AXEL HOLST

(September-6, 1860-April 26, 1931)

In the spring of 1902 a young Norwegian physician, making a world tour to study tropical diseases in their native places, visited the laboratory of Eijkrnan and Grijns at Batavia (now Jakarta) on the island of Java in the Dutch Indies, in order personally to acquaint himself with the investigations going on there on beri-beri. This physician was Dr. Axel Holst who, at that time, was Professor of Hygiene at the University of Christiania (now Oslo). Holst was particularly interested in "ship beri-beri," a disease which had long been haunting Norwegian sailing vessels. He discussed with Grijns (1, 2) the experimental work going on at Batavia and its bearing on his own interests. After his return home, Holst devoted himself eagerly to the study of "ship beri-beri" or scurvy on an experimental basis. He soon realized that the polyneuritis produced in poultry resembled tropical beri-beri much more than it did "ship beri-beri," a fact which led him to discontinue his experiments on poultry and pass over to investigations on mammalia. It was, indeed, fortunate that Holst and his coworker, Frolich, chose guinea pigs in their experiments because it was the successful outcome of these investigations which led to the recognition of the cause of scurvy, an achievement which'has ranked Axel Holst as one of the pioneers in the field of vitamin research.

Axel Holst was born in Christiania, Norway, September 6, 1860. His family was one of long-standing medical traditions, both his father and his grandfather having been physicians before him. His grandfather was Professor of Hygiene at the University of Christiania for almost 40 years while his father, Dr. Axel Holst, Sr., was a military surgeon of some renown.

Holst matriculated from Christiania Cathedral School in 1877 and passed the final medical examination in 1884. His interest in medical science was deeply rooted, and after receiving his medical degree (M.B.), he was appointed second assistant and then first assistant at the Institute of Pathology and Anatomy of the Government Hospital ("Rikshospitalet") in Christiania, working under the distinguished professor, Hjalmer Heiberg. In 1866, while he was an assistant at the Institute, Holst married Anna Midelfart, the daughter of a logging manager. At this time, Holst seized the opportunity to devote himself to the study of bacteriology, a field which had been opened up in the previous 15 years by the work of Pasteur, Koch and others, and which played a dominant role at that time in formulating our modern concept of hygiene. In 1887 Axel Holst was appointed Fellow in Bacteriology at the University of Christiania. In 1890, on the basis of his training and interest in bacteriology, Holst wrote a handbook of bacteriology, "Oversigt over Bacteriologien," which was translated into German in 1891. A second edition appeared in 1901. This book was for many years a guide for doctors and students of medicine.

In order to advance his bacteriological training, Holst obtained a traveling scholarship; and from September, 1890 until June, 1892 he studied at various European laboratories including: Kiel, Berlin, Wiesbaden, Munich, Paris (Pasteur Institute) and London. Holst was in Berlin studying with Koch when the announcement by Koch of tuberculin caused a sensation throughout the medical world. Following his return in 1892, Holst was awarded his doctor's degree (M.D.) from the University of Christiania. The title of his thesis was: "New Experiments with *Streptococcus* from Human Infections."

With this background of training Holst, at the age of 33, was made Professor of Hygiene and Bacteriology at Christiania succeeding Professor Lochmann, whose field of subjects, hygiene and pharmacology, was divided. Holst held this office until his retirement in 1930. Axel Holst was not only concerned-with furnishing Norwegian doctors with the best pos-

sible training in hygiene, but he also felt strongly and was intensely interested in the importance of the practical aspects of the study of hygiene. In his inaugural lecture the new professor emphasized strongly the importance of the study of hygiene at the practical level and while he was the first professor of bacteriology at Christiania, he applied his knowledge of bacteriology chiefly in the field of applied hygiene. He was acting Medical Officer of Health in Christiania in 1893, a member of the Municipal Board of Health, and for two years School Medical Officer at Christiania Cathedral School.

Very soon after entering into his new office he demonstrated further his interest in practical hygiene by zealously setting to work on two questions which were of immediate practical importance at that time; namely, the housing conditions of the working classes of Christiania, and the pollution of the harbor waters of the capital.

