Rickets, including osteomalacia and tetany / by Alfred F. Hess.

H. A. Harris.
U.C.H.

Glisson's "De Rachitide," 1671.

RICKETS

INCLUDING

OSTEOMALACIA AND TETANY

BY

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THIS BOOK IS INSCRIBED TO

S. S. H.

IN APPRECIATION OF HER GENEROUS COÖPERATION AND

SYMPATHETIC UNDERSTANDING

Would that you could meet the sun and
the wind with more of your skin and less
of your raiment,
For the breath of life is in the sunlight
and the hand of life is in the wind.

"The Prophet," by Kahlil Gibran

PREFACE.

No justification seems necessary for the publication of a new book on rickets. It must be evident, even to the casual observer, that a new era has come about and that many of the time-honored theories in the text-books are no longer tenable either in essence or in detail. Indeed, the advance in our knowledge during the past ten years, and the change in point of view incident to this knowledge, have been significant phenomena in the progress of modern medicine. Our concept of rickets may be divided broadly into two periods, the one—which may be termed the clinical and pathological era—comprises the long span between 1650 and 1918, and the other—that of the Newer Rickets—embraces merely a decade, from 1918 until today. The latter period, which is still in fruition, is an indirect result—a by-product of the discovery of the vitamins. Two discoveries have contributed to the birth of this Newer Rickets, neither of which has depended in any way upon the other. The first factor emanated from the biological laboratory and consisted of a method of inducing rickets experimentally in animals, rendering it possible to study various aspects under conditions which are subject to exact control and modification. This technique made it possible for the first time to gauge the comparative etiological importance of faulty hygiene and diet. The second propelling influence, following close on the heels of the first, was the discovery that the lack of ultra-violet light or energy plays the dominant rôle in the causation of rickets, and that it is a specific therapeutic agent for prophylaxis and for cure. From the date of these discoveries until today, rickets—which had awakened but a fitful interest in the clinician—has been the object of intense investigation in this country and abroad, not only in medical clinics but in many laboratories of biology, chemistry and physics. Interest was further stimulated by the discovery almost five years ago that the ultra-violet rays can also exert their remarkable action indirectly—that they can endow certain oils and foods with antirachitic properties. Later it was shown that a particular sterol—ergosterol—could be activated to a remarkable degree. This knowledge not only made available new methods of therapy, but necessitated a revision in our conception of the chemical action of these rays.

My interest in rickets was incidental to the investigation of infantile scurvy, which occupied my attention for a period of about

seven years. This was in 1916, before the renaissance period had begun, and when rickets was still a disorder which aroused but little interest and played an insignificant rôle in the medical literature. During the intervening twelve years, I have been almost continuously engaged, with the aid of numerous co-workers, in the clinic and in the laboratory, in investigations relating to rickets. The results of this work have been published in a large number of communications which have embraced various disciplines, some being concerned with chemical, physical or biological rather than with medical aspects, some being experimental, others purely clinical in character. From their nature, the communications have necessarily been distributed in a variety of periodicals which are not usually read by any one group of readers. The more significant features of the work of these years have been reappraised and incorporated in this volume.

The book is written for the practitioner of medicine as well as for the nutrition worker. It was begun about five years ago. Since then, the writing has progressed very irregularly, partly due to the pressure of other work, but more particularly to the fact that new and important observations were being published from time to time, which seemed to render delay advisable. As the result of these frequent pauses, all the chapters have had to be revised and some even completely rewritten during the past year or two. Throughout the book, results obtained experimentally in the laboratory have been weighed and appraised in the light of clinical experience, and wherever there have been discrepancies or disagreements, the clinic has been adjudged the final arbiter. A definite attempt has been made to avoid a break with the past—with the rickets previous to 1918—by presenting an unbroken exposition of both eras, welding them together into a homogeneous unit. To this end, a short historical review has been introduced at the beginning of almost every chapter. This course was followed, as there seemed to be danger that, in the enthusiasm of our newer and more objective knowledge, we might cast aside and lose the fruits of generations of valuable clinical observation.

As the result of the interest in rickets in so many fields of endeavor, the number of communications which have appeared from the clinics and from the laboratories of pure as well as of applied science, has become so great that it is almost impossible for even the specialist to keep pace with them. It is hoped, therefore, that a failure to take due cognizance of investigations will be interpreted in this light, and that it will be realized that oversight must be incident to the flood of publication. It may be added, in this connection, that no attempt at bibliographic display has been made. The aim has been rather to have the bibliography selective and comprehensive.

It is arranged according to chapters at the end of the book, and includes few works which have not been read by the author.

In order to present a more complete picture, chapters on late rickets, on osteomalacia and on tetany have been included. Our point of view regarding these disorders has also been enlarged and clarified during the past decade. For example, the conception of late rickets has been extended by the experiences of Germany and Austria during the post-war period, as well as by the recognition of renal and of cœliac rickets. The new technique used in elucidating rickets has recently been applied to osteomalacia, by investigators in Peking, and for the first time an opportunity has been furnished of comparing the radiographic appearances, the chemical analyses of the blood and the response to specific therapy of these two closely related disorders. During the past few years, infantile tetany has been studied intensively from the standpoint of the acid-base equilibrium, and has been rendered much more amenable to treatment through the introduction of the use of acid therapy, as well as of ultra-violet light.

It is realized that our knowledge of rickets is far from complete, and that new and important discoveries of various aspects, particularly in regard to pathogenesis, may be made in the not far distant future. But so much has been accomplished during the past decade and so remarkable has been the change in our clinical and scientific point of view, that the time seemed ripe to garner the harvest without waiting for additional crops.

It is with pleasure that I acknowledge my obligation to Miss Mildred Weinstock, who has assisted in carrying out much of the laboratory work incorporated in this volume. Thanks are due also to Miss Helen Rivkin and to Dr. J. M. Lewis, who assisted in several of the more recent investigations. To my associates in the clinic who have shared in the observations, and to many friends who have read various chapters in the course of their preparation and have given helpful advice, I wish to express my sincere appreciation.

A. F. H.

New York City.

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RICKETS.

INTRODUCTION.

Rickets must be regarded as essentially a climatic disorder. It probably existed in the temperate zones before these regions became civilized. No doubt civilization, with the increase in "domestication" which it entailed, led to the spread of rickets, but there are numerous indications that the disorder occurred among peoples living in a primitive state. It is more accurate to regard rickets as one of the outgrowths of industrialism and of "the industrial age," a result of the urbanization of the population—a movement which has been steadily increasing since the beginning of the seventeenth century. It is interesting to reflect that the same social conditions which led to the intensification of the "englische Krankheit," seem destined to mitigate its severity and decrease its occurrence—that science, one of the outstanding accomplishments of civilization, has discovered specific measures for its prevention. Medicine, however, cannot plume itself unreservedly on this accomplishment. It should be remembered that the road which led to this discovery was not consciously directed toward this goal, but toward the elucidation of an obscure dietary deficiency in animals. It so happened that the appreciation of vitamins was applicable to the unravelling of the problem of rickets. Our knowledge of the etiology of tetany came about by a still more fortuitous route. The startling effect of the accidental removal of the parathyroid glands was noted at a time when the significance of the endocrine organs had begun to be appreciated. For many years, both disorders had been subject to the vogues and vagaries of medicine, as they held sway from time to time—only recently both had been ascribed to the action of bacteria.

In the preface, reference has been made to the "newer rickets." This term has reference not merely to our newer understanding of its etiology, more particularly of the dominant rôle of ultra-violet light, but to the change in its clinical aspect. The "older rickets" was in general of the florid type and frequently a striking manifestation, as may be realized from numerous illustrations and descriptions in the text-books of fifty or more years ago. It was common for the extremities to be markedly bent and the chest greatly mis-

shapen. Today, the disorder generally is so mild that it readily escapes observation, and the case with marked deformity is becoming infrequent. In the negro of the northern states, however, the type of older rickets is by no means exceptional. He manifests the disorder to as great a degree as did the white child in the middle of the past century. Indeed our most serious problem, in connection with the eradication of rickets from the community, is the negro.

It is intimated sometimes that rickets is a disturbance of minor importance, in fact that it is immaterial whether or not it develops, as it is a self-limited disorder and its deformities have a marked tendency to right themselves with advancing childhood. This is an unscientific and dangerous point of view to take of any pathological condition. Experience has taught us that we are not yet in a position to gauge the significance of diseases, especially of disorders of nutrition, and that none should be disregarded or neglected. In relation to rickets, the *laissez-faire* policy is a mistake, as, although rickets does not figure directly in our mortality statistics, it plays a rôle indirectly both in the mortality and in the morbidity of the community. Many of the operative procedures incident to childbirth, which lead to the death or injury of mother or infant, are properly attributed to rachitic deformities of the pelvis. The same holds true for many of the deaths from convulsions in infancy, which are to be regarded as manifestations of tetany—a disorder which is essentially a complication of rickets. Rickets also has to be considered in connection with the pneumonia of infants. It is believed that rickets increases the susceptibility to pneumonia. Many physicians believe that it is the main factor in the exceptionally high incidence of this disease among the negroes and Italians in the large cities. Even though there is some doubt as to whether rickets predisposes to pneumonia, it seems certain that it renders the prognosis much graver and is a factor in the mortality. Finally, we should not lose sight of the fact that as yet we know little of the potentiality, in other words, of the ultimate consequences, of the numerous nutritional disturbances of infancy. There is no means of judging whether a disorder such as rickets, with its lesions of the bones, teeth, muscles and blood, as well as psychic disturbances, may not result in functional or organic disabilities in adult life.

Rickets is unique in being blessed with not only one but several specific curative agents. In addition to cod-liver oil, we have ultraviolet irradiation, irradiated foods, and irradiated ergosterol. It must be clear that the disorder is destined to become much less common and severe. By some it is thought that within the next decade, or even sooner, it will be almost completely eradicated, that it will become as rare as has infantile scurvy since the wide-spread use of orange juice. The difficulty in fulfilling this prediction is that

the diffusion and the practical application of our knowledge, more particularly in regard to diagnosis, still lag far behind. In general, physicians are far from appreciating the wide distribution of rickets. To my mind, it is still true that many more cases are overlooked than are recognized. Such being the case, our hope of eradicating rickets must rest on routine prophylactic measures, on giving specific antirachitic therapy of one sort or another, without trusting to diagnosis. Whether this end will be accomplished by means of cod-liver oil, by irradiated milk or by irradiated ergosterol, will have to be determined by practical experience. The eradication of rickets may be viewed in a two-fold light—either from the practical point of view, as the stamping out of clinical rickets, or from the ideal point of view of doing away with even the minor manifestations of the disorder, even such as are evident only by chemical analyses of the blood.

