ALFRED FABIAN HESS
— *A Biographical Sketch*

(October 9, 1875 — December 5, 1933)

The father of brain chemistry, J. L. W. Thudichum, wrote that *"Work, work, and again work* were the three main features" of the success of science (Drabkin, '58). These might easily have been the words of Doctor Alfred Hess, a study of whose life reveals that several similarities existed between these versatile giants. Both derived the stimulus for investigation from clinical patients who furnished their problems, and patients ultimately benefited from their solution. They were both men with triple careers of physician, scientific investigator and teacher. Such a career, according to Thudichum, merely demands that one is to "do the work of three men." To neither came major academic appointments and both made their scientific contributions despite a busy practice of medicine. Drabkin notes that such an individual must be prepared at times to be lonely and misunderstood. Surely Hess and Thudichum shared these fates.

Too often in our present day world do we hear distinctions made between clinical and basic researches. Too often is it implied that the physician without a full-time academic appointment in a university or medical school has no opportunity of contributing to the understanding of disease, basic physiology, nutrition, or biochemistry. Reflection on Hess's career and contributions serves admirably to illustrate the falseness of this bigoted view. Such reflection serves further to illustrate the tremendous contribution to the science of nutrition made by physicians—contributions oft-times attributed to others by the enthusiastic, academically oriented laboratory researcher and teacher.

Accordingly, on this the 26th year after the death of Alfred Hess and the year after which his illustrious collaborator, Windaus, has died, it seems particularly fitting to review his life and works. Unfortunately, neither of the present biographers had the privilege of knowing Doctor Hess. Accordingly, they have drawn heavily on the published accounts of others for the details of his life. For much of the personal information concerning him they have had the privilege of communications and discussions from those who knew him, particularly Mrs. Alfred Hess, Mrs. Helen Benjamin, Dr. Samuel Karelitz, Dr. Edwards A. Park and many others. The appraisal of his work and of its importance is, however, our own.

Alfred F. Hess was born in New York City on October 9, 1875, the son of Selmar and Josephine Hess. Until his death on December 5, 1933, at the age of 58, New York was his home except for periods of study in Europe. His father was successful in business and afforded him every educational advantage that he desired. Following attendance at private preparatory schools in New York, he spent a year at Columbia University, then transferred to Harvard where he graduated in 1897. The next year he enrolled at the College of Physicians and Surgeons in New York City and from this institution received his M.D. degree in 1901. He served an internship at Mt. Sinai Hospital, New York City, where he remained for two and one-half years. Graduate studies at Prague, Vienna and Berlin occupied the next two years. On a brief visit home during this period he courted and married Miss Sara Strauss. They returned to Europe and spent their honeymoon in Prague.

Back in New York, Hess spent a short time at the Rockefeller Institute and then entered the private practice of pediatrics which had always been his chosen field. His practice was never allowed to interfere with his scientific activities, which were carried out in several laboratories over the course of 25 years. Fortunately

he was financially independent and was able to devote an increasing portion of his time to research, most of which he financed. He never held a full-time teaching position. A fortunate result of this was freedom from administrative tasks. This practicing pediatrician became one of the foremost medical investigators of his day. His contributions to the field of nutrition were numerous and often turning points in this rapidly developing field.

His marriage was an ideally happy one for both him and his wife (Flexner, '36). Mrs. Hess was perhaps the first person to recognize that "under a modest and more or less inarticulate exterior, he had great gifts of mind and heart. She herself had her own interests throughout life. Mrs. Hess loved people. Doctor Hess loved competent persons with whom he could discuss his interests—scientific, medical, artistic or what not." He counted among his close friends such men as Abraham Flexner and Edwards A. Park, whose aid Mrs. Hess enlisted in the posthumous publication of his collected works (Flexner, '36). Despite his enviable reputation in both the United States and Europe as a medical scientist, his innate reticence and meticulously analytical approach to persons and phenomena did not lead to great social popularity.