The housing investigations were initiated at the request of the Labor Party in Christiania and were published in the "Christiania Municipal Records" in 1895, no. 29 (see also 3). In a lecture which he delivered before the Norwegian Medical Association on May 15, 1895, Holst stated that not less than 3,000 flats were overcrowded to such an extent as to be injurious to health. His work on the pollution of the water in the Christiania basin was printed as a supplement to "Christiania Municipal Records," 1901 and was also published in German (4).

During the tenure of his professorship, Holst investigated many other problems in the field of practical hygiene. In 1898 very extensive discussions were going on in the Norwegian Medical Society on the problem of prostitution control. Holst was decidedly in favor of regulation. In 1888 the control of prostitution had been suspended, and in Holst's opinion the experiences of the intervening years had shown that regulation needed to be reintroduced. His point of view, however, met with strong opposition and was not accepted.

He had been acting School Medical Officer for some years and carried out many studies in school hygiene, publishing in

1909 a brief handbook on the subject entitled: "School Hygiene — A Survey for Teachers." A study of milk control was undertaken by Holst and in 1908 he took part in heated discussions in the Norwegian Medical Society over a very serious epidemic of "milk-disease" which was prevalent in Christiania. At a still later date, September 23, 1910, Holst was appointed chairman of a combined ministerial and parliamentary commission to deal with the alcohol question. This duty he performed until 1915, making extensive inquiries and ac cumulating statistics in connection with this problem. As usual he gave the matter great care and attention notwithstanding the fact that it often became a burden to him because he felt it so futile. He, himself, took a strict stand against prohibition.

From a scientific point of view, however, the most outstanding contribution of Holst was in the field of experimental nutrition research. The factor which was of greatest significance in stimulating his interest in experimental work was his visit with Dr. Grijns in Batavia.

The prevalence of the disease "ship beri-beri" on Norwegian sailing vessels together with the epidemic character of the beri-beri which occurred in tropical regions was the occasion for Holst's long study tour (October, 1901 to the summer of 1902), which was referred to earlier. The disease, "ship beri-beri, " was under active investigation at that time by Nocht in Hamburg and also by a Norwegian Ship Beri-Beri Committee. However, it appears from the records that medical terminology of the time was so confused as to have led Holst and others to believe that "ship beri-beri" and tropical beri-beri were essentially similar and could be studied together. In his earlier work, Holst apparently did not accept the possible identity of "ship beri-beri" with scurvy, and even as late as 1918 he published a paper on beri-beri on Norwegian ships (5).

The early work of Holst, using chickens and pigeons as experimental animals, was reported first in the "Norwegian Magazine of Medical Science" ("Norsk Magazin for Laegevidenskaben") in 1907 and almost at the same time in "The

Journal of Hygiene" (6). In this report, Holst points out clearly the clinical differences between tropical beri-beri with its concomitant neuritis and "ship beri-beri" in which neuritis was comparatively rare. He states that "the recovery of patients suffering from 'ship beri-beri' is due to *fresh food*" and that "above all, fresh vegetables or potatoes were curative." Apparently the long history of scurvy on shipboard during the era of extended sea voyages was unfamiliar to the Norwegian investigators since Holst states, "Dr. Stian Ericksen of Norway in 1899 first observed that the disease appears almost solely on-board sailing ships on long voyages." Or, it may be that the appearance of the disease as it occurred on Norwegian and other northern sailing vessels was sufficiently different from classical scurvy as to warrant the designation applied ("ship beri-beri"). It is quite probable that the diets on ship were low in both vitamin C and thiamine as well as other nutrients and that a multiple deficiency disease existed. However, Holst does express the opinion in the introduction to his first papers that it seems probable that *"Ship beri-beri"* is *"a food disease showing a marked congruence with scurvy."*

Holst soon gave up his work with chickens and pigeons since it gave no information concerning "ship beri-beri," a fact which, of course, would be expected in the light of our present knowledge on species requirements for vitamin G. These experiments did show, however, that foods other than those used by Eijkman and Grijns would cause *polyneuritis gallinarum,* analogous to tropical beri-beri. Holst did accept the results of Eijkman and Grijns that there were "nutritive constituents, the presence of which prevent and conversely, the absence of which produce the disease." He states "because the experiments . . . have not thrown any clear light upon the question which has been to me the principal one, i.e. the etiology of 'ship beri-beri' . . . I, therefore, discontinued the experiments on poultry and passed over to investigations on mammalia." These experiments were carried out together with Professor Theodor Frolich and later Chief-Physician Valentin Furst. Since Dr. Frolich contributed so much to this phase of Holst's

work, it would seem appropriate to refer briefly to this outstanding pediatrician.