It is difficult to look back ten years, or to transport ourselves again to the old era—the days when the importance of ultra-violet light was not appreciated or surmised. This may perhaps be accomplished by picturing the conditions which came to pass in Germany, Austria and Poland toward the end of the World War, but, more especially, during the early post-war period. Throughout these countries, nutritional disorders of the bones—rickets, "hunger osteomalacia," "war osteopathy"—developed to a degree and extent such as had never been experienced in the history of medicine. Marked deformities of the spine and of the extremities, multiple fractures and functional disabilities by the thousand, were observed throughout the land. It is sad to contemplate that this epidemic, with its attendant misery, came about while the means for its prevention and cure were close at hand. Had physicians in 1918–1920 known of the specific value of sunlight and of artificial ultra-violet rays, the so-called "war osteomalacia" would never have been rampant. Had the discovery of the power of these rays to activate food and ergosterol been made but a few years sooner, these specific agents could have been used with telling effect. What would have been easier than to have grown yeast in large quantities and to have irradiated it? An example such as this well illustrates the importance of the advances which have been made in this field during the past few years, and the implications which may be involved in regard to the health and welfare of the civilized world.

The subject as a whole may be viewed in quite another light. The investigation of rickets is perhaps the outstanding example of the value of interweaving the basic sciences with clinical medicine and might 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.

The earliest and simplest chemical studies were carried out in the clinic. The old conception was shown to be erroneous which held that a deficiency of calcium is the essential disturbance in rickets, and it was shown that a disturbance of phosphorus must also be included in the metabolic picture. The inorganic phosphorus of the blood was found to be low. Indeed, 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 315 $\mu\mu$ or 3150 angström units, were unable to protect animals 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, such as the growth of plants, the factors involved in egg production and fertilization or the rôle of light in the cultivation of cells *in vitro*. *Today rickets has become the established criterion for appraising the biological action of ultra-violet waves in the region of 300 millimicrons.*

In reviews of this subject, it is customary 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 concurrently, 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 province of experimental biology or clinical therapeutics. Some of these studies have been carried out in conjunction or close coöperation 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 techniques 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.

CHAPTER I.

THE HISTORY OF RICKETS.

To trace the history of a disease from its earliest beginnings or to ascertain the date of its recognition is a task which is interesting but most unsatisfactory. Especially is this true of a disorder such as rickets, which is not characterized by acute symptoms such as pain or fever, and which practically never leads to death. The difficulties involved may be appreciated when it is borne in mind that we cannot identify, from the descriptions which have come down to us, the true nature of even some of the epidemic diseases which swept over Europe during the Middle Ages, in spite of the fact that their visitations were most dramatic and their clinical manifestations striking. Imagine then the uncertainties and the conflicting impressions which beset those who today attempt the diagnosis of various disabilities from accounts which were written before or shortly after the advent of the Christian era, and who not infrequently have at their command only a few stray paragraphs. It is not to be wondered at that often the imagination comes to the rescue and that the interpretations give indication of the resourcefulness of the investigator. It is thus clear that there is ample opportunity for sincere differences of opinion.

As a matter of course, endeavors were made to ascertain whether rickets existed at the period of the earliest civilizations, especially among the Egyptians, whose monuments have proved so fertile a field for archæological studies. In the light of our recent knowledge of the etiology of rickets, however, such investigations would seem to be doomed to failure. For although the cause of rickets has not been entirely clarified, it is certain that this disorder cannot flourish to a noteworthy degree in lands where sunshine is abundant. It is therefore not remarkable that no reference to rickets was found by Findlay in his examination of the translations of available medical papyri. In vain he searched the archæological records of Ebers, Brugsch and London. It may be noted in passing that Ebers mentions an interesting reference to night-blindness and xerophthalmia in Egypt about 1500 B.C., and an observation to the effect that this condition can be cured by feeding liver. The anatomist, G. Elliot Smith, states that "clear, unmistakable evidence of rickets has not been found in human bones in any cemetery in Egypt or Nubia." Although such testimony is valuable, it is not

adequate, as histological examinations of the bones of young children have not been reported. However, in all probability subsequent investigations will confirm Smith's conclusions, for if rickets did exist in ancient Egypt, it must have been of exceptional occurrence and of mild degree. In view of the fact that many are of the opinion that rickets is the most important etiological factor in dental caries and that there was probably little or no rickets in Egypt, Ruffer's statement that "dental caries occurred in all periods of Egyptian history" must incline us to the view that there are other important factors leading to destruction of the teeth. Ruffer adds that "nothing definite is known regarding the incidence of caries in children."

In discussing evidence of rickets drawn from archæological studies, the report of Jaeger should be mentioned and the examination of some bones which date back to the early Middle Ages. This investigation cites the instance of a femur found in a prehistoric grave of the Hallstatt period which showed marked lateral bowing supposedly due to rickets. The data which are presented are not entirely convincing, but the author tells us that the histological diagnosis was substantiated by such eminent pathologists as Toldt, Waldeyer and Duerck. Furthermore, he describes four femora which were found in an ossarium at Channmuenster; in these latter cases the diagnosis seems open to question as apparently it was not fortified by a microscopic examination. It is quite probable that bones manifesting rachitic lesions will be disclosed in the course of archæological investigations in Europe, especially if bones of young children are uncovered, for there can be little doubt that rickets must have occurred in this part of the world at all times.

When we turn to a later period, to the time when Greece held its sway, the evidence as to the occurrence of rickets is no more satisfactory. There are no reports of the histological examinations of bones. We have merely the writing of Hippocrates to fall back upon. It is not surprising that zealous students have discovered references to rickets in the works of the Father of Medicine, for they have found allusions to almost every other disease. To my mind the paragraph which is believed to refer to rickets is so vague that it cannot be accepted. The supposed reference is in the chapter on joints and is thus rendered in the recent translation of the Loeb Classical Library: "When hump-back occurs in children before the body has completed its growth, the legs and arms attain full size, but the body will not grow correspondingly at the spine; these parts are defective. And where the hump is above the diaphragm, the ribs do not enlarge in breadth, but forwards, and the chest becomes pointed instead of broad; the patients also get short of breath and hoarse, for the cavities which receive and send out the breath have smaller capacity. . . . They have also, as a rule,

hard and unripened tubercles in the lungs; for the origin of the curvature and contraction is in most cases due to such gatherings, in which the neighboring ligaments take part. Cases where the curvature is below the diaphragm are sometimes complicated with affections of the kidneys and parts about the bladder, and besides there are purulent abscessions in the lumbar region and about the groins, chronic and hard to cure; and neither of these causes resolution of the curvatures." Not only the description itself but the context leads one to infer that Hippocrates had in mind tuberculosis of the spine rather than rickets. That rickets did occur in Athens at that time is quite possible, but that it should have presented itself in such marked intensity as to have produced kyphosis of the spine and marked deformities of the thorax seems most improbable. So great a degree of rickets is not compatible with a climate such as that of Greece.

The first satisfactory description of rickets should be attributed to Soranus of Ephesus, who was educated in Alexandria and practiced medicine in Rome in the first and second centuries after Christ, during the reigns of Trajan and Hadrian, a period which in medicine as well as in art is known as the Graeco-Roman era. Soranus was not only the most eminent obstetrician in antiquity, but the most distinguished pediatrist; his memory was reverenced far into the Middle Ages. The description by Soranus, in his book on gynecology and pediatrics, of which we have excellent French and German translations, is clear and unmistakable but was entirely overlooked until recently. In the chapter entitled "How must one teach children to sit and to stand?" he proceeds as follows: "When a child attempts to sit or to stand, one must aid its movements. If it sits too early or too long, it will tend to become deformed, as the vertebral column bends, due to the softness of the bones. If it stands or walks too early, the legs (especially the thighs) will become crooked." He goes on to state that one observes these manifestations particularly in Rome, due to the ignorance of child hygiene and the lack of loving care by the Roman mothers as compared to those of Greece. From this account it would seem that rickets was not an exceptional phenomenon in Rome during the second century of the present era. We should expect such to have been the case in the days of Soranus, as Rome was a great metropolis at that time and rickets is common there today.

There is also little doubt that Galen, a contemporary of Soranus, refers to rickets in his work "De Morborum Causis." The specific passage may be found in W. Ebstein's interesting historical paper on rickets. It would seem, as Delpeuch suggests, that Galen was cognizant of the description of Soranus. However, he adds something to the previous account. He distinguishes between knock-knee and bow-legs, and also refers to the deformities of the chest, the

funnel-shaped and the pigeon breast. The latter he attributes to the pressure of swaddling bandages which the nurses apply, especially to female infants, in the early months of life in order to make the hips prominent. This calls to mind a report published in German by Baelz, entitled "The Japanese constriction furrow of the thorax." The author describes an encircling deformity below the nipple line produced by the pressure of swaddling clothes upon the soft bones of infants. It is also of interest, in view of modern etiological conceptions, to note that he refers to one of the acknowledged errors in nutrition, namely, excessive nourishment.

There is no further reference to rickets, at least none has yet been discovered, until we come to the sixteenth century, when Theodosius of Bologna mentioned the disorder in his medical epistles published about the middle of the century. It is worthy of note that these observations emanated once again from Italy, a fact to be attributed not to the exceptional incidence of rickets in that country, but to Italy's preëminent position in medicine. In his forty-second letter, Theodosius informs us that he was asked to see a pale infant, aged seventeen months, which could not move or sit, indeed could hardly hold its head erect, and which showed in the lower dorsal region both a gibbus and a marked lateral curvature.[1] The very age of this infant points to rickets and seems to preclude confusion with any other pathological condition. He does not comment on the frequency of this "cruel" syndrome, but rickets of this intensity must have been rare at all times.

