THE

ANATOMY AND PHYSIOLOGY OF CAPILLARIES

BY

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With a new introduction and

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PREFACE TO THE REPRINT EDITION OF 1959

> "There are men who express the age and the milieu in which they were educated but who, by the intensity of their imagination, the sweep of their knowledge, and their astounding versatility, rise high above their era and their neighbors so that they inhabit both time and eternity at once. When we analyze their minds we can identify nearly all the component elements tracing this to family and that to school and the other to social climate, and yet the compound is far more than the sum of all these elements; richer, intenser, different in quality as a diamond is different from carbon." *

This quotation describes to perfection the reason for reprinting in 1959, and unaltered, a monograph written by Professor August Krogh in 1929. This book, like its first edition of 1922, was out of print much too soon after publication and both have been almost unobtainable for many years. Now, thanks to the Hafner Publishing Company, young physiologists and clinical investigators can have again the privilege of placing this book on their shelf of classics for ready reference, stimulation and emulation.

Before this synthesis by Professor Krogh the development of ideas concerning the several functions of the blood capillaries consisted of a series of parallel, but not yet related, lineages of research in histology, physiology and pathology. Until 1922 there had been no comprehensive theory. Fortunately for all those interested in the genesis of ideas in science, Professor Krogh's own reminiscences of this period are available to us in the form of a lecture given at the Harvard Medical School in 1946 and published in ISIS in 1950. This account, reprinted below, relates the sequence of circumstances and thought that

* From "Man's Unconquerable Mind" by Gilbert Highet, Columbia University Press, 1954.

led to the formulation of a theory of capillary function and then to the experimental testing of that theory. The new experiments thus stimulated, together with Professor Krogh's intuitively penetrating synthesis of older studies, as summarized in this monograph, promptly captured, as few books have, the attention of physiologists, pathologists, clinical investigators and clinicians the world over. Yet this volume represents only one of the many areas of biology that were illuminated by Professor Krogh's imagination, knowledge and investigative versatility. Therefore, the excellent biography written by Dr. Paul Brandt Rehberg, his nearest assistant and colleague, has been added to this preface so that new readers may know the man and his other contributions to biology.

When this monograph on the capillaries is compared to Professor Krogh's other books one finds that he wrote "much more freely, much more *con amore*" as Dr. Rehberg expressed it. He seems to be an artist painting a canvas of ideas in minutest detail wherever possible, but still willing with large brush strokes or even with exploratory pencil sketches, to let the picture evolve fully rather than omit any challenging theoretical or practical implication. This is the reason for its provocative eliciting, from others, researches designed to amplify, test, or modify specific propositions.

As these studies have unfolded during the past 30 years, their basic concepts have been both confirmed and extended. On the other hand, as is true in all science, some of the quantities and some corollaries concerning mechanism have necessarily changed as new methods became available. Most controversy has focused on the phrase "independent contractility of the capillaries" and on the role of the "Rouget cell." If, however, we simply substitute the phrase "independent variations of capillary blood flow" and substitute for Rouget cells "certain scattered smooth muscle cells of metarterioles and arterio-capillary sphincters," then even this criticism becomes merely a matter of new classifications, changing definitions and, in part, semantics. The basic concept remains unchanged.

Three decades have also added quantification of filtration, absorption and diffusion, together with more detailed descriptions of their respective, and simultaneous, roles in maintaining constancies of (a) solvent volumes and (b) solute concentrations. The size of pores in the capillary wall was estimated by Professor Krogh (p. 326) to lie between 50 and 2000 Angstrom units. This figure is still uncertain and may well differ widely depending upon the region of the body studied, the method of study and the presence or absence of injury.

Determinations by physical chemists of the dimensions of the chief plasma proteins, many studies of capillary filtrate, Drinker's researches on lymph proteins and still more recent studies using radioactively tagged albumins or globulins have all supported the view that at least some pores must have diameters of more than 40 or 50 Å. From filtration and diffusion data, and assuming cylindrical pores traversing the capillary wall itself, Pappenheimer's estimate is 60 to 90 Å in normal limb capillaries. Using dextrans Grotte has postulated, in addition, certain "leaks" with diameters of 240 to 700 Å, less numerous in cervical capillaries and more numerous in hepatic capillaries. Electron microscopists are finding even larger openings in the walls of some capillaries, e.g., liver and kidney, while in other regions pores seem to be absent. This problem is still unsolved and is testing the resolving power of the electron microscope to its uttermost.