Theodor Fro1ich (1870-1947) worked for a number of years in the pediatrics department of the "Rickshospitalet" and was also an assistant at the Institute of Hygiene. From 1922 until his retirement in 1941, Frolich was Professor of Pediatrics at the University. As stated by Dr. Ragnar Nicolaysen (7), at the time of Frolich's death (August 14, 1947), Frolich at his retirement in 1941 could look back upon a long and active life in the service of science and pediatrics. He had trained most of Norway's present (1947) specialists in pediatrics and more than half of their practising physicians. There was no one who did not have kind memories of him. His speaking ability, his loving nature, and the intensity with which he performed his duties as a professor and doctor made him a most attractive personality. Influenced by his work on scurvy with Holst, he took a particular interest in infant nutrition and his influence on it was great in Norway.

Frolich had been especially interested in studying Barlow's disease (infantile scurvy). After Holst's preliminary investigations upon his return from the East, the evident relationship of "ship beri-beri" with scurvy and Barlow's disease made the cooperation between Holst and Frolich particularly fruitful. It is, perhaps, to be regretted from a research point of view that Frolich, a man of clear vision and originality, did not continue his experimental work. However, making clinical pediatrics his choice, influenced perhaps by the greater financial return to the practising physician than to the research professor, he deserves no less to be remembered.

Holst and Frolich's paper "On the etiology of scurvy" was published in the next issue of the Norwegian Magazine of Medical Science and as part II of the paper in "The Journal of Hygiene" (8). It is subtitled: "On the Macroscopical Alterations in the Tissues of Guinea Pigs which Had Been Fed Exclusively on Bread, Groats and Unpeeled Grain." The paper goes on to say, "By experimenting with the 'one-sided' diets which were used in the experiments . . . on polyneuritis

in poultry, we found that guinea pigs also contract a disease and that this disease is accompanied by very characteristic changes . . . These alterations, however, do not as a rule develop until from three to four weeks after the beginning of the experiment . . . The present section of our paper deals with the 64 animals that died in 18 days or more when fed on ground or unground oats, barley, rye or wheat and water . . . each animal received one single nutriment only. (This latter is reminiscent of the Wisconsin single grain experiments of the same era.) In the 64 animals death occurred on an average after 30 days." Holst and Frolich continued with a precise description of the characteristic symptoms involved: hemorrhages in the musculature, of the extremities, in the intercostal muscles, around numerous junctions between the ribs and their cartilages, and, less frequently, subcutaneous hemorrhages. A description is also given of hemorrhages in the stomach, kidneys, lungs, etc. Then the characteristic bone injuries are described; bone fragility that went so far that repeatedly when the tubular bones were removed from the body the epiphyses of the humeri, tibia, and femur separated from the shaft. In many cases the hind part of the lower maxilla actually crumbled between the fingers during dissection. Further, without a single exception the back-teeth were found to be loose, whereas the front-teeth proved to be loose only in some particular animals. The gums often displayed a greyish-green discoloring. Occasionally bleedings beneath the mucous membrane of the gums were detected but never wound formations.

Hemorrhages, loose teeth, and bone fragility—all these symptoms led Holst and Frolich to write, "From these observations we were led to assume that the disease might possibly be *scurvy*."

Obviously, neither Holst nor Frolich seemed to have had any particular personal experience with scurvy symptomatology in the human adult, for they compare their observations on the guinea pigs to descriptions of scurvy epidemics during the siege of Paris, in St. Petersburg, and elsewhere, going back as

far as Harvey's book "The Disease of London or a New Discovery of Scurvy" published in 1675.