Some have stated that Barth Reusner, a Swiss physician, wrote a book or paper on rickets at this period entitled "de tabe pectorea." It is supposed to have been published in Basel in 1582 and to have been therefore the first book treating of this disorder. Rehn searched for it without success in the various libraries of Europe. I have made inquiry of the library at Basel as well as other libraries in Switzerland, as well as of the British Museum, Surgeon General's Library and the Medical Military Institute in Berlin. None of these institutions could give me any information in regard to this work which is included in Ploucquet's Literary Digest. A physician named Barth Reusner lived in Basel but died in 1532. It seems highly questionable whether the first book on rickets was written by Reusner. At any rate, under the circumstances, we shall have to omit further consideration of this highly problematic work.

No writings have come down to us in regard to rickets during the fifteenth century. The only evidence during this period is that which may be drawn from various paintings by Dutch and German masters who so often included infants in their religious groups. Foote recently has written interestingly on this aspect, illustrating

[1] The Latin text of this epistle (Pro puero, etc.) will be found in Rehn's article on rickets, Gerhardt's Handb. d. Kinderheilk., 1878, **3**, 45.

his paper with numerous reproductions of paintings showing babies with the classical signs of rickets, especially the deformed thorax.

Two French writers, who lived during the first half of the seventeenth century, are credited with descriptions of rickets. The first work is by Guillimeau, a court surgeon, and treats of childbirth, to which is added a "Treatise of the Diseases of Infants and Young Children;" it was published in 1609, and translated into English three years later. The following passage shows unquestionably that the author had rickets in mind. "But we must also look and have an eye that the nurse or she that swathes and dresses him do not make him worse, and of a well-fashioned child, in all the parts of his body, do not make him deformed or misshapen, and so spoil him. For in swathing the child most commonly they bind him and crush him so hard that they make him grow crooked . . . but this crushing makes his breast and the ribs which are fastened to the back-bone, to stand out, so that they are bended and draw the vertebræ to them, which makes the backbone to bend and give either inwardly or outwardly or else to one side; and that causeth the child to be either crump-shouldered or crooked-brested, or else to have one of his shoulders stand farther out than the other. Some also bind the hips so hard that they become very small, and that hinders them from growing and waxing big, which doth much harm, especially to maids who should have large hips, that when they come of age, they may bring forth goodly children. Galen has observed that the too straight and hard binding or crushing of the hams and legs of little children when they are swathed, doth make them grow crooked-legged, and they will remain, as the Latines call it, Vari or Valgi, growing either inward or outward with their knees. This imperfection may also happen through the nurses fault, by carrying the child always upon one arm, and the same side, and by holding the child's knees hard toward her and making them stand like a bow." An excellent sketch of the rachitic deformities of the vertebral column, the thoracic wall and the lower extremities! Note the expression "bow-legs" and the suggestion that rachitic deformities of the pelvis lead to difficulties in childbirth.

Ambroise Paré, the famous surgeon of Francis I, in his "Works" published in 1633 describes the "valgus" and "varus" deformities of the legs. It is true that he does not depict active infantile rickets, but rather the deformities which follow in its wake. The interest in this description lies in the fact that it furnishes still another undoubted reference to rickets and, furthermore, implies what we had been led to infer from the writings of Guillimeau—that at this period it was not an exceptional disorder in France. This view gains further corroboration from the account of Bootius which will be referred to later.

We now come to what may be termed the English or Glissonian

period in the history of rickets; one which revolves principally around the names of Glisson and Whistler and has been the subject of heated argument and controversy, not unmixed with partisanship, for many years. The name of Bootius should be included in this group, as he was one of the writers who described rickets about the middle of the seventeenth century.

In 1645 Daniel Whistler, an Englishman, took his degree of Doctor of Medicine at Leyden and published in Latin an inaugural thesis on rickets entitled: "Inaugural Medical Disputation on the Disease of English Children Which is Popularly Termed The Rickets."[1] The work is a small monograph of some fourteen pages and is characterized by terseness and directness. It is almost a compendium, and one would hardly take it to be the first or even a very early description of a disease. At that time Whistler was but twenty-six years of age. In later life he became one of the noted physicians of his day and was elected to the Presidency of the Royal College of Physicians. It is stated, I do not know on what ground, that his character was not of the best.

In this treatise Whistler states that the disease was endemic in England, and as far as he was aware, unknown to the ancients. It had been observed about twenty-six years before this time and the name of rickets had been given to it by those who treated it empirically, although others stated that the name had its origin in a verb in the Dorset dialect, *to rucket*, which meant to breathe with difficulty. Among the seventeen diagnostic symptoms enumerated categorically we find: Swelling of the abdomen, chiefly on the right side under the hepatic region, enlargement of the epiphyses of the joints, nodosities at the costo-chondral junctions, general softness of the bones, enlargement of the head when hydrocephalus supervenes, flaccidity of the soft parts, retarded dentition and caries of the teeth, narrowness of the chest, prominence of the sternum and deformities of the thorax, labored breathing and cough. Symptoms are added, it is true, which we now recognize as unessential complications of rickets—such as scirrhus pneumonia, pleurisy, fluid in the chest and the abdomen—but I do not see how this essay can in fairness be accused of "vagueness and an absence of facts," "of showing that Whistler had little to tell about rickets from his own observation"—criticisms levelled at it by Norman Moore. To me much of it gives the impression rather of a legal brief, stripped of adornment and circumlocution. But in regard to this question it would seem that once an admirer and an ardent follower of Glisson, one forthwith loses all critical judgment, and discredits everything which threatens the security of his position.

[1] There is no copy of this thesis in the United States. The officials of the Library of the Surgeon General were good enough to have a photostatic copy made for me (at the same time that one was made for the library) from the original in the British Museum.

In 1649, one year before the appearance of Glisson's work, Arnold Boate or Arnoldus Bootius published a treatise entitled "De Affectibus Omissis," which contains a chapter on rickets, "de tabe pectorea." Bootius, who spent much of his life in Ireland, wrote that he had seen many cases of this disorder, which was becoming increasingly frequent, and furthermore that he had had numerous opportunities of performing necropsies on infants suffering from rickets. He described carefully the well-known malformations of the chest and cranium, the enlargement of the wrists and ankles, and the deformities of the spinal column. It is evident from the following citation that he writes from first hand knowledge: "Not only does this disease exist in England and Ireland, but in other regions it is probably also present, and so far as Gaul is concerned, to my knowledge, it most certainly exists. Indeed, in the space of three and a half years since these things were written I have seen various children here in Paris laboring with the disease, and by these methods familiar to me and by the principles indicated I have happily been able to effect a cure." It will be noted that Bootius began to write his book as early as 1645 or 1646, the very time when Whistler published his inaugural address.

Furthermore, in 1652, Arnold published a posthumous work of his brother Gerald, entitled "Irelands Naturall History." According to the preface, Gerald finished this book in the year 1645, dying in 1649. The following interesting account is from the chapter on rickets: "Among the reigning diseases of Ireland the Rickets also may with good reason be reckoned, a disease peculiar to young children, and so well known to everybody in England, as it is needless to give any description of it; and yet to this day never any Physician, either English or of any other nation, made any the least mention of it, no not in those works which are expressly written of all manner of diseases and accidents of little children.

"In Ireland this disease is wonderfull rife now, but it hath nothing neer been so long known there as in England, either through the unskilfullness or neglect of the Physicians (the most part whereof in both kingdomes to this day are ignorant not onely of the manner how to cure it, but even of the nature and property thereof) or that really it is new there, and never before having been in Ireland, hath got footing in it only within these few yeares."

Another bit of evidence which shows that rickets was widespread and well known before 1650, may be drawn from the work of Thomas Fuller, entitled "Good Thoughts in Bad Times," which was published in 1647. Under the heading of "A New Disease" he writes as follows: "There is a disease of infants (and an infant disease having scarcely as yet gotten a proper name in Latin) called the rickets; wherin the head waxeth too great, whilst the

legs and lower parts wain too little. A woman in the west hath happily, healed many, by cauterizing the vein behind the ear."

We now come to Glisson's work which "will always remain one of the glories of English medicine." This treatise was published in Latin in 1650 with the *imprimatur* of the Censors of the College of Physicians and was entitled "De Rachitide sive Morbo Puerili qui vulgo The Rickets dicitur," a title which calls to mind that of Whistler's essay. It was prepared by a committee of three appointed by the college, the two other members being Dr. Bate and Dr. Regemorter. At first seven other Fellows of the Royal College collaborated in its composition, later three of this number were appointed a committee, but finally Glisson's knowledge and activity became so overshadowing, that the others "committed the whole work to be woven by him alone," fearing that otherwise the treatise "should arise deformed, misshapen and heterogeneous." The purpose was to investigate a disorder which had made its appearance some thirty years previously in the counties of Dorset and Somerset. A year later the work appeared in English, in a translation made by Phil. Armin; Dick states that two practically identical editions were published in London during this year. In 1660 a second edition was issued in London. The third edition, published in Leyden in 1671, has the well-known title page, which we have reproduced, portraying a rachitic patient in a physician's examining room; on the wall may be seen a scoliotic vertebral column and a bowed femur.

Francis Glisson was born in Dorsetshire in 1597 and died in London in 1677. He graduated from Caius College, Cambridge, and was a Fellow of the Royal College of Physicians of London. For over thirty years he was Regius Professor of Physic at Cambridge, but also lectured on anatomy—which included normal and pathological anatomy—at the Royal College of Physicians in London. He was also an orthopedic surgeon of distinction; in fact, it seems quite possible that his attention was directed to rickets through an interest in the deformities which this disorder occasioned. The Glisson sling, which he devised, has been copied and variously modified by modern orthopedic surgeons. His book on the *Anatomia Hepatis*, remembered especially for its description of the liver capsule, which still bears his name, indicates both the breadth and the precision of his intellect. In the opinion of Boerhaave he was the most exact of all anatomists. In addition to his academic duties he practiced medicine in Colchester, where he lived for many years. In the wide scope of his activities, which call to mind the versatility of the artists of the Renaissance, he may be compared to Thomas Willis who occupied the chair of Natural Philosophy in Oxford at that time and was not only an anatomist of distinction, but one of the foremost clinicians of his day. It was the period of

the birth of scientific thought and activity in England. Harvey had just announced his discovery of the circulation of the blood (1628); Francis Bacon had published his *Novum Organum* (1620); and the Royal Society was about to be founded (1660). Glisson was one of its original Fellows.