These are only examples of the many areas in which outstanding gaps in quantitative information were brought clearly into view by Professor Krogh as he developed corollary after corollary up to the very limit permitted by the data then available. It is this fertile, but controlled, imagination which makes Professor Krogh's "Anatomy and Physiology of the Capillaries" an inspiring model to young investigators in any field and in any decade.

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February, 1959

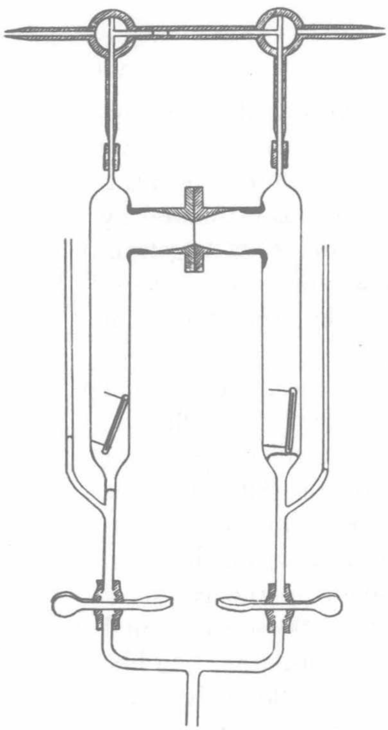

FIG. 3

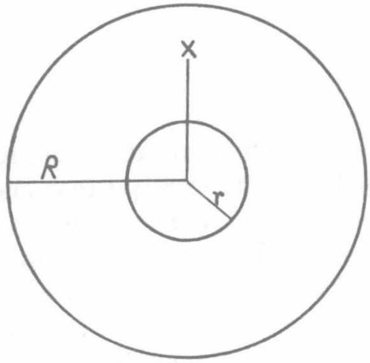

FIG. 5

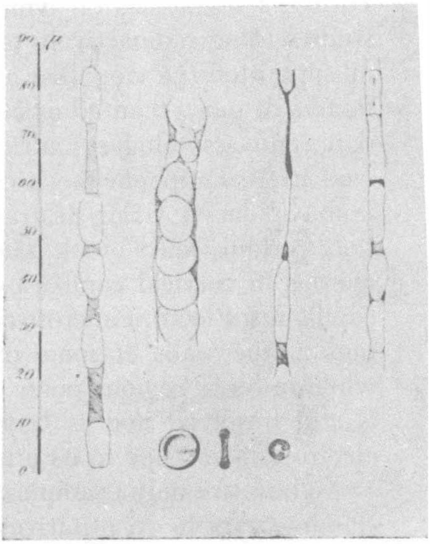

FIG. 6

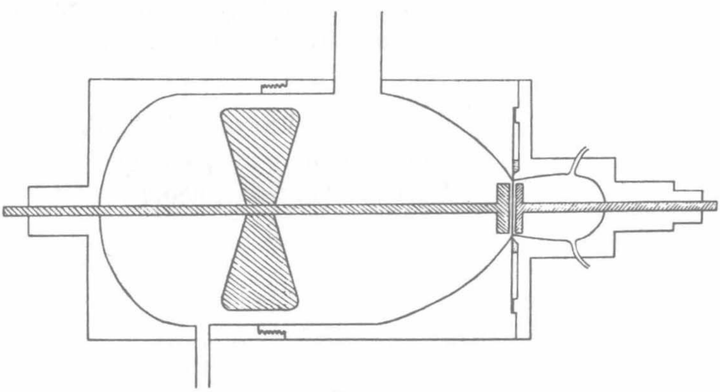

FIG. 4

Reminiscences of Work on Capillary Circulation *

A lecture to the students in the Harvard Medical School, 1946

BY AUGUST KROGH

MY very close friends, Dr Cecil Drinker and Dr E. M. Landis, suggested to me that I might tell you about the background for, and history of, my work on capillary circulation. This suggestion did not very much appeal to me, but on second thought I found that it might be a useful thing to do and therefore consented. I have to go back rather far in order to show you the train of circumstances leading up naturally and almost inevitably to this study.