In addition to the gross symptoms noted, Holst and Frolich also studied the histological changes which occurred in the guinea pigs. They report some muscle fiber changes, but in general confined their observations to the bones where they found alterations which "are, in all essentials, wholly identical with those found in human scurvy." This was particularly notable in the bone-marrow. They studied the effect of starvation (cf. modern inanition controls and pair-feeding techniques) and showed that starvation-marrow in no way resembled the bone-marrow of their scorbutic guinea pigs. They state, "scurvy *cannot* be caused in guinea pigs either by simple starvation or by diets of *any* kind; *on the contrary the disease originates in these animals as well as in man as a result only of a certain special diet.*" In order to obtain further evidence as to whether the disease in their guinea pigs was identical with scurvy, Holst and Frolich tried the preventive effect of some foods known as "antiscorbutics" from human experience and found that apples, lemon juice, and particularly cabbage protected guinea pigs from the typical lesions.

Of major importance in considering the contribution to nutrition made by Holst and Frolich was the thorough study of the nutritional disease which they had produced so as to be able to positively identify it and thus make available to future workers this experimental tool.

At the time of Holst's work there were three rather widely held theories as to the cause of scurvy. These existed despite the classic work of Lind and many others showing the nutritional nature of the disease and the curative value of certain fresh foods.

The first theory was that the malady was infectious. Although this idea prevailed rather widely, it had no real evidence in its support. A second and more popular theory was that scurvy was caused by the ingestion of damaged food. The third theory supposed that the disease was caused by a deficient diet — a diet containing too little fresh food. With re-

spect to the latter theory, Holst states: "It .seems to us that the facts by which Lind, Hirsch and many other writers have supported this theory are in every respect convincing, and they agree with our own experiments as to the influence of fresh cabbage, apples, potatoes, and so on . . . We may . . . draw attention to the fact scurvy has repeatedly arisen where the food consisted of the same or about the same nutriments as we have used in our experiments with guinea pigs." He concludes: "Thus, also epidemiological facts speak in favor of the opinion that the described disease in guinea pigs is identical with human scurvy."

In an addendum to this paper the authors report experiments with dogs on similar diets. As would be expected in light of present knowledge, the dogs failed to come down with the symptoms characteristic of scurvy. How fortunate it was that Holst chose the guinea pig as the mammal with which to study "ship beri-beri"!

In view of the fact that it is now recognized that there were other workers who had produced scurvy-like symptoms in guinea pigs it should be mentioned, in justice to Holst, that he did refer to the earlier work of Bartenstein (9) although not that of Bolle (10) nor Smith (11). Holst stated, however, that he thought the "interesting disease of Bartenstein must . . . be placed in a class by itself."

Holst lectured on his investigations before many groups including: the Norwegian Medical Society (1907); the Epidemiological Society of London (1907); the Annual Meeting of the British Medical Association, Sheffield (July, 1908); the Society of Tropical Medicine and Hygiene, London (1911); the International Congress of Hygiene, Washington (1912); and elsewhere.

Because of the varied opinions held at the time, it was only natural that a heated discussion arose when Holst first reported his work before the Norwegian Medical Society. On this occasion his principal opponent was Dr. Torup who had already completed his elaborate preparation for Nansen's arctic ex-

peditions and who believed scurvy to be a result of the ingestion of " spoiled" foods. Even Hess, the American pediatrician and authority on scurvy, as late as 1917 stated (12) that infantile scurvy was due to the toxins produced by intestinal bacteria as a result of "malnutrition." While Holst was very much interested in continuing his experimental work, the lack of support and the pressure of administrative duties prevented his doing so. This is evidenced by a statement made by Frolich in his memorial address on Professor Holst (13) "It is much to be regretted — as a matter of fact it engendered much bitterness in Holst's mind — that the wretched economic conditions under which Norwegian science had to work in the pre-war years, made it impossible to carry on a continuous program within this most significant field of study, a field in which Norwegian science had played such a leading part." From the writings of Holst (14) we quote, "As we have had nobody to assist us, we regret not to have been able to apply the method for measuring the antiscorbutic value . . ., etc." It is in this paper also that Holst first uses the term "vitamins." Other papers on scurvy were published by Holst and his co-workers (14-18). These included studies on the effect of processing on the antiscorbutic value of foods (15); on the comparative symptomatology of guinea pig scurvy and infantile scurvy (by Dr. Frolich) (17); on the conservation and extraction of the specific components from antiscorbutic foods (18); and after the war one paper on the preservation of the antiscorbic properties of cabbage by dry storage (19). In addition, Furst in his laboratory (16) found that "dry peas and grain, which do not prevent the experimental disease, acquired pronounced antiscorbutic properties when moistened and allowed to germinate. This process converts them into 'fresh vegetables'."