At the outset Glisson discusses the origin of the common name of the new disorder—"The Rickets." It was a subject which clearly did not appeal to his intellect to judge by his impatient exclamation "but we trifle too much in staying so long upon these trifles." However, etymology had an established position in dignified treatises, so he accorded it proper consideration. Since this time many have taken part in a literary battle, a tempest in a teapot, which has raged about this question. The number includes even so distinguished a scientist as Virchow, who favored the spelling "rachitis." The crux of the matter hinges on whether the word "rickets" had its origin in the vernacular of the day or in the Greek tongue. Whistler, as we have noted, attributed its source to the word "rucket" in the Dorset dialect. The fact that rickets is generally acknowledged to have been recognized first in Dorsetshire gives added weight to this testimony. Skeats believes it is derived from the Old English word "wrick" or the middle English "wrikken," denoting to twist, as "to wrick one's ankle." Some trace it to the Anglo-Saxon word "rieg," signifying a protuberance. Whichever of these interpretations is correct, a point which we shall never know, they all agree in ascribing the origin of the word to English sources. The other view is that the name was imposed, as Glisson puts it, by "learned men who were skilful in the Greek tongue," who observing the "conspicuous debility of the spine in this affect," termed it after the Greek name for spine (ῥαχις), and that "the common people by the error of pronunciation might somewhat pervert the name so given." If one insists upon a classical derivation, Glisson suggests that "by coyning a Latin Substantive out of the Greek Adjective *Rachitis-idis* let the ordinary English name *Rickets* be retained, or in stead of it, to gratifie more curious ears, you may substitute the *Rachites*." This suggestion led Virchow to state that "Glisson's appellation is due to a faulty latinization of the Greek word," which, as a matter of fact, is not the case. Glisson merely accepted the popular name for the disorder, in which it would seem that he was wise. As Glisson concludes: "and thus much, if not too much of the name;" "but who baptiz'd it (the rickets), and upon what occasion, or for what reason, or whether by chance or advice it was so named, is very uncertain." The popular name has been adopted only in English, in all other languages the Greek or Latin idiom has been followed. In German the disorder is generally termed "rachitis," in French "rachitisme," in Italian "rachitide," in Spanish "raquitis" and in Russian "rachit."

It should be added that frequently it is dubbed by the Germans "die englische Krankheit," due to the pioneer description of Glisson.

Glisson believed that rickets was a new disease which had never been described before. He writes: "This is absolutely a new Disease, and never described by any of the Ancient or Modern Writers in their practical Books which are extant at this day, of the Diseases of Infants. But this disease became first known (as near as we could gather from the relation of others after a sedulous inquiry) about thirty years since, in the counties of Dorset and Somerset, lying in the western part of England, since which time the observation of it hath been derived unto other places, in London, Oxford, Cambridge and almost all the southern and western parts of the kingdom; in the northern countries this affect is very rarely seen, and scarcely yet made known among the vulgar sort of people." Glisson was clearly mistaken in his historical conception of rickets. Rickets was by no means a new disease. As we have shown, Soranus and Galen had described its frequent occurrence in Rome, centuries before England had been civilized. Moreover, from what we now know of the etiology of rickets, of its dependence on sunlight, it could not have been newly born in the seventeenth century but must have been of frequent occurrence in a climate such as that of Rome and more especially of northern Italy.

It is not absolutely correct to say, with Thomas Barlow, that rickets is a disorder which is probably coeval with civilization, for civilization was cradled in tropical or subtropical lands, rather than in the cold, sunless countries of the north. With the trend of population toward the northern parts of Europe with their long winters and deficient sunshine, rickets must have been of increasing frequency and severity. The growth of large cities in these northern countries, with the coincident deprivation of sunlight and the concomitant crowding, gave additional impetus to this disorder. Dick suggests that rickets may have developed first in the bleak, low-lying and marshy land of Flanders, that it made its appearance as a national disease for the first time in the history of the world in the great towns in northern Europe. He points out that in the fourteenth century Bruges had a population of more than 200,000, and that other towns of the Hanseatic League were increasing rapidly in their population. In his opinion, with which I quite agree, rickets probably existed in the Netherlands and in the towns of northern Germany as early as the fifteenth century. At the time Glisson described rickets, it had assumed probably an endemic character, having existed to a lesser degree and extent ever since England had been inhabited. Nor was Glisson correct in the belief that his was the first description of this disorder. Whatever may be our interpretation of the sources of Whistler's essay, it undoubtedly gives an excellent description of rickets. It seems hardly fair to surmise, as

has been done, that this account was filched from the conferences of Glisson and his committee, for this committee was appointed only in 1645, the year in which Whistler published his dissertation. It is difficult to pass judgment on questions of priority after an interval of almost three centuries, and I would not become involved in this discussion were it not that it seems to have been uncritically dealt with by so many biographers. In my opinion rickets was of common occurrence in Europe in 1645 or 1650—both Whistler and Glisson state that by that time it had been given a popular name, "the rickets"—and must have been known to and discussed by physicians as well as by laymen. It appears first in the Bills of Mortality of London in 1634 with a notation of 14 deaths; in 1659 the number of deaths attributed to it had risen to 476.[1] Whistler no doubt saw many cases of this disorder in the clinics of London as did Bootius in Paris. What could be more natural than that a young man should select this new and interesting disorder as the subject of his graduation thesis. No plagiarism nor dishonesty need be attributed to him.

There can be no comparison between the intrinsic merits of the works of Whistler and of Glisson. Glisson's is the mature and well balanced product of a master; it is, moreover, one of the first English monographs treating of a single disease, which it moulded once and for all into a sharply-defined clinical entity, leaving indeed little to the future clinician or pathological anatomist. For example, he gives us the following sketch of the rachitic infant: "The younger children who are carried about in their nurses arms, when they are delighted and pleased with anything, do not laugh so heartily, neither do they stir themselves with so much vigor, and shake and brandish their little joints, as if they were desirous to leap out of their nurses hands; also when they are angered they do not kick so fiercely, neither do they cry with so much fierceness, as those who are in health." In addition to this graphic picture, he describes with the greatest care the individual signs of the disorder—the swellings about the wrists and ankles, the undue flexibility of the joints, the deformity of the chest—the lateral compression associated with the prominence of the sternum which suggested "the keel of a ship" or "the breast of a hen"—"the knotty junction of the ribs with the cartilages or gristles, and the swelled and extended abdomen."

Although Glisson, however greatly we may admire his talents,

[1] These Bills of Mortality require interpretation, a task which is difficult, and to some extent impossible. For example, among the causes of death from 1655 to 1658 in London and the places adjacent, 1598 are ascribed to rickets, 191 to liver-grown spleen and rickets, 3377 to convulsions, 3915 to teeth and worms. It is evident that this large number of deaths could not have been due to rickets. Probably marasmus was included in the group. The significant feature, however, is the immense increase in the figures during the short interval of twenty or twenty-five years subsequent to 1634, the date when rickets was first recorded.

cannot be accorded priority in the description of rickets, he was the first to describe another nutritional disorder of children, namely, infantile scurvy. So great has been the fame of "De Rachitide" that it is only recently that the medical profession has realized that the recognition of scurvy in infants belongs to Glisson rather than to Barlow, who gave us the first pathological anatomical report of this disorder, or to Moeller who regarded scurvy merely as an acute form of rickets. Could the differentiation between rickets and scurvy be more sharply delineated than in the following paragraph: "The scurvy is sometimes conjoyned with this affect. It is either hereditary or perhaps in so tender a constitution contracted by infection, or lastly, it is produced from the indiscreet or erroneous régimen of the infant, and chiefly from the inclemency of the air and climate where the child is educated. For it scarce holdeth any greater commerce with this disease than with other diseases of longer continuance, wherein after the same manner the blood in time contracteth for the most part this peculiar infection, yet it must be granted that this effect doth somewhat the more dispose to scurvy in regard to the want of motion and exercise."

But not all of this classic is written from this modern scientific viewpoint; there are many lapses into the galenic and metaphysical vagaries of the day. It is amazing to be led from a modern clinical description of rickets based on keen observations and inductive reasoning to page after page of wearisome metaphysical argumentation based solely on intellectual subtleties. Ingenious arguments are advanced to show that rickets is a cold distemper, that it is moist and consists in a penury, paucity and stupefaction of spirits. It was impossible for Glisson to break entirely with the past, just as it was for Harvey in his classic exposition of the circulation of the blood —both are highly tinged with mediæval mysticism. "De Rachitide" was written during a transitional period, a time when medicine was struggling to free itself from the domination of the old humoral concept and attempting to put its trust in observation rather than in theory. As a pathologist and clinician Glisson was a modern, but as a physiologist he was still a Galenist, with an unquestioning belief in the triple nature of the constitution of the body.

While Glisson was still alive, John Mayow, whom Ruhräh justly calls a "neglected child of genius," published his "De Rachitide" (1669). At this time, he was but twenty-six years of age. This treatise is a short and concise account, calling to mind the form of Whistler's essay but adding little new. Five years later it was republished by the University of Oxford in the celebrated treatise entitled "Tractatus Quinque," where, in one essay, Mayow set forth his advanced conceptions of respiration. He showed in his "De Respiratione" that oxygen, the term coined by Lavoisier in the following century, was necessary in order that a candle should

maintain its flame, and argued that this "spiritus igneo-æreus" was also essential for respiration and life. This pioneer investigation was completely lost sight of. One hundred years later Priestley and Lavoisier came to the same conclusions as the result of somewhat more refined and extended experiments. In 1685 an English translation of this "De Rachitide" was published at Oxford, and two years later an English edition bearing the popular title, "The Mothers' Family Physician or the Infants' Doctor. Being a discourse of the Disease in Children commonly called the Rickets." This little book will be found in the Library of the Surgeon General. Mayow's point of view in regard to the genesis of the deformities differs from that of Glisson. He states that "the Bones are sufficiently nourished; but not the musculous Parts." He likens the bending of the ribs by the intercostal muscles and of the spine by the back muscles to that of a cord bending a sapling. Under therapy we are informed that "the Scab or Itch coming upon this Disease confers much to the cure thereof." In addition to the use of various clysters, cathartics, emetics, blood-letting, leeches and vesicatories, he recommends earth-worms and hog lice as specifics.

