# Ergebnisse der Physiologie
# Reviews of Physiology

# 65




Springer-Verlag Berlin · Heidelberg · New York

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Biologischen Chemie und experimentellen Pharmakologie

# Reviews of Physiology

Biochemistry and Experimental Pharmacology

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With 45 Figures

Springer-Verlag Berlin · Heidelberg · New York 1972

ISBN 3-540-05814-1 Springer-Verlag Berlin Heidelberg New York
ISBN 0-387-05814-1 Springer-Verlag New York Heidelberg Berlin

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Library of Congress Catalog Card Number 62-37142. Printed in Germany

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# Contents

# Einar Lundsgaard, 1899–1968

Poul Kruhøffer and Christian Crone

Einar Lundsgaard, professor of Physiology at the University of Copenhagen, was a leading figure in that dramatic chain of events which constituted what A. V. Hill called "the revolution in muscle physiology". By a major intellectual achievement he changed the concepts of metabolic energy transformation and he will forever remain one of the great figures in the gallery of Physiologists of Metabolism.

Lundsgaard was born in Copenhagen in Denmark just before the turn of the century as the son of a doctor in private practice. Among his ancestors were several men of law, mostly civil servants. His father had been occupied with research and had received the Gold medal of the University of Copenhagen for a scientific study of prostatic hypertrophy. Lundsgaard would later receive a similar distinction at the same university.

His mother, who was of the Salomon family, was a strong and dominating personality who made heavy demands on her children to do their duty and accomplish what was necessary to consolidate the social position. Altogether Lundsgaard grew up in a climate which was rather common among well-to-do middle class academics in the beginning of this century where hard work and concentrated intellectual effort were rated very highly. This atmosphere undoubtedly marked Lundsgaard—as so many others of his generation—and made of him a rather closed and even inaccessible person. In his youth he was a more outwardly directed person than later when a slightly depressive temperament became more evident. This led to a rather sceptical attitude towards the utility of science and also towards the increasing interest of politicians in academic affairs.

He looked upon research as a fundamentally personal effort and probably never felt really at ease in collaborative so-called team work. He had pupils, but never tried to create a "school". His most prominent Danish pupil was Herman Kalckar who in the thirties worked on phosphorylation in Lundsgaard's laboratory. Even Fritz Lipmann calls himself a pupil of Lundsgaard—although they never worked formally together.

Lundsgaard's special abilities as a scientist stemmed from an unusual talent to reduce a problem to its essence. He had an analytical mind with great sense for generalization and a striking flair for logical deductions. All

this gave him an unusual power for rigorous formulation of problems and for profound interpretations of experimental observations. These special intellectual capacities flourished in full richness when in the early 1930's he revolutionized the concepts of the chemistry of muscular contraction. Later, his rigorousness reduced his experimental zeal. It was as though he—by his penetrating analyses—hampered his own research by submitting potential experiments to the very hard test it was to pass through his analytical brain. As he once said when he received the great Scandinavian distinction, the Anders Jahre prize, "I have two Natures within myself, Aladdin and Noureddin. Although it is Aladdin who has brought me the most important results, I feel rather closer to Noureddin, who by intellectual and analytical achievement, won his victories."

Already as a medical student LUNDSGAARD began to work in the Institute of Medical Physiology in the University of Copenhagen. This institution, which had been founded by CHRISTIAN BOHR, was at that time in the hands of VALDEMAR HENRIQUES, whose main research fell within the realm of metabolism. LUNDSGAARD was a devoted pupil of HENRIQUES, whose fine character impressed him deeply, and he started research within his teacher's field.

LUNDSGAARD'S first scientific work dealt with the ability of protein and amino acids—administered in various doses and by various routes—to produce a rise in the blood sugar concentration in rabbits, dogs and human beings. The effects of ammonium salts were also studied.