I graduated in Zoology in 1899, but I had become interested in physiology as a young student in 1895 and had been admitted in 1897 to the laboratory of Professor Christian Bohr, the father of the physicist Niels Bohr. Immediately after graduation Bohr gave me the job as assistant in his laboratory. (It may interest you to know that the salary on which one could then live in Denmark would correspond to $250.00 a year.) Christian Bohr was the chief champion of the theory that gases, and especially oxygen, were "secreted" by the epithelium of the lungs into the blood. I accepted this theory, but we were agreed that the experimental evidence was scarcely conclusive and should be improved; about 1905 I proposed, in order to obtain more decisive evidence, to undertake studies of the tensions of oxygen and CO_2 in the alveolar air and in the blood by means of methods which I had developed mainly for studies on insects. This work, carried through by Mrs Krogh and myself during the years 1905–10, varied in different ways, and led to the unexpected result that no evidence could be found for any secretory work, while the evidence for gas transport by simple diffusion seemed to be quite convincing. You will understand, I think, that although we had worked only on lungs the results gave us a personal, but rather strong, belief that diffusion would be found almost everywhere to be the mechanism for gas transport in organisms. This became, as I will presently show you, an important factor in the subsequent work on capillaries.

Another important factor was the study, undertaken in collaboration with my friend I. Lindhard, on muscular work in man. I was made a lecturer in physiology in the Science School of the University in 1908, and somewhat later Lindhard was made a lecturer on the theory of Gymnastics. I was given a small laboratory in 1910, but Lindhard had none and neither of us had any assistance. We therefore decided to work together and to study muscular work in my laboratory. Methods were gradually

* Reprinted with permission of the editor of ISIS.

developed, and the one most important from our present point of view was a method for determining the circulatory minute volume in man by means of nitrous oxide.

This method could be used both on resting subjects and during fairly heavy muscular work and, although it was perhaps not too accurate, it certainly did show the enormous increase in the total circulation rate induced by muscular work and clearly necessary to supply the amounts of oxygen actually used up. It also became clear at a fairly early stage that this increase in oxygen consumption must take place mainly in the working muscles (including the heart) and must reduce the oxygen content of the venous blood coming from these muscles to a very low figure, at least below 20 per cent. of the arterial, while during rest the venous blood would be half to two-thirds saturated with oxygen.

The third factor was a book on the "Respiratory Exchange of Animals and Man," which I was asked to write for a series of biochemical monographs being published in England. The book was to deal only with the respiratory metabolism during rest; from the available literature it was concluded that the oxygen tension in tissues and particularly in muscles was probably very low and that the tension might be the limiting factor for the rate of oxidations.

The final arterioles in muscles are more or less at right angles to the muscle fibres; they branch out into a comparatively large number of capillaries which run parallel to the fibres and finally — that is after about ½ mm — unite into small veins which are again at right angles to the fibres. On a cross section vertical to the fibres, the injected capillaries show as stained dots between the fibre cross-sections, and sometimes even running inside a fibre. (See fig. 1.)