The eighteenth century contributed little or nothing to our knowledge or understanding of rickets; there was merely an uncritical acceptance of Glisson's views. During this period, however, rickets became increasingly popular as a subject for medical theses in the various schools, and we find in Ploucquet's Digest or Repertorium of Medical Literature, a quarto published in 1809, eight columns of titles on works treating of "rhachitis." Many of these theses came from Edinburgh, some from the Continent—Leipzig, Strassburg, Leyden and Vienna are all represented. In the supplement to this medical digest, which appeared four years later, it is of interest to note the record of a work by an Englishman (Cheyne) bearing the title "The English Malady," the synonym for rickets which later was adopted by the Germans.

Not only did numerous theses appear from Germany, but scattered reports indicate that the Germans were cognizant of rickets soon after Glisson's description, as well as that it was of frequent occurrence in that country. In an account, month by month, of the various diseases observed in Berlin during the year 1701, v. Muellen refers to rickets. He mentions it in connection with scurvy, stating that until recently it had been of exceptional occurrence, but that the Gallic exiles had recently brought it into Germany, and that it was attacking the infants sporadically as well as in several epidemics. Rickets is again mentioned in recounting the diseases of 1704. Another account of rickets to be found in these ponderous tomes is that of Camerarius, published in 1730. This writer describes rickets as it attacked the children of Nueremberg. He writes that even the strongest infants became

deformed from the disease, which caused a distortion of the ribs and their cartilages, swelling of the abdomen, and paralysis of the legs, so that the children could no longer stand. Respiratory spasms and convulsions are specifically mentioned, two of the cardinal signs of tetany! He refers to the appearance of worms in the feces following purgation, an observation made also in Wezlar somewhat later. The disorder is attributed to the coarseness of the food, to the giving of cold fluids, and exposure of the body of the young children to cold air.

The illustrious Boerhaave (1668–1738) believed that the disorder came about as the result of some venereal poison, a view shared by his famous pupil von Swieten. The latter, the founder of the great Vienna school of medicine, makes the interesting observation that rickets occurred most frequently among the children of the Spanish and Portuguese Jews who lived in the ghettoes. The conception of rickets as a manifestation of syphilis was given additional impetus by the writings of Portal, a famous French clinician who lived at the end of the eighteenth century and who may be regarded as the precursor of Parrot, who strongly upheld and promulgated this etiological viewpoint toward the end of the succeeding century. Indeed it is only recently that French pediatrists have relinquished the idea of rickets as a manifestation of congenital syphilis.

An interesting account of rickets at the very beginning of the nineteenth century is found in a paper by Wendelstadt on "The Endemic Diseases of Wezlar." Wezlar was a town of about 8000 inhabitants and, according to the author, one of "the larger cities." It was situated in Hessen, in a hilly country surrounded by several rivers, and its streets were exceptionally narrow. We learn among other things that it was famous for rickets. There were entire streets where in house after house individuals might be found who were crippled from rickets, especially in the cobblers' street. As to the etiology of rickets, Wendelstadt writes: "Our streets are very poor and miserable, and the area of the city is small, and everywhere is crowded with people, wagons and cattle." "Rickets is a disease which attacks children only between the ages of one and two years. According to our custom they are fed with pap and starch even while in swaddling clothes; as much is put in as can be forced down." "If the children could go about actively in the streets and country all might go along without much damage . . . but as this is not the case, but as just the children must sit indoors, their digestion suffers severely . . . which ends in death or if they continue to live, they develop thick joints, cease to be able to walk or have deformed legs. The head becomes large and even the vertebral column bends. It comes to pass that such children sit often for many years without being able to move; at times they cease to grow and are merely a burden to those about them. If

they recover they often develop into monstrosities, or if things go well they become deformed individuals." This is an interesting picture of conditions in a German town some one hundred and twenty-five years ago. The rickets here described evidently is the severe form, which by some has been termed "infantile osteomalacia," a degree which today is almost never seen in this country except in an occasional negro infant in a large metropolis. The account gains added interest as it pictures conditions in a rural community and not a large commercial center tainted by modern industrialism.

The nineteenth century proved somewhat more fruitful than the eighteenth in advancing our knowledge of rickets. About the middle of this period Trousseau, the celebrated French clinician, in conjunction with his pupil Lasègue, clarified the problem by showing the essential unity of rickets and osteomalacia, disorders which until then had been regarded as distinct and unrelated clinical entities. Even at this late date, some two hundred years after Glisson's first description, it was found possible to add a new symptom to the picture of rickets. Elsaesser, a German, showed both in the clinic and at necropsy that areas of softening frequently develop in the cranial bones of infants and that these foci of "craniotabes," as he termed them, constitute a sign of considerable diagnostic importance. Somewhat later Kassowitz of Vienna crystallized still more sharply the clinical picture of rickets, drawing attention more particularly to the characteristic seasonal incidence of the disorder, a phenomenon which has proved of great significance in relation to its etiology.

During the latter part of this century the study of rickets was approached from an entirely new angle. It was the period of the application of chemistry to medical problems. This method was soon applied to rickets and investigations were undertaken to determine the chemical processes which occur in the course of this disorder, and the nature of the metabolic changes involved. The name of Friedleben, associated with a long list of German investigators, stands out prcëminently in this new field. To my mind, the foremost contribution to rickets during the nineteenth century is the elucidation of its histological pathology by Pommer in 1885. Even if his conception of the characteristic and essential pathological lesion—an excess of osteoid tissue—may not fully stand the test of future investigations, it was of the greatest value as it furnished us, for the first time, a uniform criterion of rickets. It has been the foundation of all subsequent histological and experimental studies, and has done more than anything else to bring unity of description into the study of nutritional diseases of the bones.

We have reached the twentieth century, the era with which this monograph is especially concerned. It is a short span which stands

out in bold relief from the two and a half centuries which preceded it. Its distinction is that it deals with entirely new factors and concepts—with experimental rickets brought about and controlled at will in the laboratory, with vitamins, with specific nutritional factors and with ultra-violet light, and with the chemical examination of the blood and the radiographic picture. These years usher in what must be regarded as the second great chapter in the history of rickets. As the result of this new impetus, the status of rickets has changed—interest has again become acute and activity intense, and advance in knowledge promises to be greater in the first half of this century than in the preceding two hundred and fifty years. Quickened by these newer viewpoints, we no longer are groping helplessly, but have been able to formulate important questions which are being intelligently investigated in the laboratory and in the clinic. It is the renaissance in the history of rickets.

CHAPTER II.

THE GEOGRAPHICAL DISTRIBUTION OF RICKETS.

The classic treatise on the geographical distribution of diseases is the German handbook by Hirsch, published in 1886. In his consideration of rickets from this aspect, it is evident that the author met with unusual difficulties. He deplores the "meager contemporary data on the geographical area of rickets" and concludes that "our information from the past is too scanty; and even in modern times the accounts of rickets in various parts of the world afford insufficient materials for estimating its present geographical distribution." An interesting and valuable paper on this subject was published in 1890 by Palm, who writes that he was engaged in an extensive practice in Japan for some years, during which time he became interested in this topic. He states that "with a view to eliciting information first hand from medical men practicing among the native population in China, India and elsewhere, the writer has addressed a series of questions to medical missionaries in these countries with regard to the occurrence or absence of rickets, the habits of the people and their climatic and sanitary conditions." This task was carried out assiduously and carefully and was extended to include almost all the countries of the world. As a result of these data gathered by means of correspondence, Palm came to the conclusion that the main etiological factor in rickets is a lack of sunlight, that it is prevalent in those sections of the world where there is but little sunshine, and is comparatively rare where sunshine is abundant. It is remarkable that a statistical survey of this character, based on indirect and personal testimony, enabled Palm to make one of the most important deductions in regard to rickets that has been brought forward since its earliest description. This survey by Palm, undertaken and carried out unaided, demonstrates the possibilities of a study of geographical distribution in the elucidation of the etiology of disease. It is a method that might well be employed in the investigation of other obscure nutritional disorders which are widely disseminated. For example, in our present state of confusion it would be of value to have information of this character in regard to the distribution of dental caries, a disorder of world-wide interest and importance. The inherent inexactness of this method of investigation is compensated for, in part, by the comprehensive view and the panoramic survey which it affords.

It is self-evident that an investigation of the incidence of a disease presupposes the correctness of the diagnoses, and that a considerable number of cases are not being overlooked. Herein lies the fundamental weakness of almost all the investigations and statistics relating to rickets Until very recently physicians have shown a lamentable ignorance of its primary clinical manifestations. Some have included in the category all cases associated with retardation in teething or in walking; others have relied solely on the development of deformities of the legs; whereas many have confused atrophic conditions of infancy with rickets. This criticism applies to the children's specialist as well as to the general practitioner throughout Europe and the United States. It is only lately, since the newer knowledge has heightened interest in rickets, that physicians have bestirred themselves to master its clinical signs. The result of such non-conformity has been, as will be brought out in discussing the incidence of rickets throughout the world, that we are confronted with the most remarkable hodgepodge of statistics that is to be found in relation to any disorder. It is not uncommon—in relation to one and the same locality, at practically the same period—to meet with absolutely contradictory data furnished by clinicians of high standing.

But another factor has served to introduce confusion into the statistics culled from various sources. During the past few years, in addition to the uncertainties resulting from oversight or ignorance, a lack of conformity has resulted from the fact that the clinical conception of rickets has undergone a radical change, that new methods of diagnosis have been introduced which reveal to us cases which until recently escaped recognition. I have reference more particularly to the use, for early diagnosis, of the Roentgen rays and the estimation of the inorganic phosphorus of the blood. Gauged by these more delicate tests, the geographical distribution of rickets is universal.