The work which they did on the experimental production of scurvy in the guinea pig undoubtedly ranks Holst and Frolich with those other pioneers of vitamin research: Lunin and von Bunge, Eijkman and Grijns and Hopkins. On looking back over the work of Holst one wonders what other important dis-

coveries he might have made if he had been given as much encouragement financially and otherwise in his fundamental research as he was given in carrying out the practical aspects of his position as Professor of Hygiene. In the writings of Holst, himself, one notes this same "is it practical" point of view. Yet, in the light of present day knowledge we know that the basic work he did was the most practical and the so-called practical aspects were of little lasting importance. For example, Holst states (6), "In these experiments, however, the beef was more strongly heated than in the manufacture of tinned meat." The chickens fed this meat all died of neuritis, because of the heat lability of thiamine — Holst felt that the results were not of practical importance because the meat had not been processed in a conventional manner.

Let us next look at the character and personality of the man Holst, insofar as we can visualize it from the reports of coworkers that have come down to us (13, 20, 21). The painting of Professor Holst gives a fine impression of the colorful personality which he seems to have been, de Besche characterizes him as highly gifted and filled with a great interest in the tasks ahead. Considering his natural endowments and personality, it was only natural and to be expected that he would make a name for himself. He was a full professor at 33; and became president of the Norwegian Medical Association at the early age of 38 illustrating the high regard in which he was held by his professional colleagues.

He set about each task with great enthusiasm and "wholeheartedness," and by his forcefulness saw the realization of many of his ideas. He was an exceptionally gifted speaker of remarkable and distinctive eloquence and also a lively and witty debater. During a debate his energetic sallies against his opponents at times provoked criticism and spirited counterattacks. Quoting again from de Besche, "he always spoke easily, concisely, and pointedly. And, his excellent oral presentment of a case lent him great strength. As a debater he was striking and aggressive, and we could not fail to see the merry fighting spirit beaming from his lively eyes. Often he

displayed a refreshing sense of humor, his discourse being seasoned by numerous barbs. When he was at his best, it was a treat to listen to him . . . The same qualities distinguished him as a public speaker, and it may well be understood why on occasion, he has been named the best orator in our country."

As a research worker he much preferred to pursue his goal uninhibited by the ideas of others and to work out his problems independently. At times this characteristic led him to suggest that he would rather not read what others had done on the subject on which he himself was working lest he be influenced by the opinions of others. However, in his classic papers already discussed he showed an excellent knowledge of most of the prior work.

He was, in general, a man of reality, holding scientific views in line with the scientific thought of his time. Occasionally his fervent interest in his subject might obscure his sense of criticism, but more important was the fact that he approached each new problem with vigor and enthusiasm. Frolich (13) commented thus, "A new experiment often founded on a passing idea would captivate him entirely for days and weeks at a time. It might then well happen that after long working hours his disappointment would be great. On the other hand, how great was his joy when his experiment had successfully fulfilled his expectations."

In summing up his personality, de Besche says, "When we think of Axel Holst as we met him, whether in every day life, fully occupied with the work and questions of the day, and indeed with all the activities of human life, lively, keen on discussing any problem, or as we met him on festive occasions, this phrase comes readily to our lips — a brilliant personality."

With the passing years Holst was entrusted with many administrative tasks. He was an able administrator, becoming completely engrossed in every task, even those thrust upon him. He was president of the Norwegian Medical Association in 1898-99 and again in 1902-03; as well as chairman of the Association, 1908-10. He was Norwegian deputy to a number

of international congresses including Brussels in 1899, Berlin in 1907, and Berlin again in 1910 for the Koch memorial. Finally in 1919-21 he was Rector of the University of Christiania.