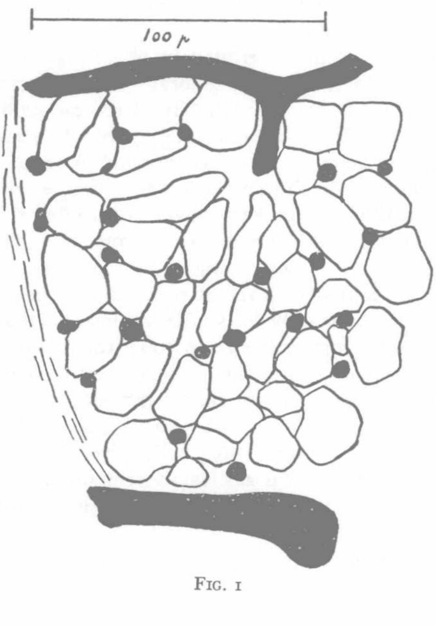

FIG. 1

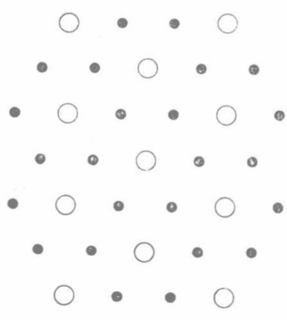

FIG. 2

You will understand that, while I had undertaken to write only on the metabolism of organisms and their parts at rest, I could not, with the background I have sketched to you, well avoid speculating on the function of this mechanism during work; and such speculations could not, with the premises enumerated, avoid bringing me into considerable difficulties. I felt pretty certain that the supply of oxygen to the fibres must take place by diffusion from the capillaries. Every capillary could be conceived as a tube with walls permeable to oxygen and surrounded by a cylinder of tissue through which oxygen would diffuse toward the periphery, being reduced all the way by the metabolic processes. Now, if the supply was just right during rest, so that the oxygen pressure at the surface of the cylinder would be negligibly small no increase in the rate of flow through the same capillaries could make it sufficient during work, when oxygen was used up, say, at a tenfold rate. If, on the other hand, the density of the capillary network was sufficient to provide by diffusion all the oxygen necessary during heavy work, the arrangement would be very wasteful during rest and would result in an oxygen pressure in the tissue practically identical with that of the venous blood.

One day, while pondering over this problem in the University library, the idea suddenly struck me that the anatomical arrangement would work beautifully if it could be assumed that during rest, only a certain small fraction of the capillaries, suitably distributed, are open to the passage of blood while all the rest are closed; and that increasing numbers are opened with increasing work. This mechanism would become ideal if local lack of oxygen forced the opening-up of the nearest capillary, while a certain higher concentration of the dissolved gas allowed the capillary to close, so that, in the resting muscle, or during moderate work, capillaries would open and close in a certain alternation. While discussing this idea the same evening with my wife, who was always my nearest colleague, I illustrated it with a diagram something like that in fig. 2, and the outcome was that it seemed worth while to make an experimental test.

At this stage allow me a few words on the role of ideas. An idea or an hypothesis is a very insignificant, but very essential, part of almost any scientific investigation. Most ideas are wrong and almost all are faulty; but even so, experiments have to be planned so as to give an answer, if possible, to the question: right or wrong. Most ideas are quite vague. Nothing, short of experimentation, helps more to clarify them and bring them to the testing stage than discussion with a sympathetic and critical colleague.

In the case under discussion, the experiments to test the idea had to be rather diverse in nature and I must describe the studies undertaken *seriatum*, while they were in reality pursued alternatively as material became available, as methods were developed, and as apparatus was constructed and used.

A fundamental problem was to measure the diffusion of oxygen through tissues, and especially through muscle, to make sure whether the supply of oxygen could or could not be a case of oxygen diffusion. These measurements presented a peculiar difficulty. Christian Bohr had introduced the conceptions of invasion and evasion of gases into and out of fluids, in the sense of overcoming a specific resistence against passing the very surface of the fluid to or from the gas phase, and he had attempted to measure invasion constants. I had been able to show in earlier work that his invasion constants were too low because they included an undetermined amount of diffusion, but it was still possible that invasion might interfere with diffusion-rate determinations when these were made from one gas phase to another, which was technically quite a simple problem, to be solved by means of the apparatus shown in fig. 3. A membrane of muscle, connective tissue, gelatine, or other substances, and of known area and thickness, was placed between two glass containers of which one was filled, say, with pure oxygen and the other with pure nitrogen. The gas in each could be mixed by the plates shown in the figure; these could be moved from outside by means of magnets, an iron wire being sealed into the glass tube. By means of an oil-drop manometer, the pressure difference between the two sides of the membrane causd by different diffusion rates of the two gases concerned could be kept at zero and, after a suitable time, the gases were taken out and analyzed.