From the standpoint of diagnosis it may be stated that there are two periods in the history of rickets—the one beginning about the middle of the seventeenth century and extending without great change until about the year 1920, and the second comprising the short interval since 1920. During the first span of some two hundred and seventy years, Glisson's teaching formed the bulwark of clinical interpretation, and irregularities in diagnosis resulted from lack of knowledge or lack of care, rather than from essential differences in viewpoint. During the second period, however, objective methods of diagnosis were introduced, which rendered it possible to compare rickets in various lands and even to gauge its relative severity. These newer methods are now being employed extensively in this country, in Europe and even in parts of the Far East, so that the time is not far distant when an accurate geo-

graphical survey will be possible, based on roentgenological examinations of the bones and chemical tests of the blood. At present, however, we must rely largely on the well-established clinical signs, which, it should be added, have been reappraised and refined on the basis of objective criteria.

DISTRIBUTION OF RICKETS IN THE UNITED STATES.

Accounts of the distribution of rickets throughout the United States are typical in their lack of uniformity. This is true, especially when we go back about fifty years. Data are found which would seem to indicate that rickets was practically non-existent in the cities of the United States at that time, whereas other data, relating to the same districts, call attention to its wide dissemination. Parry's paper on rickets, which was published in 1872, is by far the best account which had appeared in the American literature up to that time. It is interesting to note his account of the incidence of rickets in various cities of the eastern part of the United States. He quotes Condie, who stated in 1868 that "fortunately rickets is an affection of comparatively rare occurrence." Bauer, who published a book on orthopedic surgery, in the same year, stated that rickets "is one of the rarest maladies on the western continent." An orthopedist probably would have in mind rachitic deformities, more particularly of the spine and of the legs. Meigs and Pepper, whose Treatise on Diseases of Children was the standard of that day, "could not avoid the conclusion that rickets must be a vastly more common affection among the poorer classes in London than in the same classes in our large American cities." Parry, however, encountered rickets in 28 per cent of the outpatients of a large hospital in Philadelphia, which shows that he must have been a clinician of exceptional acumen. He states that there was a wide-spread belief among the medical profession that the disease was confined to the Old World, but that in his experience it was met with quite as commonly in Philadelphia as in the large cities of Europe. Jacobi made the statement in 1894, before an orthopedic congress at Washington, that "thirty years ago there was no rickets in the United States except very rarely a stray case." It is evident that one can find authority for either the absence or the frequent occurrence of rickets fifty years ago in the populous sections of the United States.

Haven, writing of Boston, records about 5 per cent of rickets in children under seven years of age, but some 42 per cent among the colored children, in spite of the fact that the colored people were lavish in their expenditures for food and rent and "could not take the children out-of-doors to a less extent than the Irish population." Fruitnight, describing conditions in New York a few years later

(1893), complains that "owing to the large influx of immigrants and the consequent development of environing conditions analogous to those which obtain in the overcrowded centers in the Old World, such as impure and insufficient air, lack of ventilation, improper and inadequate food and the like, together with the increased difficulty of supporting a family properly—a result of this excess of workers—rachitis has become one of the most important and most common of the diathetic diseases met with among the humbler classes of our population." Snow of New York wrote an article about this time on the great frequency of rickets among the Neapolitan people in American cities, stating that two-thirds of their children develop rickets in spite of the fact that almost all of them are breast-fed. In a paper published in 1899 on "The Frequency of Rickets in Infancy in Boston and Vicinity," Morse estimated rickets in children under two years of age, among the poorer classes, as being about 80 per cent. It would seem that, as Fruitnight and Jacobi stated, with the augmenting population, rickets was rapidly increasing in the large cities of the United States. More recently, in 1917, Hess and Unger have given us figures in regard to the incidence of rickets in New York City. They reported that almost all of the infants in a negro community, whether breast-fed or bottle-fed, were found to have rickets, and that the same was true to only a slightly less extent in the Italian districts of the city. The negro section had a population of about 9000 and in 1915 bore the unenviable distinction of having the highest mortality of any neighborhood in the city. Its infant mortality-rate was 314 per 1000, respiratory diseases taking an exceptional toll.

In a paper published in 1921 they wrote: "Rickets is the most common nutritional disease occurring among the children of the temperate zone. Fully three-fourths of the infants in the great cities, such as New York, show rachitic signs of some degree." These statistics were based mainly on clinical rather than on laboratory examinations, more particularly on the presence of beading of the ribs. In 1922 these investigators, reporting on the "Significance of Clinical, Radiographic and Chemical Examinations in the Diagnosis of Infantile Rickets," showed that when examinations were conducted in March, and laboratory as well as direct clinical methods were resorted to, rickets was found to be practically universal.

There is little doubt that similar conditions obtain throughout the eastern area of the United States. Recently Eliot has summarized her experience in New Haven as follows: "One hundred and seventy-nine or 83 per cent showed evidence of mild rickets by Roentgen ray examination before eight months of age; 6 per cent showed it later. The total incidence of rickets in the demonstration group was 86 per cent. Our investigations have shown that a slight

degree of rickets is well nigh universal in our clime and in our state of society." This high incidence was obtained, even though chemical tests of the blood were not carried out.

There are very few accounts of the distribution of rickets in our southern states, either among white or negro infants. In 1894, Acker, writing on rickets in negroes, stated that although there are numerous works relating to the negro, he could find no reference to rickets in the Surgeon General's Library. It is suggestive of the status of medicine in the South before the Civil War that no reference to rickets among the negroes was made by physicians writing at that period. Acker adds that from the fact that mention is made that children suffered from bow-legs, it can be assumed that the disease was prevalent in slave times. Undoubtedly, such was the case. Of Washington, Acker writes that "negroes are almost without exception rachitic." De Buys in 1924 gave an account of rickets in the city of New Orleans. His survey included 197 babies—62 white and 135 colored—which were examined in March. He writes that "according to clinical manifestations of rickets the disease was present in every case in this study. The disease was more marked in the colored subjects than in the whites." When we bear in mind that this survey was purely clinical, carried out without the aid of refined laboratory tests, and that it included only breast-fed infants, it is clear that rickets must be almost as prevalent, although perhaps not as severe, in the cities of the southern states as it is in those of the north. New Orleans lies at about 30°, whereas New York is situated above 40° North Latitude.

In view of the fact that sunlight plays such an important rôle in the etiology of rickets, it may seem peculiar that rickets should occur with almost equal frequency in New Orleans, Washington and New York, but a glance at the table, which gives the "Yearly Average Number of Hours of Actual Sunshine in Cities in Various Countries," shows that the amount of sunshine is practically the same in these three cities, so that judging by this criterion the incidence of rickets should be approximately the same in all three areas. As a matter of fact it will be found that a table of this kind presents in summary form a picture of the geographical distribution of rickets throughout the world. Cities in the temperate zone cannot be compared with those in the tropics as the quality of the sunshine is of quite different character in these parts of the world, but on comparing areas within similar zones, it is surprising to find the degree of parallelism between the yearly amount of sunshine and the incidence of rickets. It will be noted in the table that the city having the smallest amount of actual sunshine is Glasgow. This is likewise the city in which rickets prevails to the largest extent and in greatest intensity. London falls next in rank in regard to hours of actual sunshine, with only one-half the amount of

sunshine enjoyed by New York. There can be no doubt that the large degree of rickets in London is due mainly to this comparative lack of sunshine, as living conditions are much the same as in New York.

TABLE 1.—YEARLY AVERAGE NUMBER OF HOURS OF ACTUAL SUNSHINE IN CITIES IN VARIOUS COUNTRIES.

United States and Canada.		*Europe.*	
Seattle (Washington)	2022	Glasgow (Scotland)	1086
Toronto (Canada)	2048	London (England)[2]	1227
Portland (Oregon)	2095	Stockholm (Sweden)	1418
Spokane (Washington)	2492	Leningrad (Russia)	1427
New Orleans (Louisiana)	2519	Utrecht (Holland)	1469
New York (New York)	2557	Brussels (Belgium)	1570
Washington (Dist. Col.)	2598	Breslau (Germany)	1642
Chicago (Illinois)	2632	Paris (France)	1663
Bismarck (N. Dakota)	2700	Berlin (Germany)	1672
Honolulu (Hawaii)	2840	Zürich (Switzerland)	1693
San Francisco (Cal.)	2878	Cracow (Poland)	1733
Denver (Colorado)	2946	Berne (Switzerland)	1783
Tampa (Florida)	2948	Vienna (Austria)	1852
San Diego (Cal.)	3049	Oslo (Norway)	1949
Phoenix (Arizona)	3752	Budapest (Hungary)	1963
		Sofia (Bulgaria)	2145
Other Countries.		Bucharest (Roumania)	2238
Sydney (Australia)	2125	Palermo (Sicily)	2261
Tokio (Japan)[1]	2171	Rome (Italy)	2362
Tsing-tao (China)	2202	Athens (Greece)	2655
Buenos Aires (Argentina)	2396	Madrid (Spain)	2909
Dairen (Manchuria)	2687	*West Indies.*	
Cairo (Egypt)	3238	Ancon (Canal Zone)	2155
		Port of Spain (Trinidad)	2245
		Colon (Canal Zone)	2413
		San Juan (Porto Rico)	2720
		Port-au-Prince (Haiti)	3056
		Kingston (Jamaica)	3169

[1] For the year 1923.
[2] Observed at Greenwich.

Forbes and Green have given us an account of rickets as it occurs in Denver, Colorado. Among some 500 children under the age of two years, rickets occurred to some extent in almost one-third, being as usual most prevalent among the colored infants. The investigators conclude that "severe rickets is not common in Colorado as evidenced by the relatively few orthopedic corrections necessary. Only 1 case of bow-legs was encountered in a survey of 503 infants. Mild rickets is much less common in Colorado than in eastern states." No doubt this comparative freedom from rickets is to be attributed largely to an abundance of sunshine, as may be inferred from Table 1. But it should be borne in mind that Denver is situated at an altitude of over 5000 feet, so that the intensity of the ultra-violet rays is exceptionally great. This report may be compared to that in relation to Ogden, Utah, a city of about 35,000 inhabitants and situated at an elevation of about 4310 feet. Rickets was found by E. H. Smith in about 18 per

cent of these children, who are living under excellent hygienic conditions in a latitude similar to that of New York City. It should be added that no radiological or chemical tests were carried out in this study.

