell has been increasingly utilized in recent years in investigations of the biological activity associated with certain high molecular weight solutes (*2*, *3*, *8*). In this analytical cell a porous plate overlaid with filter paper divides the cell into two compartments. This permits occurrence of analytical sedimentation, observed by the usual optical methods, but prevents remixing of the contents of the two chambers at the end of an experiment. The sedimenting boundary of the characteristic substance suspected of being biologically active may then be brought to various known positions in the cell in different experiments, the rotor rapidly decelerated, and the biological activity remaining in the top compartment of the cell determined. If one finds that the residual activity is exactly proportional to the amount of the characteristic substance remaining in the top chamber, one has apparently eliminated the possibility that impurities of either significantly smaller or significantly larger sedimentation rates than that of the characteristic substance are the active principles.

It is not clear, however, that this conclusion is justifiable under the following set of circumstances. Let us suppose that we have a solution containing a characteristic substance (hereinafter referred to as CS) in relatively high concentration (1–10 mg/ml), together with a very small amount of an active principle (AP), which is responsible for all of the particular biological activity in this mixture. Let us further assume that the sedimentation constant of the AP is larger than that of the CS. Upon performing a separation-cell experiment with this mixture, might not the small thermal gradients occurring during sedimentation, or the vibration of the rotor, be sufficient to disrupt the AP sedimenting boundary, since the density gradient across this boundary would be very small? Furthermore, might not the AP then be distributed relatively uniformly ahead of the stable CS boundary, but not be convectively transported across it? Under these circumstances, the gradient of activity through the cell might very nearly coincide with the gradient of concentration of the CS, creating the illusion that the CS is the active principle.

In order to examine this problem, which is of considerable interest, for example, in the study of plant viruses (*2*), we must know more about the behavior of very dilute solutions in the ultracentrifuge. The usual optical methods for determining sedimentation rates are not sensitive enough to permit the study of solutions of concentration lower than about 0.1 mg/ml. Bacteriophage particles, however, offer the possibility of studying this problem. Their concentrations can be followed accurately by infectivity measurements in extremely dilute solutions. Despite the fact that some of these bacteriophages have a morphology which makes the term ''molecules'' inapplicable to them, they behave like protein molecules in the usual sedimentation and diffusion

[1] Presented before the American Chemical Society at the meeting in Philadelphia, April 9–13, 1950.

[2] Postdoctoral research fellow, National Institutes of Health, United States Public Health Service.

[3] Contribution No. 1427.