geologist has extended his exploring and collecting work to all lands that can be reached and studied. Wonderful series of fossils have been found in western North America, a work of collecting which had just begun in Darwin's day, when no one had any conception of the astonishing museum of long-vanished animal life which is entombed in the rocks of arid and semi-arid America. As we have already learned, one of Dr. Leidy's securest titles to fame is the great work which he did in revealing and reconstructing this record. Likewise, Africa, Asia, and even parts of Europe, have all yielded up treasures of fossils, of which Darwin had no inkling. He himself was one of the first to discover the richly fossiliferous beds of Patagonia, but he had not the smallest conception of what was to be found there sixty years and more after his explorations in South America.

There has thus been a veritable flood of new discoveries which put the evolutionary conception to the severest possible test. The result has been that that conception has been supported and strengthened in a wonderful way, and is far stronger and more universally accepted than it was sixty years ago. No competent person would maintain that all problems have been solved and all difficulties removed; far from it, but those difficulties are plainly due to lack of information. The record of the development of living things which is contained in the rocks is like a book from which many pages, even whole chapters, have been torn out. On the other hand, many chapters have been preserved, of which the fullness and precision make a perfectly unambiguous and most eloquent support of the theory. More than ever is it true, that by far the best, most probable and most convincing interpretation of the facts of paleontology is that offered by the theory of evolution.

This result is all the more striking when the state of the other sciences in 1859 is taken into consideration. Physics, chemistry, astronomy, and even mathematics, have been more or less completely reconstructed since that time. The principal theories which then dominated physics and chemistry have nearly all been abandoned in favor of newer interpretations. The advance of discovery has been fatal to the older conceptions. This is not true of the theory of evolution which, as stated above, is more thoroughly established and more universally accepted than ever before.

In 1876-7 Huxley delivered a series of lectures on evolution in New York; and the lecture entitled (I quote from memory) "The Demonstrative Evidence of Evolution" was devoted to the discoveries of American paleontology, and more particularly to the genealogy of the modern horses, as that had been worked out by Professor Marsh. Huxley himself had been the first to attempt a scheme of equine evolution; but, as he had access only to European material, he could make but an approximation to the later conceptions. When he saw Marsh's finely preserved fossils, arranged in chronological order, he was convinced that he had before him an actual and positive demonstration of the evolutionary theory. It wasn't that, perhaps, but it was evidence of so high a degree of probability as to be convincing. That Leidy, though a thorough-going evolutionist, has little to say concerning the interpretation of the fossils, which he discovered and described, seems at first sight surprising. But he was, in fact, laying the foundations of the theoretical structure. It was he who first showed the chronological stages and modifications in the history of many families, horses, camels, rhinoceroses, wolves, cats, etc.; and that he did not categorically draw the obvious conclusions was due to his belief that theoretical discussions should wait upon the acquisition of more complete material.

These are the more important of the applications of paleontology. Can it be a matter of surprise that Leidy, with his remarkably clear and broad outlook over the world of nature, should have felt that paleontology was the main work of his life?

WILLIAM BERRYMAN SCOTT
PRINCETON UNIVERSITY

THE CONTRIBUTION OF BIOLOGY, CHEMISTRY AND PHYSICS TO THE NEWER KNOWLEDGE OF RICKETS[1]

THE investigation of rickets is an outstanding example of the value of interweaving the basic sciences with clinical medicine and may well serve as a text to illustrate "the contributions of other sciences to medicine." It is an axiom that many disorders have been elucidated only with the aid of chemistry and animal experimentation, but the instances are few in which biology, inorganic and organic chemistry and various forms of physics have been resorted to so frequently and to such a degree. Although decreasing in incidence and severity, rickets still undoubtedly is the most common nutritional disorder of early childhood in the temperate zones. It has been the object of intermittent study ever since Glisson first described signs and symptoms of the "Englische Krankheit" in 1650. Our acquisition of knowledge concerning its various aspects may

[1] Presented as part of a symposium on "The contributions of other sciences to medicine" at the annual meeting of the American Association for the Advancement of Science, Nashville, Dec. 28, 1927.