These studies formed a natural starting-point for subsequent work which in 1929 brought him a doctorate of medicine. The subject was the *specific dynamic action of foodstuffs*, in particular that of proteins. The dissertation, written in Danish, gave a critical and very comprehensive survey of the literature and contained data from numerous experiments on the effects of amino acids and a number of nitrogen-free organic substances on the oxygen uptake of various animals. The most prominent observation was that various amino acids whether administered perorally or parenterally produced very nearly the same increment in oxygen uptake per gram of nitrogen administered; moreover, a similar increment was elicited by ammonium lactate, whereas sodium lactate had little effect on the oxygen uptake. Thus the findings clearly indicated that the action of amino acids to accelerate oxygen uptake is associated with the amino groups, not with the carbon skeletons. No definite conclusion was drawn as to the more intimate nature of the phenomenon, but LUNDSGAARD later (1942) investigated the effect of amino acids and ammonium salts on the $O_2$-consumption of isolated, perfused livers. Finding here increments in $O_2$-uptake per gram of nitrogen metabolized similar in magnitude to those observed in intact animals per gram of nitrogen administered he concluded that the high specific dynamic action of amino acids is mainly due to energy used in transformation of ammonia into urea.

By good fortune, one may say, LUNDSGAARD'S early investigations on the specific dynamic action became the breeding ground for his most important scientific contributions: the discovery of the *blockade of glycolysis by monoiodoacetate,* and the exploitation of this tool to show that *the energy of muscle contraction is based on phosphate bond energy.*

The good luck came during his studies on the specific dynamic action of various substances. He decided to investigate the specific dynamic action of monoiodoacetate. At that time there was great interest in the metabolic effects of iodinated compounds, because of the discovery of iodine in thyroxin. LUNDSGAARD was interested in glycine substituted with iodide, but could not get hold of the substance, so instead he used what he could get locally, monoiodoacetate. When injected into animals a universal muscle spasm developed ending with death of the animal and complete muscle stiffness (rigor). This observation became the starting point for important discoveries of the energetics of muscular contraction.

In a series of experiments and papers LUNDSGAARD demonstrated that lactic acid formation is not indispensible for muscle contraction and that other processes, including the splitting of creatine phosphate, serve as energy-suppliers more closely related to the contraction process proper.

The importance of LUNDSGAARD'S work for the advancement of muscle energetics can only be fully appreciated with some knowledge of the concepts which prevailed when his first paper appeared in Biochemische Zeitschrift in 1930; at this time he was thirtyone years of age. Some of the main points may be briefly outlined as follows:

Following FLETCHER and HOPKINS' fundamental studies (1907) on the formation and disappearance of lactic acid in muscles the view had become widely accepted that glycolysis constitutes the direct energy-supplying process for muscle contraction and thus is inseparably linked with the mechanical process. At the end of the twenties this view was still maintained by OTTO MEYERHOF and A. V. HILL, who had shared the Nobel Prize in 1923. The nearly constant relation between the mechanical performance and the lactic acid formation in contracting muscles (near constancy of "the isometric coefficient for lactic acid") was one of MEYERHOF'S prominent arguments.

In the latter part of the twenties there had been voices of doubt. In 1925 EMBDEN reported formation of considerable amounts of lactate in muscles *after* the termination of a tetanic stimulation under anaerobic conditions and therefore claimed that muscle contraction and lactate formation were not inseparably linked together. MEYERHOF, who—contrary to EMBDEN—used indirect stimulation, was unable to confirm these findings. He therefore strongly repudiated EMBDEN'S argument claiming that the post-stimulatory formation of lactate had been caused by overstimulation leading to a post-stimulatory contracture. Attempts by EMBDEN and co-workers to design experiments

giving more indirect support for their view received strong criticism from MEYERHOF and HILL.

Some important discoveries had been made within the few years preceding the appearance of LUNDSGAARD's paper. Creatine phosphate ("phosphagen") had been independently discovered in muscle by P. and G. P. EGGLETON and by FISKE and SUBBAROW in 1926. The EGGLETON's reported some breakdown of the substance during contraction, and resynthesis during aerobic recovery conditions. Two years later they described the breakdown to be greater, relative to lactate formation, in the earlier than in the later stages of activity. Breakdown during contraction and partial resynthesis during recovery in muscles exposed to anaerobic conditions was reported in 1928 by NACHMANSOHN working in MEYERHOF's laboratory. The heat of hydrolysis of creatine phosphate had been found by MEYERHOF and LOHMANN to be considerable (some 11–12 kcal/mole). In spite of these findings no definite role had been ascribed to creatine phosphate in muscle contraction—and this also applied to ATP (adenylpyrophosphate) discovered independently in muscle in 1929 by LOHMANN and by FISKE and SUBBARROW.