There are few statistics in regard to other cities of the United States, but they are hardly necessary for it is quite possible to estimate the incidence of rickets. There is no doubt that it is common throughout the United States, that its severity must be less in areas such as Colorado and Southern California, and that in Arizona and New Mexico and the other southernmost states of the Union it must be far less common and of milder intensity. Although there have been no statistical reports from the Northwest, Moore's studies of rickets indicate not only that it is prevalent but that moderate and severe forms may be encountered. The climate of such cities as Portland and Seattle is comparable to that of the Scandinavian coast.

DISTRIBUTION OF RICKETS IN ENGLAND, SCOTLAND, AND IRELAND.

We meet with similar discrepancies in accounts of the frequency of rickets in England and Scotland. Some one hundred and fifty years ago (1773) Fordyce wrote as follows in regard to rickets in London: "I speak within the bounds of truth when I assert that there must be near 20,000 children in London and Westminster and the suburbs ill at this moment of the hectic fever attended with tun-bellies, swelled wrists and ankles or crooked limbs, owing to the impure air which they breathe, the improper food on which they live or the improper manner in which their fond parents or nurses rear them up." Fordyce probably refers to diseases other than rickets, but no doubt many of the deformities which he describes must have been due to rickets. In 1871 Ritchie wrote that about one-third of the children under two years of age suffered from rickets. This was in Manchester, which has always been noted for the prevalence of rickets. Statistics of London published about the same time (1868) by the illustrious pathologist Gee give a similar percentage. On the other hand, in 1874 the eminent children's specialist of London, Charles West, wrote: "I have never seen an infant, while sufficiently suckled by healthy nurse or mother, present any of the symptoms of rickets even though the hygienic influences by which it was surrounded were in other effects unfavorable." It is evident that West had only the picture of severer rickets in mind and did not recognize the milder forms. In view of the fact that rickets was first described by English physicians who practiced in London, it is especially interesting to compare the severity of the disease as it occurs there with that of New York and of the

capitals of Europe. From the accounts in the literature and a limited opportunity for personal observation it would seem that the type of rickets is more severe in London than in New York, Paris or Berlin. We should expect this to be the case, judging by the yearly amount of sunshine in London, especially the scanty quota which it receives during the winter and autumn months.

There has been but one attempt at an organized survey of the geographical distribution of rickets. In 1884 the Medical Congress appointed an International Committee for the prosecution of various collective inquiries in regard to the etiology of several diseases, to be based upon a widely extended inquiry of their distribution. Rickets was one of these diseases. Although the committee was able to realize this scheme to only a limited extent, owing to the fact that "little interest could be aroused in the collective work in the large countries of Central Europe," something was accomplished in relation to the United Kingdom and it is of interest to review these data some forty years later. The conclusions, published in 1889, were based on about 3000 reports which were returned to the committee properly filled in. The inquiry paper asked simply whether "bent-bones, usually the leg bones, accompanied often with enlargement of the lower end of the radius and the sternal ends of the ribs" were common in the district. A map was prepared, based on these data, of the distribution of rickets in England, Ireland, Scotland and Wales. As the report states, "it is obvious that the results of such an inquiry as this can only be interpreted in a broad and general sense."

It was found that rickets was most frequent "in large towns and thickly-peopled districts, especially where industrial pursuits were carried on," and was far less common in the rural districts; and secondly, that there was "a greater tendency to rickets in the rural parts of the south of Great Britain than in those of the north." In Scotland, rickets was reported as very prevalent "in the industrial zone between the Firths of Clyde and Forth. It preponderated markedly in the Clyde valley and the north of Ayrshire and is all but universal in Glasgow and its suburbs." Edinburgh and its suburbs were reported to have rickets to a marked degree.

It is to be noted that almost the whole of London and the greater number of its outlying suburbs are represented on the map as being centers of rickets. In the enlarged metropolitan map the wealthy residential districts of Mayfair and Belgravia show a less intense incidence of rickets.

"Rickets is reported to be common in the two largest and busiest towns of Ireland—Dublin and Belfast," but less common in Cork and Limerick. On looking over the map, it is found that almost all large towns are centers of rickets, and even towns of moderate size and "it is not until we reach the rank of the small market town of

4000 or 5000 souls" that the degree of rickets begins to appear appreciably less.

The report of the Local Government Board for 1915 and 1916 contains comments which confirm the conclusions of the collective investigation of 1889. It states that "a map of the coal measures of the country would almost serve as a map of the chief areas in which child mortality is excessive." "In other words, the areas of the greatest prevalence of rickets and of the greatest child mortality correspond within their narrow limits to the areas of the greatest density of population and to the geographical distribution of the great industrial centers which have arisen around the coal measures of the country."

In considering the geographical distribution of rickets, it is of great importance from a social point of view to differentiate between mild and severe rickets, between the type of disorder which, as far as has been ascertained, leaves behind no damage and the severer types which result in deformities of the skeleton, more particularly of the legs and bony pelvis. In this respect statistics are generally wanting. Here and there we meet with a survey giving us this important information. In 1922 an inquiry was made by Newsholme into the prevalence of deformities resulting from rickets in North Riding. This survey comprised an examination of over 6000 boys and 6000 girls in the elementary schools of that district. Among 262 crippled children under the age of sixteen years, it is stated that 14 per cent resulted from rickets. The pigeon-chest was the commonest deformity, comprising one-fourth to one-third of the total number of cases. These children were found to be not only physically backward but below standard in their studies. If these statistics are to be considered representative, they indicate the crippling effect of rickets in this part of England.

The collective investigation of 1889 emphasized the preponderance of rickets in the Clyde Valley and stated that it was almost universal in *Glasgow* and its suburbs. All reports agree on the marked incidence and exceptional severity of rickets in Glasgow. Findlay in his excellent survey of 1918 wrote significantly that "it was only with the greatest difficulty that Sister Elinor could find among the patients of the Dispensary of the Royal Hospital for Sick Children a sufficient number of non-rachitic families for the needs of the present research." The studies of the Medical Research Council of Child Life in Scotland, published in 1926, tend once more to confirm these statements. In the appendix of this report we find an account, by the visiting worker, of the difference in rickets between Glasgow and Dundee. She writes that it is common for a child in Glasgow after commencing to walk to "go off its feet," in other words that rickets was not only much more prevalent but much more severe in Glasgow and that "in nearly all the families

with the deformities, the children had been breast-fed but had seldom been taken out." This high incidence in Glasgow is to be attributed partly to natural defects—to a prëminent lack of sunshine—but also to social and economic factors brought about by man. "I have not seen any slums in Dundee," writes the visiting worker, "to compare with those in the worst districts of Glasgow."[1]

DISTRIBUTION OF RICKETS IN OTHER PARTS OF EUROPE.

Reports in regard to rickets in *France* are meager, but there is every reason to believe that its distribution differs little from that in the other countries of Europe. In 1897 Baumel reported at the International Medical Congress at Moscow that he had found in Montpelier 4.5 per cent of rickets among some 8000 children, varying in age from infancy to fifteen years. It is evident that these figures underestimate its frequency; probably they refer to moderate and marked cases, and include a large number of older children. Budin, the celebrated children's specialist who did so much to further infant welfare in France, wrote in 1907: "As for rickets, not a single case has occurred in any of my consultations since I first began in 1892." This statement is even more extreme than that of West in regard to London, and merely indicates that mild forms of rickets were not recognized by Budin. Marfan comes closer to the mark in the statement that in the hospitals of Paris 1 out of every 2 children between the ages of six months and three years showed evidences of rickets. It is his impression that severe cases are becoming less frequent, a belief which is shared by most clinicians in Europe and in the United States.

Statistics relating to *Germany and Austria* are remarkably scanty, considering the number of German text-books on pediatrics and the amount of literature on this subject. The standard texts written during the past twenty-five years refer to the great frequency of rickets but fail to give statistics. This is an apparent rather than a real defect, however, as such data probably would be approximate and little better than a broad and general statement. Engel, in 1923, published a study of rickets in Dortmund. He tells us that the number of cases is "alarmingly great," and that 10 per cent or about 5000 of the children between the ages of two and ten

[1] Glasgow is a city of about a million inhabitants, and lies in the valley of the Clyde. The districts near the river are hardly ever free from dampness, and the climate is mild but moist. The area covered by the city is enormous and it is difficult for most of the poor population to get out into the real country. Over 62 per cent of its population is housed in one or two-room houses. There are 56.6 persons to the acre, compared to 25.5 in Dundee and 12.9 in Edinburgh. These figures are from the recent report of the Medical Research Council and indicate that much could be done in Glasgow to offset the natural disadvantages of moisture and deficient sunshine.

years suffer from severe or very severe rickets. Davidsohn writes that in 1909 about 37 per cent of the children under six years of age cared for in the Berlin Foundling Asylum showed rickets, and that in 6.4 per cent the disorder was present in a very severe form. From personal observation in this clinic, in the following year, I am of the opinion that these figures are an understatement of the real conditions. Ten years later, immediately after the World War, he stated that this percentage had increased to 50 per cent and that 13 per cent manifested severe rickets.

The reports regarding the increase of rickets during and immediately following the World War are most unsatisfactory compared with those relating to tuberculosis among young children. The percentage of rickets did not seem to increase; considering that rickets is almost universal among infants, it is evident that an increase would have been practically impossible. However, an augmentation in the number of severe cases was noted by many observers. In the course of their routine vaccinations in the post-war period, the hygienist Selter, as well as Hilgers, noted this change. Furthermore, there can be no doubt as to the increase of "late rickets" as the result of the war. Franqué stated in 1923 that in Striegen 95 per cent of all the children entering school were rachitic, and that in Dortmund 20 per cent of those three to five years of age could not walk.

In the discussion at the Moscow Congress in 1897, Escherich said that in Vienna 97 per cent of the infants between nine and fifteen months, attending the polyclinic, showed signs of rickets. This statement, made thirty years ago, is significant of the clinical acumen of Escherich, for at this time few of the children's specialists of Europe detected rickets in more than one-half or two-thirds of the infants. The recent report of the group of English workers, "Studies of Rickets in Vienna, 1919–1922," corroborates its high incidence and severity in the post-war period. Probably several factors tended to bring about this exceptionally high percentage of rickets. It has been noted by various observers during the past fifty years that rickets, osteomalacia and tetany are especially prevalent in Vienna and that the cases are severer there than in Berlin and in other large cities of Germany. This is somewhat strange in view of its more southerly location and the fact that it has more hours of sunshine yearly than the cities in northern Germany. It must be admitted that no satisfactory explanation is forthcoming for this comparatively high incidence of rickets and allied disorders. The wretched housing conditions in Vienna probably are an important factor in bringing about such a situation.