Because of his interest in the improvement of public hygiene, Holst began to work as early as 1893 for the establishment of a postgraduate course in social medicine for physicians in the state's employ. This measure he managed to put into effect in 1929 a year before his retirement.

Holst was a member of the Norwegian Academy of Science, the Society of Tropical Medicine and Hygiene of London and other learned societies.

On April 26, 1931, at the age of 70, Professor Holst died in Oslo.

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LITERATURE CITED

1. BREIREM, K. 1951 Mangelsykdommer hos husdyr. Tidskrift for Det Norske Landbruk., *58:* 105-140 (see p. 106-7).
2. JANSEN, B. C. P. 1950 C. Eijkman. J. Nutrition, *42:* 3-8 (see p. 7).
3. HOLST, A. 1896 Untersuchungen uber die Wohnungen des Arbeiterstandes in Christiania. Archiv. fur Hygiene, *86:* 109-161.
4. HOLST, A., M. GEIRSVOLD AND S. SCHMIDT-NIELSEN 1902 Uber die Verunreinigung des stadtischen Habens und des Flusses Akerselven durch die Abwasser der Stadt Christiania. Ibid., *43:* 153-218.
5. HOLST, A. 1918 Uber die Beriberi-Krankheit und ihre Ursachen auf norwegischen Schiffen. Centralblatt fur Bakteriologie, *81:* Abt. 1, 56—72.
6. ---------- 1907 Experimental studies relating to "ship beri-beri" and scurvy. I. Introduction. J. Hygiene, 7: 619-633.

7. NICOLAYSEN, E. 1947 Minnetale over Professor Th. Frolich. Det Norske Videnskapsakademi, Arbok, pp. 72-77.
8. HOLST, A. 1907 Experimental studies relating to "ship beri-beri" and scurvy. II. On the etiology of scurvy. J. Hygiene, *7:* 634-671.
9. BARTENSTEIN, L. 1905 Beitrage zur Frage des kiinstlichen Morbus Barlow bei Tieren. Jahrb. fur Kinderheilk., *61:* 6.
10. BOLLE, C. 1902-1903 Zur Therapie der Barlowschen Krankheit. Ztschr. fur dietet. u. physik. Therap., *6:* 354.
11. SMITH, T. 1895 Bacilli in Swine Diseases. U.S.D.A. Bureau of Animal Industry Ann. Rep. 1895-96, p. 172.
12. HESS, A. F. 1917 Infantile scurvy. Am. J. Dis. Children, *13:* 98-109.
13. FR0LICH, T. 1931 Minnetale over Professor dr. Axel Holst. Det Norske Videnskapsakademi Arbok 1931, pp. 46-49.
14. HOLST, A. 1911 The etiology of beri-beri. Trans. Soc. Tropical Medicine and Hygiene, *5:* 76-78.
15. HOLST, A., AND T. FR0LICH 1912 Uber experimentellen Skorbut. Ein Beitrag zur Lehre von deren Einflusz einer einseitigen Nahrung. Zeit. fur Hygiene und Infektionskrankheiten, *73:* 1-120.
16. FURST, V. 1912 Weitere Beitrage zur Atiologie des Experimentellens. Ibid. *73:* 121-154.
17. FR0LICH, T. 1912 Experimentelle Untersuchungen Uber den infantilen Skorbut. Ibid. *72:* 155-182.
18. HOLST, A., AND T. FR0LICH 1913 Uber experimentellen Skorbut. II. Uber Mitteilung. Weitere Untersuchungen uber das Konservieren und Extraktieren der spezifischen Bestandteile der antiskorbutischen Nahrungsmittel. Ibid., *75:* 334-344.
19. ---------- 1920 On the preservation of the antiscorbutic properties of cabbage by drying. J. Tropical Medicine and Hygiene, *23:* 261-263.
20. DE BESCHE, A. 1931 Axel Holst. Minnetale i Medisinsk Selskap. Norsk Magasin for Laegevidenskapen, *92:* 550-552.
21. GR0N, FR. 1934 Axel Holst. Norsk Biografisk Leksikon, *4:* 277-280.

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