From MEYERHOF's monograph "Die chemischen Vorgänge im Muskel", which appeared 1930, it is evident that at the time of writing he was still convinced of the essential role of glycolysis in muscular contraction. It is equally clear that the recently acquired knowledge of creatine phosphate—including that provided by himself—was causing trouble and was only reconciled with the accepted view by means of some purely hypothetical assumptions. According to one of these creatine phosphate should undergo no actual breakdown during muscular contraction but only a "labilization" not associated with a release of the heat of hydrolysis.

When in his early studies, performed in Copenhagen, LUNDSGAARD subjected the rigor-muscles of monoiodoacetate poisoned animals to a closer examination, he found, by a simple colorimetric method, that they were no more acid than those of normal, resting animals; and that no shift in reaction towards the acid side occurred in them after death. Concordantly, the lactate concentration was found not to differ from that of normal, resting muscles and no post-mortal increase in lactate content could be demonstrated.

Realizing what a powerful tool monoiodoacetate might be in a closer inquiry into the chemistry of muscle contraction LUNDSGAARD went on to study in poisoned frogs the performance of muscles in which rigor had not developed; inactivation by denervation prior to the poisoning was found to delay markedly the onset of rigor and proved useful in securing muscles in this condition. It turned out that on electric stimulation they were capable of performing an appreciable number (50–100) of twitches without an increase in lactate content—while a rather large increase occurred in unpoisoned muscles

at a similar mechanical performance. This observation made it immediately clear that glycolysis is not essential for muscle contraction.

LUNDSGAARD went further in his first paper by showing that in poisoned muscles performing an exhausting series of contractions a complete breakdown of creatine phosphate took place. Simultaneously there occurred an equivalent increase in other organic phosphates (according to analysis mainly hexose-monophosphates) but no change in inorganic phosphate content. The last observation showed incontestably the untenability of MEYERHOF's postulate that creatine phosphate undergoes only labilization and no splitting during muscle contraction. Altogether the observations published in his first "muscle paper" formed a sound basis for LUNDSGAARD to advance the hypothesis that a splitting of creatine phosphate is the direct energy-supplying process for muscle contraction and that the process of lactate formation is initiated by this splitting and provides energy for a resynthesis of creatine phosphate. By this hypothesis LUNDSGAARD directed attention to *"energetically coupled reactions"* and to *a phosphorylated compound as an energy source.* These concepts became, as is well-known, immensely fruitful for biochemical research. It is natural to mention in this context that LUNDSGAARD was also the first to herald *oxidative phosphorylations.* This happened later, when, from the observation that the working capacity of monoiodoacetate poisoned muscles was appreciably greater in aerobic than in anaerobic conditions, he drew the conclusions that resynthesis of creatine phosphate can be driven by oxidative processes.

LUNDSGAARD informed MEYERHOF of his findings prior to publication, and in the wording of FRITZ LIPMANN, who was then working with MEYERHOF, the message "shook up the Meyerhof laboratory". It redounds to MEYERHOF's honour that his reply was an invitation to LUNDSGAARD to carry out further studies in his laboratory. So LUNDSGAARD went to the lion's den, which had just been moved from Berlin to Heidelberg. There he met a modern laboratory accommodating a number of outstanding persons, K. LOHMANN, D. NACHMANSOHN, H. BLASCHKO, DEAN BURK, FRITZ LIPMANN, and SEVERO OCHOA to name some. During his five months' stay he extended his studies by experiments performed on pre-rigor muscles isolated from poisoned frogs and maintained under strictly anaerobic conditions. Besides confirming the absence of lactate formation during contractions, he determined the correlation between the mechanical performance and creatine phosphate breakdown. The results showed that, contrary to recent findings of others in unpoisoned muscles, the breakdown of creatine phosphate ran fairly parallel to the contraction performance; yet there was some tendency towards a decline in the breakdown towards the end of an exhausting series of contractions. Despite this small deviation the data were taken by LUNDSGAARD as further evidence for his hypothesis that creatine phosphate breakdown constitutes the direct energy-supplying process for muscle contraction.

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With his own contribution to the collapse of another hypothesis in mind he was, however, very careful to emphasize that his, too, might be just another approximation towards the truth. In fact, he pointed out as a possibility that both lactic acid formation and creatine phosphate breakdown might be coupled with a third process, which in turn was directly coupled with the contraction process proper. Actually he was quite close to being the first suggesting ATP breakdown-resynthesis to be the third component of the energy delivering machinery. He had also found out with the imperfect methods then available that, besides a tendency towards diminishing breakdown of creatine phosphate with approaching exhaustion, some breakdown of ATP occurred towards the end of an exhausting series of contractions.