The determinations made in this instrument had to be compared with measurements in which no gas phase was involved. Such measurements were undertaken in the apparatus shown in fig. 4. The large chamber would contain any suitable fluid kept well mixed right up to the membrane surface and saturated with a gas. In experiments with O_2 or CO the small chamber holding 1.5 ml was filled with a reduced haemoglobin solution and the gas content determined after a suitable time, when the gas tension was still negligibly small. No Van Slyke machines existed at that period, but very reliable results could be obtained by the analytical methods developed by Barcroft.

All the determinations were fairly consistent and showed no detectable influence from the evasion and invasion processes postulated, and, as a matter of fact, special experiments showed that these processes are extremely rapid compared with diffusion rates. The diffusion rate for oxygen in muscular tissue was defined as the number of milliliters penetrating per minute through a thickness of 1 micron and a surface of area 1 cm^2, when the pressure difference is 1 atmosphere. This was found to be on an average 0.14 ml at 20° C and increasing about 1 per cent. per Centigrade degree. The diffusion in water and even in 15 per cent. gelatine is much more rapid (0.28), and that in connective tissue slightly slower.

The result was utilized as follows. We assume each capillary to supply, by diffusion, a cylinder of tissue surrounding it in which O_2 is used up at a certain rate; then a mathematician can work out a formula from which the necessary O_2 tension-difference between the capillary and the circumference of the cylinder can be calculated. A number of injection preparations of muscles from different animals were made and the capillaries counted in cross sections. From the countings, the average cross-sectional area supplied by each was calculated and showed only moderate irregularities in the distribution of capillaries. This area was taken as a circle and its radius (R) made out (fig. 5). The average diameter of capillaries was assumed to be equal to the red cell diameter ($2r$) and these figures, together with the most probable figure for the metabolism of the muscular tissue, were inserted in the formula. This method of calculation is quite rough, but, as shown in the last column of Table I, the pressure differences found are in all cases so low, well below 1 mm of mercury, that there cannot be the slightest doubt that diffusion of O_2 from the capillaries — if they are all open — will always be amply sufficient.

TABLE I

Calculated Maximum Oxygen Tension Difference ($T_o - T_r$) between Blood & Muscular Tissues of Four Species[1]

	Weight (*kg*)	Metabolism (*cal/kg/hour*)	Number of capillaries per mm^2 cross-section of muscle	R (μ)	Diameter of red corpuscles ($2r$) (μ)	T_o–T_r (*mm Hg*)
Frog	0.04	0.4	400	28	15	0.25
Horse	500	0.5	1400	15	5.5	0.1
Dog	5	3	2500	11.3	7.2	0.2
Guinea pig	0.5	6	3000	10.3	7.2	0.3

Moreover, during rest a large number, and during work a decreasing number of capillaries *can be* closed without impairing the oxygen supply, provided the open ones are fairly regularly distributed — but are they? Direct observation seemed the only way to settle this point.

[1] From A. Krogh, The number and distribution of capillaries in muscles with calculations of the oxygen pressure head necessary for supplying the tissue, *Journal of Physiology* 52:409, 1918–1919.

Such observations were made or attempted in many different ways and I shall mention only some of them. The first were qualitative only. Suitable thin muscles in the frog were very cautiously made accessible to microscopic observation by transmitted light. Such muscles are usually quite pale and circulation is observed only in a few capillaries, while a few others may contain red corpuscles which do not circulate. Tetanization of such a muscle for a few seconds produces, after a latent period of 15–20 seconds, a greatly increased circulation and a large number of capillaries then become visible. In the course of some minutes the majority of these vessels again disappear from view.

Many observations were made both on frogs and on mammalian muscles in reflected light, by which vessels down to a depth of about ½ mm could be seen, and approximate estimates of the distance between open capillaries could sometimes be obtained. These varied in resting muscles of the frog between averages of about 60 microns in the *m. rectus abdominis*, which is always well supplied up to ½ mm. In resting guinea pig muscles the average distance was about 200 microns. Exposure and stimulation would always open up more capillaries, and when spontaneous contractions were occasionally observed in guinea pig muscles, the result would be the same.