It has often been said that Hess did not desire recognition in the form of a university professorship or the sharing in the Nobel Prize. Abraham Flexner, in his biography ('40), states that this failure of academic recognition did not worry Hess, but left him all the more time for research. "He was quietly amused by the fact that he was passed over, but it did not sour or disappoint him." It is evident that Alfred Hess would have been less than human had he been able to view such disregard with complete indifference. It is more probable that his equanimity was such as to mask his disappointment.

In a letter to a friend he wrote, "Work, work, work. Success comes perhaps too late but always lasts too long. Men live on their reputations." In the judgment of Flexner ('36), "it could be said (of Hess), if it could be said of any man, that he lived in the spirit of the injunction: work while it is still day for the night cometh wherein no man can work."

Throughout his scientific interests he was extremely sensitive to human suffering. One of his earliest ('14) professional concerns resulted in a paper entitled "The neglect to provide for the infant in the anti-tuberculosis program." With his characteristic thoroughness in pursuing matters another paper appeared 4 years later entitled "A tuberculosis preventorium for infants." It is said that he limited his practice to infants under the age of 5. However, his personal warmth as a physician and his unstinting giving of all of his talents led to the care of children of close friends until they had more than reached adulthood.

Doctor Samuel Karelitz of New York recalls asking Doctor Hess in consultation concerning an infant extremely ill with what is now recognized as erythroblastosis fetalis. Doctor Hess came to the bedside from a dinner party and proffered wise advice. He became engrossed in the problem and over the next few weeks, in his zeal to do all that he possibly could to help, repeatedly called or sent Doctor Karelitz references or some new fact concerning the disease.

As a scientist, Hess proceeded slowly and deliberately to analyze problems which usually came to his attention through such clinical experiences, and then proceeded to reduce these to a critical question which could be studied either in infants or the laboratory. His studies on infants were made at the Hebrew Infant Asylum, which he transformed from a well-meaning but old-fashioned institution into a modern establishment with medical and nursing staffs. He always felt that results obtained in experimental animals must not be considered seriously for clinical application until they had been confirmed in the human. His observations in the human were oft-times uncanny on their quantitative aspects. For example, he compared the efficacy of the potato and fruit juices as anti-scorbutics, demonstrated that certain preparations of dried milk retain a significant degree of anti-scorbutic activity, and that pasteurization reduces the anti-scorbutic potency of fresh milk. Hess's recognition of the effect of oxidation on

destruction of ascorbic acid led him to point out in his Harvey lecture of 1921 (Hess, '21) that it should be "possible so to alter the process of manufacture or of the preservation of foods to increase their anti-scorbutic content, and render them more nearly equivalent of fresh food." Wide recognition is now given to this principle that food processing should be designed to preserve nutrient values.

In this same lecture Hess emphasized that deficiencies should not be associated exclusively in our minds with specific diseases such as scurvy or rickets. He spoke of latent nutritional deficiencies and the impairments which result therefrom. On the other hand, his nicety of judgment was such that he insisted upon objective evidence of therapeutic benefit in instances of latent deficiency before attributing symptoms to a lack of nutrients. He was never guilty of the exaggerated claims of the over-enthusiastic nutritionist for the benefits derived from additional vitamins. Indeed, in the Cutter lecture delivered at Harvard Medical School, February 14, 1922 (Hess, '22) he stated, "I should like to refer briefly to an aspect which is well known to the children specialists and to other clinicians, but is rarely considered by the laboratory investigator of nutrition. I refer to the opposite of disorders due to deficiency, to disorders resulting from an excess, from an over-supply of one or more dietary factors. It seems quite possible that experiments, which, under prevailing point of view, are judged solely by the criterion of an adequacy of the various food elements, may be more correctly interpreted as due in part to an over-supply of some factor." It is unfortunate, indeed, that this balanced judgment of nutrition so well displayed by Hess did not characterize all of the nutritional writing and thinking during the subsequent 30 years! It is only within the present decade that this sense of balance seems to have been restored to much of nutritional thought.