During some later studies he also got near to disclosing the position of ATP. In his 1934 paper (in the Festschrift to HENRIQUES) the breakdown of ATP towards the end of an exhausting series of contractions was found to amount to about half of the initial content. A diminished creatine phosphate breakdown (per unit of mechanical performance) was also found for the pre-exhaustion period and the calculated fall in energy (heat) release from this process was rather closely matched by the calculated energy (heat) release from the ATP breakdown. Yet, because determinations of the fate of ATP in experiments of different design did not fit into the picture, he desisted from proposing ATP an immediate energy source for the contraction mechanism proper. This proposal was made by LOHMANN in the same year on the basis of his finding that ATP or AMP is required for enzymatic breakdown of creatine phosphate in muscles extracts.

In the 1934 paper it was also reported that in poisoned muscles kept anaerobic at low temperature a considerable creatine phosphate breakdown takes place *following* a short tetanus. Furthermore, the ratio between the creatine phosphate breakdown observed *during* the tetanus and the heat liberation calculated from the mechanical performance was found to be considerably smaller at low temperature than at room temperature. In other words, during the tetanus there arose a "debt of creatine phosphate breakdown" which was "paid" during the recovery. By these findings LUNDSGAARD became the first to provide clear evidence against his own working hypothesis of creatine phosphate as the immediate energy source for the contraction process and he concluded that creatine phosphate breakdown, like glycolysis, is only a restitution process.

In earlier studies, important results were also obtained on unpoisoned muscles under anaerobic conditions. It was found that during a series of isometric contractions a gradual rise in lactate formation "goes hand in hand" with the gradual fall in creatine phosphate breakdown previously reported by NACHMANSOHN. Moreover, the isometric coefficient of heat calculated from the heat which should be formed by the two processes together was found

to be almost constant throughout the contraction series and quite close to that determined directly by A. V. HILL in myothermic experiments. These findings gave strong support to the view that glycolysis and creatine phosphate breakdown are the only quantitatively important energy-supplying processes during anaerobic conditions, and that the former process is triggered by the latter. Other experiments revealed that during recovery from a short tetanus not only is creatine phosphate resynthesized but lactate is formed as well. Calculations from the available thermochemical data showed that the heat absorption by the former process should be very nearly identical with the heat release by the latter. LUNDSGAARD'S interpretation that the efficiency of the coupling between the two processes is close to unity is subject to criticism. His finding was, however, important because it showed that the already known delayed anaerobic resynthesis of creatine phosphate, rather than being inconsistent with the existence of a small but positive "anaerobic delayed heat", is a component of a reasonable explanation of that phenomenon. Together with other of his findings it served to bring the interpretation of myothermic data out of a deadlock.

LUNDSGAARD essentially stopped his experimental work in muscle physiology in 1934. Motivated, undoubtedly, by his experience with monoiodoacetate he went on to study the metabolic effects of phlorizin with the intention of elucidating the *mechanism of active transepithelial transport of glucose* (hexoses) in the intestine and the renal tubulus. At that time VERZAR'S "Umbauhypothese" had just been given a specific formulation by WILBRANDT and LASZT: that active intestinal absorption of hexoses is brought about by phosphorylation and dephosphorylation in the epithelium. Furthermore POULSON had attributed phlorizin-induced glycosuria to inhibition of the tubular reabsorption, and KAYS had shown that the kidney and the intestinal mucosa have a high content of phosphatase in common. LUNDSGAARD showed that the intestinal absorption of glucose—but not of amino acids—can be markedly inhibited by introduction of phlorizin in the intestine. He was also able to show that in different tissues phlorizin in similar concentrations exerts a profound inhibition of various phosphorylations and dephosphorylations associated with the intermediary carbohydrate metabolism. This led him to accept WILBRANDT and LASZT'S hypothesis and to propose that phlorizin blocks the intestinal absorption of glucose by inhibiting its phosphorylation or the dephosphorylation of glucose phosphate. On the basis of similar evidence this view was also extended to the tubular reabsorption of glucose. The phosphorylation-dephosphorylation hypothesis and LUNDSGAARD'S view on the mechanism of action of phlorizin on the transepithelial transfer of glucose were later shown to be untenable. For many years they served, however, as potent stimuli to research, which in LUNDSGAARD'S laboratory led to valuable informations on the formation of phosphate esters in the intestinal mucosa.