Much time was spent in attempts to find a vital injection method which would make possible approximately quantitative estimations, the idea being that the capillaries that were open at the time of injection would become injected; a number of suspensions, mostly of stained micro-organisms were tested, but they were never quite satisfactory. Finally, India ink, dialysed for several days against Ringer solution to remove antiseptic substances added, was selected in spite of the fact that agglutination would set in after a comparatively short time. Several years later Dr Cecil Drinker worked out in my laboratory the use of graphite suspensions which were much more satisfactory. I shall not go into details, but only show a table of average results on the frog and the guinea pig.

TABLE II

Numbers of Capillaries & Oxygen Tension Differences ($T_o - T_r$) between Blood & Muscular Tissues of Frog & Guinea Pig during Rest & Exercise [2]

	O_2 consumed per minute in vol. per cent. of tissue	Number of capillaries per mm cross-section	R (μ)	$2r$ (μ)	T_o–T_r (*mm Hg*)	Capacity of capillaries per vol. per cents of tissue
FROG MUSCLE						
Minimum, Rest	0.03	10	180	4.4	10	0.015
Work	0.3	325	31	6.8	1.2	1.2
GUINEA PIG MUSCLE						
Rest	0.5	31	100	3	45	0.02
Work	5	2500	11	5	1.4	5.5
Maximum	10	3000	10	8	1.2	15

In the resting muscles of the frog with ten open capillaries per mm² there must be lack of oxygen in considerable portions of the muscle, but during work, with 325 open capillaries per mm² the oxygen pressure in the muscular tissue becomes practically equal to that of blood. Similar relations hold in the muscles of the guinea pig. The last column of Table II shows the total volume of capillaries in per cent. of tissue or, what amounts to the same, the percentage of capillary blood present in the muscles during rest and work.

These results make good the contention that the distances between open capillaries are closely related to the metabolic requirements, but of the shifting of open capillaries

[2] From A. Krogh, The supply of oxygen to the tissues and the regulation of the capillary circulation, *Journal of Physiology* 52:457, 1918–1919.

from one position to another in the resting muscle I was never able to obtain convincing proof. Such proof has only recently been brought by the much superior technique of Dr Melvin Knisely.

I would like to draw your attention to the figures in the table giving the average diameters ($2r$) of capillaries. In the resting muscles, these are very narrow and the red cells must suffer considerable deformation in the passage. This is well shown in fig. 6. The extreme pliability and perfect elasticity of the corpuscles is an astonishing fact.

These first experiments were followed, over a series of years, by many others describing the mechanisms by which capillaries contract or dilate, the diffusion of other substances through the capillary wall and the relation between these processes and the mechanics of the flow of blood through the capillaries.

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AUGUST KROGH*

NOVEMBER 15, 1874 — SEPTEMBER 13, 1949

P. BRANDT REHBERG

Schack August Steenberg Krogh was born in Grenaa, Jutland. His ancestors had emigrated from Holstein and Schleswig, where his father's family had settled as small farmers three hundred years earlier. Krogh's father was a brewer, though he had been trained as a shipbuilder. Ships and the sea were some of Krogh's unceasing interests.