Abraham Flexner has described Hess's method of work—a method which it would be well for more to emulate ('36), "He began the day by disposing of his mail and then turned to some current journal. Almost everything he read suggested ideas, but before he began on any specific problem he would spend hours and days and weeks looking up the literature of the subject so as to avoid repetition and trimming of his conception down until it became a relatively simple statement of the end which he undertook to reach. In a very high degree he possessed the capacity to reduce in this way complex problems to a manageable Tragestellung.' He had a way of noting on small white cards items, ideas, and points of view which seemed spontaneously to germinate in his mind. In discussions with his subordinates complete frankness prevailed, and he was always ready to modify his problem when good reasons were given. Unexpected results did not frighten him, nor did he lightly discard them. On the contrary, they led to further investigation with a result that his problem often changed as he worked, but he never settled down to experimental work without a long and patient process of reasoning beforehand. He was one of those rare scientists who do not refrain from experiment because of lack of elaborate apparatus or material. On the contrary, simple apparatus and a relatively small number of experimental animals thoroughly and carefully studied usually sufficed to convince him whether he was right or wrong in his hypothesis. In dealing with students he was impatient if they began by using even so simple a mechanism as a stethoscope. He had a way of saying, 'Tell me what you *see.* Often the most important and accurate facts are obtained by observation. '

"His devotion to knowledge as such is perhaps best illustrated by his willingness to turn over his ideas to others whenever he reached the point at which his own fundamental training failed him. He did not stop an investigation. He did not endeavor to carry on clumsily. Having reached the point at which his own competency ceased—and he was an infallible judge in this respect—he turned over a definite problem to someone else. He had a certain prophetic vision which one of his associates describes as 'uncanny' as to the probable results which would be obtained, and he therefore did not hesitate to urge and stimulate those who, in his judgment,

could solve the problem which he had in the shape in which he was ready to turn over to them."

One may summarize Hess's experimental method as follows (Flexner, '36). He first defined clearly and precisely in words the problem itself. Secondly, he considered and often listed known facts on the subject. Thirdly, he listed those facts which were wanting but which were necessary to solve the problem at hand. He then translated the problem into experimentation. The first probe was a simple, direct, crude experiment with a minimum of sophistication of method. Methodology might later be refined if necessary, but his aim was always to demonstrate a principle and not to become overly involved in the refinement of details which he left to others. He was never satisfied with a conclusion, no matter how logical, unless it had been subjected to experimental tests. He was ever aware of the cost of an experiment and weighed the expenditure of time, of effort or resources against the probable importance of the findings and then decided whether the work was worth the cost.

In the appraisal and interpretation of results Doctor Hess examined the data on the controls first, and only when these were satisfactory would he consider the experimental results. If unsatisfactory, the failure of the controls had to be examined if necessary by additional experimentation. Every effort was made to eliminate personal bias through the use of "blind technique." One experiment led to another in a logical sequence based upon the findings at hand. He did not plan more than one experiment ahead.

He read two to three hours each day in the literature of his subject and in his reading studied the facts or data presented in the paper and drew his own conclusion. He stated that by this method one is just as likely to obtain very valuable information from the poor article as from the good one.

One of his assistants of many years, Mrs. Helen Benjamin, writes, "One of Doctor Hess's most outstanding characteristics was his extraordinary preoccupation with his work. Indeed, it seemed at times as if he had no other interests or hobbies. (He once said that his wife was his only hobby.) I recall his coming to the laboratory in the morning every once in a while full of enthusiasm for some newly planned research which he had thought out in detail the night before—during a concert. The music, he said, hardly disturbed him at all.

"Another incident which demonstrates the same quality deals with a visit Doctor Hess made to the library for some reference material. The volume he asked for was a very old one and the librarian had great difficulty in finding it. She finally returned from the stacks about 20 minutes later covered with dust and full of apologies. 'Not at all.' said Doctor Hess, 'I was so busy thinking that I didn't notice that you took so long. Besides I've decided on a completely new approach. I think I won't bother with that reference at all.'