From LUNDSGAARD'S phlorizin papers one point deserves special mention. In muscle extracts phlorizin was found to reduce the formation of lactate from glucose considerable more than the lactate formation from glycogen. From this LUNDSGAARD concluded that the biological breakdown of glycogen does not start with hydrolysis, and, knowing that hexosephosphates can be formed from glycogen, he suggested that the initial process is a *phosphorolysis*.

LUNDSGAARD'S interest in phlorizin led him to study the effects of this substance in eviscerated animals and isolated perfused kidneys, livers and hind limbs, and from the middle of the thirties such preparations became major tools in his own and his associates' investigations of metabolic problems.

The problems to the elucidation of which these tools were first applied were *the effects of insulin and its mode of action*. Before LUNDSGAARD became head of the Institute, NIELS AA. NIELSEN, had worked out there a technique for organ perfusion. In his thesis he had shown that insulin promotes the cellular uptake (utilization) of glucose in perfused hind limbs but had been unable to detect any effect of insulin on the uptake or release of glucose in isolated, perfused livers. These findings were confirmed in greatly extended studies by LUNDSGAARD, NIELSEN and ØRSKOV. In the liver perfusion studies an interesting observation was reported: Whereas one preparation of crystalline insulin was without effect on the course of the glucose concentration of the perfusion blood another crystalline preparation elicited—when the same number of units were added—a prompt and pronounced release of glucose from the liver. This last observation must be regarded as a forerunner of the discovery of glucagon. The results obtained with the perfused livers made LUNDSGAARD spokesman of the view that insulin is without *immediate* effect on the carbohydrate metabolism of the liver. This view was challenged by a Belgian group who claimed that insulin elicits an uptake of glucose in the liver which greatly exceeds that induced in extra-hepatic tissues. Their argument was that maintenance of a "normal" blood glucose concentration in dogs receiving super-maximal doses of insulin had been found to demand infusions of glucose at much higher rates in intact animals than in hepatectomized (or eviscerated) ones. Although LUNDSGAARD realized that it is questionable whether information on possible *direct* effects of insulin on the liver can be obtained by this approach he decided to repeat the Belgian studies using, however, cats as experimental animals. Finding no difference between glucose uptakes of intact versus hepatectomized or eviscerated animals LUNDSGAARD felt further assured that (in cats at least) insulin does not exert any direct effect on the glucose exchange between blood and liver. This question must still be regarded as open.

In the 1930's LUNDSGAARD carried out experiments on eviscerated cats to study the effect of the blood glucose concentration and of insulin on glucose uptake of muscles. He carried out determinations of the glucose concentration

in muscles and found that even during maximum rates of glucose uptake the calculated intracellular glucose concentration remained unchanged and close to zero. Since, consequently, there was no parallelism between the rate of cellular glucose uptake and the glucose concentration difference between blood and muscle cells he concluded (1939) that glucose does not pass into muscle cells by simple diffusion and that the uptake-promoting effect of insulin must be exerted on some special ("active") transport process in the cell-membrane. Some years later LUNDSGAARD and coworkers produced further evidence on the nature of the action of insulin and its specificity by showing that in perfused hind limbs, insulin is completely without effect on the cellular uptake of another hexose, fructose.

With his article in 1939 LUNDSGAARD was the first to forward the hypothesis that the main action of insulin on muscle tissue lay in the cell membrane itself. This view gained considerable support in the 1950's through the work of LEVINE and co-workers and is still considered of central importance in theories of the mode of action of insulin.

In 1938 LUNDSGAARD published a short paper which contributed greatly to the knowledge of the *metabolism of alcohol* in the mammalian organism. By liver perfusions it was demonstrated that this organ has a great capacity for oxidation of alcohol to acetic acid. Together with the observation that the elimination of alcohol from the body is almost completely abolished by evisceration this led to the conclusion that the breakdown of alcohol is almost exclusively dependent upon the liver and that the first—and rate-limiting—step is a partial oxidation to acetic acid which is subsequently oxidized completely in extrahepatic tissues. These findings provided a reasonable explanation of the fact that the rate of alcohol elimination is unaffected by muscular exercise. It was later shown by E. J. HOLST—working in LUNDSGAARD'S laboratory—that similar features apply to the metabolism of glycerol, and it was demonstrated by LUNDSGAARD that ethanol suppresses the metabolism of glycerol considerably.