Krogh, who was the oldest of six brothers and sisters, had already been taught to read and write by his mother at the age of five. Soon after his sixth birthday she wrote in a letter: "August reads almost too fluently, as he frequently out of sheer eagerness omits the signs. We have begun with German, geography and arithmetic. Next fall, if it please God, I shall hand him over to the secondary school in an adequate state; then he himself must take care of his education." Krogh's aversion to official punctuation remained characteristic of him; he put the punctuation marks as it pleased him. After the summer vacation, at the age of six, he was sent to a small secondary school. According to his own opinion, however, going to school did not markedly influence his development. Outside school he cultivated his early awakened interest in nature. At an early age he was interested in animals and for hours he would follow the behavior of insects and spiders. Likewise, with the help of Rostrup's *Flora,* he botanized eagerly in the surroundings of Grenaa. At the age of twelve he had read from beginning to end the large popular Danish encyclopedia available at that time. At this early age he also tried his hand at experimenting, performing—though not always successfully—the chemical and physical experiments he had read about. He had to content himself with the limited material within his reach in the small country town, and he himself assumed that this fact helped to develop his later remarkable ingenuity in improvising apparatus from the few and primitive things at his disposal. As a rule, Krogh's apparatus was inexpensive, and he maintained his economizing attitude even after large funds had been put under his control. Also he exhibited by this time a thorough or rather an exaggerated economy with paper; later in his life he used the tiniest possible scraps of paper, a habit which made it seldom easy for others to decipher his writing.

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* From the Zoophysiological Laboratory, The University of Copenhagen. This appreciation of Professor Krogh first appeared in Danish in the Year Book of the University of Copenhagen. At the request of the Editors, Professor Rehberg very kindly prepared an English translation for this *Journal.*

In 1889, when in his fifteenth year, he became a voluntary disciple in the navy. It was his intention to be a naval officer, partly because he could not advance in school until he was sixteen years old and eligible for the preliminary examinations. However, after an expedition with the inspection boat *Hauch* he renounced this plan, passed the preliminary, and later, in 1893, the final examination at Aarhus cathedral school. Krogh hesitated: should he study physics or choose zoology in which he had taken an interest through his older friend, the zoologist William Sørensen (who spent many holidays in Grenaa and with whom Krogh used to scour the fields)? He passed the university "prelims" and then wrote an extensive outline of his plans. With this he persuaded his father to give him permission to study zoology. At this juncture Krogh was fortunate: William Sørensen, who was ahead of his time in comprehending the general significance of physiology for zoology, suggested that Krogh should attend Christian Bohr's lectures for medical students. Krogh followed Sørensen's advice—a step which turned out to have a decisive influence on his future. After the very first lecture he understood that here was his proper field and, in 1899 when he received his master's degree, he was appointed assistant at Christian Bohr's laboratory of medical physiology at the University of Copenhagen.

However, prior to this appointment, Krogh had begun to devote himself to zoophysiological problems. As a student he investigated the hydrostatic mechanism of *Corethra* larvae, a peculiar type of mosquito larvae which, by means of completely closed air sacs acting as a swim bladder, is able to regulate its buoyancy in water in the same manner as fishes. Krogh did not solve the mystery of their curious organs, but for use in these studies he worked out a method for the microscopic analysis of small air bubbles which, however, was not published until 1911.[1] It is typical of Krogh's first publications that they are based on an understanding of physics which was rarely found in biological circles at that time. He wrote about the significance of turgescence for plants, hydrostatic conditions in the animal kingdom, gases in sea water, and sap rising in plants—frequently in the form of a criticism of the interpretations of other scientists whom he showed were lacking the necessary knowledge of physics. This ability to apply physical knowledge to biological domains remained typical of Krogh's work, which was always distinguished by a brilliant intuitive perception of physical conditions, especially in microscopic dimensions. In contrast, when he was forced to use chemistry in his work, one had the impression that his chemical knowledge was acquired knowledge.

Krogh's ability to find the cause of discrepancies in other investigators' results was well developed at that time and always played an important part in his scientific studies. Many years later, he himself explained his

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[1] On the hydrostatic mechanism of the Corethra larva with an account of methods of microscopical gas analysis. Skand. Arch. Physiol., 1911, *25*, 183.

view in the following way: "When experimental results are found to be in conflict with those of an earlier investigator the matter is often taken too easily and disposed of, for instance by pointing out a possible source of error in the experiments of the predecessor, but without inquiring whether the error, if present, would be quantitatively sufficient to explain the discrepancy. I think that disagreement with former results should never be taken easily, but every effort should be made to find the true explanation. This can be done in many more cases than it is actually done; and as a rule it can be done more easily than by anybody else by the man 'on the spot' who is already familiar with essential details, but it may require a great deal of imagination and very often it will require supplementary experiments."[2]

The time spent in Christian Bohr's laboratory became of utmost importance to Krogh through the insight he gained there into the significance of quantitative work and the necessity of proving whether a theory is quantitatively sufficient. Quantitative work was especially attractive to him, the more so when the existing technique was unsatisfactory and accuracy was paramount. This principle, together with physical intuition, was to be typical of much of his work.