"Along with this kind of absent-mindedness, which sometimes gave the appearance of a disregard for the feelings of others, Doctor Hess had a sparkling but occasionally biting sense of humor. The combination earned him a few enemies. Yet without exception those who knew him well and understood his quirks held him in great affection and esteem. He was nevertheless a prodigious worker, willing to drive himself hard and often remarking that 'nothing comes easy/ Yet the most characteristic pose for a portrait would have been seated at his desk, apparently relaxed, his activity hidden from easy sight in his unusually scintillating mind."

His scientific approach to a clinical problem can be illustrated from a paper published with Victor C. Myers in the Journal of the American Medical Association for December 6, 1910, entitled "Carotinemia: a new clinical picture." This description of carotinemia followed his observation of two infants receiving a daily ration of carrots during the testing of the food value of dehydrated vegetables. In the course of the short space of the 4 pages of this report we can discern the evolution of this subject in his mind. He provided a complete clinical description, suspected on clinical grounds its pathogenesis and confirmed the hypothesis by feeding carrots to other children on the same ward. The pigment was detected in the plasma and its solubility in purified pe-

troleum benzin was noted, and it was distinguished from xanthophyll by solubility tests. The range of individual variation was predicted on the basis of observations in 4 patients and there is indicated a continuing interest in the preparation of an extract of carotene from carrots, its parenteral administration and its excretion in the urine. There is evidence of a thorough review of the previous clinical and experimental literature. Other than some more quantitative observations, the subsequent 49 years have added very little to the understanding of carotinemia in infants.

In everything which he undertook, Hess was equally as thorough in his observations, as imaginative in planning experiments, and as keen in his judgment of their clinical application as in this important but simple clinical observation which must have escaped the attention of physicians for many years previously.

Although usually thought of in relation to nutrition, the contributions of Alfred Hess to medical science cover many fields. He described the use of a simple duodenal catheter in infants only two years following its introduction for adults and made some of the first observations on the pancreatic enzymes in infancy. The technique that he described is still a valuable tool in the study of fibrocystic diseases of the pancreas. He had an early interest in infectious disease, particularly in tuberculosis. Much of this experimental work was carried out in the laboratory of Doctor William H. Parke in the New York City Health Department. His bibliography of 227 published papers includes such a diversity of non-nutritional subjects as "Fatal Obliterating Endophlebitis of the Hepatic Veins," "An Examination of Excised Tonsils," "Car Conductors as Dissimenators of Tuberculosis," "German Measles (Rubella): an Experimental Study," "Institutions as Foster Mothers for Infants." He was first to recommend splenectomy in idiopathic thrombocytopenic purpura. In the course of his early studies on the coagulation of the blood in scurvy he noted and described thromboplastin. Both observations were important discoveries in their own right.

The major nutritional interests of Doctor Hess are summarized in two classic monographs ('20, '29) which appeared in 1920 and 1929. The monograph on scurvy is comprehensive and was written after 7 years of intensive study both in man and with guinea pigs. It merits comparison as a mile post in our knowledge of scurvy with the treatise of Lind ('53) and remains the authoritative source book next in date after 1753. Although the chemical nature of ascorbic acid was unknown and analytical chemical methods were not to be established for another decade, there is little that one can now add to the definitive description of the clinical and pathologic picture, prevention and treatment of infantile scurvy given in Hess's monograph. One particular chemical contribution was Hess's demonstration of the catalytic action of minute amounts of copper in the destruction of the anti-scorbutic vitamin in milk, which was reported with Unger in 1921.

His most basic contributions to nutrition were made during the course of studies on rickets which occupied his entire attention during the last 14 years of his life. His first paper on the subject was published in 1917 and demonstrated the effectiveness of cod liver oil in the protection against rickets of Negro infants. He became interested in the seasonal and geographical variations in the incidence of rickets, related these observations to sunlight, and then proceeded to study systematically the influence of sunlight and other sources of irradiation (mercury vapor and carbon arc lamps) on both human and experimental rickets. This led methodically to observations on the ability of ultraviolet irradiation to impart anti-rachitic properties to foods and to cholesterol and its derivatives.