be divided broadly into two periods, the one—which may be termed the clinical and pathologic era—comprises the long span between 1650 and 1918, and the other—that of "the newer rickets"—embraces less than a decade, from 1918 until to-day. The latter period, which is still in full fruition, is an indirect result—a by-product—of the discovery of the vitamins. Using this new concept as a fulcrum, and abandoning the old and fixed idea of producing rickets experimentally by limiting the intake of calcium, Mellanby successfully brought about this disorder in puppies by depriving them of a specific fat-soluble factor. It is true that he mistook what we now recognize as the fat-soluble vitamin for the antirachitic factor, but there can be no doubt but that he succeeded in inducing true rachitic lesions. Shortly thereafter investigators in this country—McCollum and his coworkers, as well as Sherman and Pappenheimer—produced typical histologic lesions in the rat by means of rations deficient in phosphorus.

The first factor which led to the era of "the newer rickets" emanated therefore from the biologic or physiologic laboratory and, as has been the case so often in connection with infectious as well as nutritional disorders, consisted of the ability to reproduce at will a disorder in an experimental animal. The second propelling influence following on the heels of the first, although having no connection with it, was the demonstration by Huldschinsky in 1918 of the importance of light, of the fact that ultra-violet radiations are a specific preventive or curative antirachitic agent. From this time until to-day, rickets—which for two and a half centuries had awakened but a fitful interest in the clinician—has been the object of intense investigation in many of the biologic, chemical and physical laboratories both in this country and abroad.

The earliest and simplest chemical studies were carried out in the clinic. Iverson and Lenstrup, of Copenhagen, as well as Howland and his coworkers in this country, showed the old conception to be erroneous which held that a deficiency of calcium is the essential disturbance in rickets, and proved that it is the phosphorus ion which dominates the metabolic picture. The inorganic phosphorus of the blood was found to be low. Indeed, due to the wide prevalence of rickets, it was shown later that there is what may be termed "a phosphate tide" in the blood of infants, an ebb during the winter months followed by a flood in the spring with the advent of sunshine. We shall find that the later chemical studies, those on the sterols, have been far more complex and have taxed to the utmost the resources and ingenuity of experienced organic chemists.

Up to this time chemistry and pathology had aided the clinician in the solution of his problems. As soon as it had been demonstrated that certain light waves are a specific curative agent, it was necessary to turn to physics for information. Naturally, the first point of attack was the segregation and definition of the specific radiations which were endowed with this remarkable therapeutic property. By means of filters of known penetrability it was soon found that ultra-violet radiations of greater length than about 320 $\mu\mu$, or 3,200 engstrom units, were unable to protect animals from rickets which were fed a diet deficient either in phosphorus or in calcium. This observation proved to be of interest not only to clinicians but to the large number of workers who were actively engaged in studying various biological processes, for example, the growth of plants, or the factors involved in egg production and fertilization or the rôle of light in the cultivation of cells *in vitro*. *To-day rickets has become the established criterion for appraising the biologic action of ultra-violet waves in the region of 300 millimicrons.*

In 1924, less than four years ago, it was shown by me and almost simultaneously by Steenbock that the specific ultra-violet radiations exert their action not only on animals exposed to their influence, but also indirectly on various foodstuffs. As is well known, milk, flour, oils, cereals, etc., can be rendered antirachitic by this means—activation being restricted to the same band of ultra-violet light as in the case of animals. This newer knowledge, combining as it did physical and chemical aspects, led to renewed activity in these fields of endeavor. The first question was to attempt to discover the substance in the food which underwent this remarkable transformation. This study, although having made steady progress, is still incomplete and is being actively pursued in various laboratories both in this country and abroad. It was ascertained within a few months that it is the non-saponifiable fraction and not the fat in the foods which is essential to activation. At the end of 1924 both Steenbock and I were able to report that it is the cholesterol in the animal cell, or phytosterol, its counterpart in the vegetable cell, which undergoes specific alteration. Cholesterol purified by repeated crystallizations, which from the standpoint of rickets is inert, could be rendered highly antirachitic by subjection to ultra-violet irradiation for a minute or less. Its melting-point, specific rotation and chemical constitution had undergone no apparent change in the course of the procedure, and it seemed as if the new product were an isomer of cholesterol. During this period studies were being carried out concurrently in the physical laboratory. The problem of the activation of cholesterol lent itself readily to an investigation by means of absorption spectra. It was found that the well-known absorption bands of cholesterol were definitely altered as a result of irradiation, that the sterol becomes more permeable to certain definite wave-lengths of ultra-violet light. This work, into which we shall not enter in detail, was first undertaken in this country, and has more recently been refined and extended by Heilbron in Liverpool, and Pohl in Goettingen. Furthermore, by means of the use of monochromatic ultra-violet light, it was shown that the uppermost limit of the antirachitic field may be placed at 313 μμ, and that even at this point its action is feeble. When we bear in mind that the shortest rays of the sun which reach the surface of the earth rarely are less than 300 mm. in length, it is evident how circumscribed is the area of specific solar radiations. *A difference of a few millimicrons or millionths of a millimeter determines whether or not waves are specific or ineffective.*