Another ability, also of great importance for Krogh, was his capacity for "visual thinking," as he called it. He was able to see before him the image of an apparatus, projected into space; he could preserve this image, improve it, and get it to move. He made use of this ability when he constructed an apparatus, when he scrutinized the descriptions of other investigators' experiments, and when he reflected upon the way in which an organ functions. Krogh never made a drawing before having seen in this way the apparatus ready before him; if he drew at too early a stage he felt hampered. In a paper on "visual thinking" he described this habit of thought which he assumed to be the background of all his other abilities.[3] In this paper he also mentioned that his brain frequently worked unconsciously and he perceived many ideas during sleep. His memory was queerly specialized: animals, plants, and apparatuses were remembered directly while he, for example, was unable to recall special pages in a book or faces. On the other hand, he retained by heart—but purely intellectually—the quotations and verses which enchanted him, while he was unable to recollect chemical formulae.

Another special gift should be mentioned here, namely, that of observation. He was able to detect minute details, for example, in a microscopic picture of living tissue or in a complicated experimental arrangement. Thus, during his study of the capillaries, he worked with much lower

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[2] The progress of physiology. Am. J. Physiol., 1929, *90,* 243; also in Science, 1929, *70,* 200.
[3] Visual thinking. An autobiographical note. Organon, Warsaw, 1938, *2,* 87.

microscopic magnifications than any of his numerous collaborators, but time and again he surprised them by describing the details he could observe at low magnification.

Krogh's first extensive work, his thesis in 1903 on skin and lung respiration of the frog, appeared as a synthesis of his own zoological interests and Christian Bohr's principles of respiration physiology.[4] Here he showed that oxygen metabolism occurs primarily through the thin lung walls with their short diffusion path, while the more easily diffusible carbon dioxide escapes essentially through the skin. The dissertation shows strikingly Krogh's sense for quantitative viewpoints.

Krogh's investigation which was first to gain international renown is a good example of his typical abilities. The Imperial Academy of the Sciences of Vienna had offered a prize for investigations into the participation of free nitrogen in respiratory metabolism. This task required scrupulous accuracy and for a long time Krogh was concerned with it in his thoughts. Finally he arrived at the conclusion that it would be necessary to control the temperature in the respiration apparatus more accurately than usual. Therefore, the whole apparatus should be immersed in water, a procedure which would be feasible only if it were very small. Consequently, Krogh constructed a small apparatus, and it appeared that the results of previous investigators were erroneous because of faulty temperature control. In this investigation his unique capacity for designing apparatus, his critical sense, and his ability to work quantitatively were already fully developed. Krogh demonstrated that nitrogen does not participate in the respiratory metabolism, and he won the offered prize.[5] This treatise is an impressive example of his working method, which he later applied to his long series of investigations into respiratory physiology.

In his doctoral thesis Krogh pointed out that the respiration of toad's skin can be assumed to be due exclusively to diffusion, while, on the other hand, he wholly supported Bohr's views on lung respiration, stating that it occurs predominantly by means of secretory processes and is regulated by the nervous system. However, in the years to come, he became more familiar with respiratory processes and he came to realize that neither in his own works nor in those of other scientists could a valid proof of this view be found. With the methods available, no answer could be given to the serious controversial question of whether the gas exchange in the lungs takes place by a passive or an active process. New apparatus yielding much greater accuracy had to be constructed. The most important one was Krogh's microtonometer with its associated micro gas analysis ap-

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[4] *Frøernes Hud- og Lungerespiration.* København, Gyldendalske Boghandel, 1903, 114 pp.
[5] Experimental researches on the expiration of free nitrogen from the body. Skand. Arch. Physiol., 1906, *18,* 364.