By the spring of 1925 it had been established that the anti-rachitic dietary factor was distinct from fat soluble vitamin A; that rickets could be prevented by either cod liver oil or by exposure to ultraviolet light; that foodstuffs developed anti-rachitic potency after exposure to ultraviolet rays; that cholesterol or a closely related sterol could be rendered anti-rachitic by

similar means; and that activation of cholesterol was attended by a change in its optical spectrum.

Hess was aware of all of this information and had confirmed most of the observations in his own laboratory. In March, 1925, he wrote to the German chemist, Adolph Windaus, who had devoted his life to studying and classifying compounds related to cholesterol. His request that Windaus join the fight against rickets by giving attention to his sterol problem received a courteous reply. However, it was not until more than a year later that further communications from Hess bore fruit. Hess obtained a whole series of cholesterol derivatives from Windaus and irradiated these with ultraviolet light and tested the products in rats. Initial studies established the fact that cholesterol itself was not the compound so activated. In the February, 1927, issue of the Proceedings of the Society for Experimental Biology and Medicine appeared a paper by Hess and Windaus entitled "Development of marked activity in ergosterol following ultraviolet irradiations." This reported that rickets had been cured in rats by as little as 0.003 mg per rat per day. This brief, succinct, classical paper contains but 206 words. It ends with the sentence, "This is a complete report."

The following year Windaus was Awarded the Nobel Prize in chemistry for the work that culminated in this report. Although Hess was not included in this honor, Windaus repeatedly gave him credit for his part in stimulating this research and he shared with Hess the monetary portion of the award as evidence of this indebtedness. (These funds were used to finance additional researches.) In a paper presented before the Prussian Academy of Science on July 1, 1937, Windaus stated that "his studies had always followed a systematic rate of development, namely, one study suggested the next, but in the question of the anti-rachitic vitamin it was not so—I indicate that the stimulus to participate in the vitamin studies was given by Alfred Hess of New York." Windaus died in June, 1959. The correspondence between these two collaborators is currently being prepared for publication by Doctor Samuel Karelitz.

Although many of Hess's friends felt that he should have received the Nobel Prize as well, as has been pointed out by Ashley Weech ('58) the acclaim received by Windaus was of great importance. "The experience of Hess in 1925 of being unable to persuade an organic chemist to collaborate actively in solving a medical problem was by no means unique. Research in the basic sciences in its effort to achieve the status of applied research was oriented toward industry rather than biology or medicine. The awarding of the prize to Windaus changed all this. In 1929 Hess himself complained at the number of communications appearing from laboratories of pure as well as of applied science had become so great as to make it almost impossible to keep pace with them." Perhaps the efforts of Hess to marshall the abilities of others to solve the clinical problem which occupied his attention may have been in large part responsible for the extensive collaboration which now exists between many sciences and medicine.

Many honors did come to Alfred Hess. His early endeavors earned him membership in the American Pediatric Society and later the Association of American Physicians. He delivered a Harvey lecture in New York, the Cutter lectures at Harvard, the Ingleby lectures at Birmingham, England, and was awarded the honorary degree of Doctor of Science by the University of Michigan. In 1927 he received the John Scott medal from the Franklin Society and, 4 years later, the John Mather Smith Award for his work on nutrition.

Hess continued to work under high pressure despite warnings by his physician that he should reduce his pace and give up public speaking because of hypertension and minor cardiac attacks. He disregarded this advice and insisted on speaking at a nurses' graduation exercise on December 5, 1933. He suddenly collapsed and died in his automobile on the way home.

Time does not dim, but highlights, the contributions of Hess. Perusal of his collected works 25 years following his death is more like reading current literature than history. His thinking was so sound and his judgment so fine that little that he

authored had less pertinence and validity today than when it was written. Not least among his contributions is the example which he set for nutritional scientists in his clinical curiosity, his method of work and pattern of investigation.

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