It was soon evident that only a very small fraction of the cholesterol becomes activated following irradiation, less than one per cent. This observation raised the question in the minds of several investigators, as to whether it is truly the cholesterol which is transformed or some associated sterol—a subject which during the past year has been studied by Windaus and myself, as well as by Rosenheim and his coworkers in London. It developed that another unsaturated sterol—a sterol with 3 unsaturated bonds—is mainly concerned in the elaboration of the antirachitic factor, namely ergosterol, which heretofore has been extracted from ergot and from yeast, but which is now being found more widely distributed in nature. It would lead too far afield to discuss the moot question of the activation of cholesterol and other sterols. In brief, it may be stated that it has not been shown definitely that cholesterol, as well as ergosterol, can not be activated. In this connection, the minuteness of the amount of irradiated ergosterol required to protect an animal should be emphasized; it has been found that *1/10,000 of a milligram or 1/10,000,000 of a gram daily is sufficient to confer protection.* When we bear in mind that this infinitesimal amount is given by mouth, it is difficult to conceive that the specific antirachitic factor exerts its curative action directly and bodily on the various epiphyses throughout the body.

Parallel with these investigations on ultra-violet radiations and the sterols, which engaged the attention of the physicist and of the chemist, the question was being considered as to how these newer ideas could be brought into consonance with the well-established fact of the specific antirachitic properties of cod-liver oil. At first the two phenomena seemed irreconcilable, but, as you know, it soon was demonstrated that the activity of cod-liver oil in rickets rests on the same basis as that of foods which have been subjected to irradiation—that both are dependent on the action of a specific sterol. In passing, it should be added, however, that it has not been shown that the therapeutic activity of cod-liver oil is confined to the effect of this sterol.

In my review of this subject, it has been necessary to treat the advances in the fields of biology, chemistry and physics as if they took place consecutively. As a matter of fact, they have progressed at one and the same time, new discoveries by the physicist being made at once the basis for some newer chemical investigation and both in turn leading perhaps to interesting developments in the provinces of experimental biology or clinical therapeutics. Some of these studies have been carried out in conjunction or close cooperation with the clinic, others have been made in laboratories devoted solely to investigations in pure science. In the light of recent studies of the vitamins and hormones, it would seem that, in general, this probably will be the method—if it can be called a method—of advancement in the future. It is questioned often whether newer technics and discoveries in medicine will be evolved by the clinician in ward and laboratory, or whether, as it becomes necessary to delve ever deeper into the realms of pure science, the clinician, in spite of his modern training, will not become dependent upon the discoveries of the physicist, the chemist and others occupied with the basic sciences.

No one can answer this question with any degree of certainty. It seems probable nevertheless that for some time to come the clinician—owing to his strategic position in the broad realm of medicine—will continue to make valuable and even basic contributions to our store of knowledge, and that the recent experience in the field of rickets will from time to time be repeated in other provinces of clinical medicine. It can, however, be safely predicted that in order to gain this newer knowledge we must once more call to our aid in varying degree biology, chemistry and physics.

ALFRED F. HESS

NEW YORK, N. Y.

ACOUSTICS OF AUDITORIUMS*

A CONSIDERATION of recent investigations led the writer logically and unexpectedly to the conclusion that good acoustics in an auditorium may be obtained by making it like the outdoor theater of the Greeks. Also, it is concluded that better acoustics appears likely if a study is made of the way in which speech and music are generated, with special consideration

* An address given March 1 at the Physics Colloquium, University of Illinois.