Another of LUNDSGAARD'S associates, N. BLIXENCRONE-MØLLER, studied the *formation of ketone bodies* in perfused livers and showed conclusively, by comparison of the oxygen consumption and the ketone body output, that KNOOP'S theory of formation of only one ketone body per fatty acid was erroneous. The formation of a greater number was another example of a very incomplete oxidation and LUNDSGAARD advanced the view that—in analogy with alcohol and glycerol—the oxidation of fatty acids in the body starts almost exclusively by way of a primary oxidation to ketone bodies in the liver. New information, provided also by a co-worker in his laboratory, made him soon give up this idea, but his interest in the hepatic formation of ketone bodies and in the interaction between the metabolism of the liver and that

of the "peripheral" tissues served as an important stimulus to research and to the formation of new concepts.

In 1950 LUNDSGAARD presented evidence that substances formed *extrahepatically affect the metabolism of the liver* and increase its rate of oxygen consumption. During hundreds of liver perfusions he had been intrigued by the fact that during the first half hour of a perfusion the rate of oxygen consumption fell to about half of the initial magnitude. The observation was now made that the initial rate could be re-established by introducing a hind limb preparation into the blood perfusion circuit or by letting a hepatectomized animal serve as blood donor for the liver. LUNDSGAARD was able to show that none of a large number of constituents of blood could be responsible for the phenomenon, but he did not succeed in disclosing its nature. The problem was taken up in the laboratory by IRVING B. FRITZ and although he did not solve in either, it carried him into important research on the metabolic function of carnitine.

As it is seen from this account of LUNDSGAARD'S scientific contribution, he remained faithful to the two tissues whose metabolic processes interested him particularly: *liver* and *muscle* and he made several far reaching discoveries which have greatly helped the understanding of metabolic transformations.

LUNDSGAARD was professor of Physiology at the University of Copenhagen from 1934 until he retired in 1967. He created an institution in which free research was a prominent feature. He never forced his assistants into research projects of his own unless they had a desire to work in his particular branch of the discipline. This attitude had as an effect that when a period of great expansion for Danish Physiology started in the 1960's a group of physiologists, trained in various fields, were ready to lead development into broader areas.

LUNDSGAARD had finished his medical studies in 1923. He published in 1926, at the age of twentyseven, a complete textbook of Physiology, comprising 700 pages. This textbook demonstrated its author's masterful command of his discipline. It was published over the years in 8 revised editions and served as the backbone of physiological knowledge for a whole generation of Scandinavian doctors.

Thanks to his intellectual integrity and his impeccable honesty LUNDSGAARD acquired a strong position in the medical faculty and at an early age he became member of the supreme governing body of the University.

He received international recognition as reflected in various honours bestowed upon him. In 1937 he delivered the Harvey Lecture in New York and became an honorary member of the Harvey Society. He received honorary degrees in the Universities of Montreal (McGill) and Paris. He was president of the 20. International Congress of Physiology in Copenhagen (1950).

In Scandinavia he received many scientific distinctions. As earlier mentioned he received the Anders Jahre prize (1964) in Oslo. In 1960 he received

the Thunberg medal in Sweden. He was a member of the Danish Academy of Sciences and Letters since 1938 and became president of the section of Natural Sciences within the Academy in 1962. He served in this position until his death.

His connections with foreign countries were founded when in his youth he spent time in various European laboratories. In 1930 he worked with MEYERHOF, visited EMBDEN and later worked in the Physiological Laboratory at University College, London. He worked for shorter periods of time at the Marine Biological Station in Plymouth and in the Physiological Laboratory in Cambridge.

At his retirement a special Symposium was held in Copenhagen to commemorate his scientific contributions. At this occasion a series of lectures were given by DOROTHY NEEDHAM, DOUGLAS WILKIE, HERMAN KALCKAR, RAGNAR GRANIT, IRVING B. FRITZ, and FRITZ LIPMANN.

Already at the time of retirement LUNDSGAARD was not feeling well and although he continued to work in an office in his old laboratory it was obvious that he was no longer at full force. He probably knew that he was seriously ill, but did not want to admit it, until finally he developed signs of intestinal obstruction. Within a week after admission to hospital he died from an extensive renal carcinoma, in December 1968.

For those who have known LUNDSGAARD he stands as a strong person and an honest scientist who put his stamp on Danish and on International Physiology.

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