Hirsch states that in Scandinavia (Norway and Denmark) rickets "has a subordinate place in the statistics of sickness relating to the earliest years of life." This view is based on scattered

reports published some fifty years ago. In 1898, Johannessen made a careful investigation of the occurrence of rickets in *Norway*. He states that Norwegian physicians were of the same opinion as Hirsch and considered rickets rare in Norway, placing it in the group with the Faroe Islands, Iceland and Greenland where rickets is supposed to be infrequent. Johannessen remarks significantly that the people of Norway were so well acquainted with this disorder that they did not consult a physician but treated it with cod-liver oil. He writes that "the first time that rickets is mentioned in medical reports is in 1853 in the southern part of the country." Later it was shown that the disorder existed throughout the land. It occurs frequently in the large manufacturing districts and in the cities, but also extensively in the plateaus of the interior of the country and in the high-lying valleys; it exists also along the coast in the neighborhood of the fjords and in the most northern parts of the country, even to 71 degrees latitude." In Oslo, he found that 32 per cent of the children had rickets and, a point of greater moment, twice this number of infants six to eighteen months of age. Among 1313 cases only 14 are supposed to have shown signs of tetany and 13 of laryngospasm. In an ambulatory station in Bergen, Looft found in 1897 that 75 per cent of the children under two years of age had rickets. A factor of interest in connection with these statistics is that both Johannessen and Looft found the period of greatest incidence to be May and June; in other words, the peak was reached a month or two later than in the more southern European countries and in the United States. This seasonal prolongation of acute rickets was to be expected in view of the long winter period. Table 1 shows that Oslo has an average of 1949 hours of actual sunshine a year, a somewhat greater total than the other capitals of northern Europe.

There has been a medical myth that rickets does not occur in the *Faroe Isles*—that tiny archipelago which lies in the Atlantic Ocean between England and Iceland. Only recently Rasmussen has written a report on this subject in relation to one of the medical districts of these islands. He followed the condition of 141 children in 19 villages from 1920 to 1922, and found that 34 per cent of the breast-fed and 71 per cent of the bottle-fed babies developed rickets. This situation he attributes partly to the fact that, owing to the adoption of free-trade, margarine has replaced fish oil in the dietary of the people, and that the amount of sunshine is exceptionally meager, only 954 hours annually in the capital, Thorshavn.

Dannmeyer (1927) tells us that in *Iceland*, although the diet is similar to that of the inhabitants of the Faroe Islands, rickets does not occur. He accounts for this difference by the fact that in Iceland there is plenty of intense sunlight, whereas in the Faroe Islands fog is almost constant, due to the proximity of the gulf

stream; he states that these islands receive yearly hardly 100 hours of actual sunshine!

Among the children of the Laplanders definite rachitic changes may be found, as noted recently by Ylppö and other physicians.

In connection with a consideration of these northern countries, it may be added that rickets is by no means uncommon in *Newfoundland*. There are no statistics bearing on this territory. However, one of my assistants visited St. John's a few years ago and observed numerous children with bow-legs running about the streets of this city. It would seem that in the two greatest centers of the world for the export of cod-liver oil—St. John's and Bergen—rickets still flourishes!

An inquiry into the occurrence of rickets in *Switzerland* is of particular interest as it sheds light on the relation of *altitude* to the development of this disorder. This question was raised first by Maffei in 1844 who, writing on cretinism in the northern Alps, stated that whereas cretinism developed in the mountains, rickets developed in the flat country. At a height of 3000 feet he reported no rickets except among immigrants, and at 2000 to 3000 feet he found it to be very rare. Professor Feer of Basel in 1897 wrote an excellent monograph on the geographical distribution and etiology of rickets, which considers the incidence of rickets in various countries and gives an especially good account of its distribution in the several cantons of Switzerland. In this connection it may be mentioned that the British survey of 1889, which we have quoted extensively, stated that rickets was rare in the Scottish Highlands. On the other hand Kassowitz, one of the most distinguished authorities, wrote that in some of the mountain villages of Austria, situated 3000 feet above sea level, he encountered cases of most marked rickets. Feer carried out his survey by corresponding with some 270 physicians in the various parts of Switzerland. His conclusions were as follows: "Rickets comes about in all parts of Switzerland. Its incidence in general runs parallel with the concentration of the population. Among the children of industrial workers it occurs more often, all other conditions being the same, than among those following agricultural pursuits. Rickets was found throughout the Alps, even in the little settlements situated at the highest altitude. On the other hand, its character in the High Alps becomes milder and its occurrence less frequent as we ascend to greater altitudes; in such localities the disorder is more marked among the children of people who have immigrated, than among those of parents who were born at this altitude." To substantiate these conclusions, Feer furnishes data of the occurrence of rickets in towns of the Jura and of the Alps situated 3000 feet or more above the sea level, for example at Aigle and at Arosa. He examined a large number of children at Davos which is situated at a height of about 4500 feet and is ideally located.

In this town there were numerous cases of marked rickets, and some of moderate degree in children whose parents had been born and brought up in this neighborhood. The same was true at Pontresina; at a height of 3500 feet Feer saw the most marked case of rickets which he encountered in the mountains—that of an infant aged twenty-one months, whose mother was born in Pontresina. It is an interesting side light that he found rickets in the children of the proprietor of the Alpine Hôspice on a mountain pass 7000 feet high. These children were born at this altitude and had always lived there. The climate in this Alpine pass is severe and the children during the first years of life do not get out-of-doors very often during the nine months of severe winter. It is evident, therefore, that altitude alone does not suffice to protect against rickets, although the marked increase in the ultra-violet component of solar radiations and the lessened absorption by the earth's atmosphere at these high levels augment the intensity of the rays.

A study of rickets in the Alps also furnishes conclusive evidence against the opinion that inhabitants of *districts in which the drinking water is rich in lime* are protected against rickets. Feer states that the Jura district is "a calcareous mountain range 800 to 1600 meters high and furnishes a water exceptionally rich in calcium." In spite of this fact, rickets exists to the same extent there as in other areas where the water is comparatively devoid of calcium. From what we know of the effect of lime in the intestinal tract it would seem quite possible that its presence in high degree in drinking water might tend to the development of rickets by precipitating the phosphates in the canal. It would be interesting to ascertain whether tetany occurs less frequently where the drinking water has a high calcium content.

In a consideration of the occurrence of rickets in *Italy* a distinction should be made between the northern and southern parts of this country, as the former is cold and rugged rather than mild and sunny. Strangely enough the first "institutes" ever organized for the care of rickets were established in some of the cities of northern Italy, notably in Bologna. This in itself is telltale evidence of a high incidence of rickets.

In 1926 in the course of a visit to Florence, I had ample opportunity to convince myself that rickets is of frequent occurrence in this city. Instances of bow-legs and knock-knee were not uncommon among the children in the hospitals as well as among those in the streets. Children's specialists in Florence confirmed these observations.

We should expect a decided diminution in the incidence of rickets in Naples, a city always associated with sunshine and a balmy climate. Hirsch states "Southern Italy, the southern provinces of Spain, and still more of Turkey and Greece enjoy a notable immu-

nity from it." On the other hand, Fede reported at the International Medical Congress at Rome in 1894 that he had met with 2635 cases of rickets in the course of seven years in the pediatric clinic at Naples. Rickets in Naples is no doubt due to the miserable living conditions which obtain among the poor of that city, to the crowding and to the narrow streets which shut out the sunlight. There is, however, another factor which must be thought of—namely, whether the offspring of southern races are more susceptible to rickets when subjected to unfavorable climatic influences. I have in mind the exceptionally high incidence of rickets which has been recorded among the Italians living in various parts of the world—in Switzerland, in Argentina and in the United States. Some years ago Snow emphasized the frequency of rickets among the southern Italians living in Buffalo, in spite of the fact that almost all of the infants were nursed.

Rickets seems to be not uncommon in *Sicily*, if we may judge by reports from Palermo. In 1899 Callari reported that 47 cases of marked rickets had been treated in his surgical clinic between the years 1887 to 1897. What is more to the point is the fact that there is an institute for rickets in this city similar to those in the cities of northern Italy. It must be remembered that the number of hours of actual sunshine is less in Palermo annually than in New York City.

There are few accounts of rickets in *Greece*. Maccas stated that among some 1500 children attending the dispensary in Athens he saw only one or two cases of typical rickets. Hirsch quotes Stephanos to the effect that rickets is a rare disease in Greece, most often seen in a few poverty-stricken villages in the marshy sections of the country and in some mountainous parts of Euboea. As mentioned in the previous chapter, the fact that Hippocrates fails to refer to rickets probably is to be ascribed to its rarity in Athens or to its mild character.

Marfan, than whom there is no better observer, tells us that during a visit to Constantinople in 1907 he investigated the question of rickets in that city. It had been stated that this disorder did not occur in *Turkey*. "Our surprise was great to find that the wards of this hospital, especially the surgical wards, were filled with rachitic children who had been admitted with deformities so marked as to require surgical intervention. Radiographs of the bones of these patients left no doubt as to the rachitic nature of the lesions." Marfan states that physicians testified, and he himself ascertained, that rickets is frequent and often severe in Constantinople and that there is no immunity of race; lesions were noted in the children of Turks, Greeks, Armenians and Jews.

Caspari writes that rickets occurs in *Palestine*, in Jerusalem and in Haifa, during the winter when the children are kept in the house

all day on account of the wind and rain. It is less severe than he had been accustomed to seeing in Berlin, except among the colored Sudanese children, who developed the typical deformities of the bones.

It is self-evident that rickets must be prevalent in *Russia*. The climate is severe and there is a comparative lack of sunshine. In Leningrad, for example, the annual amount of sunshine is on the average 1427 hours, or about 1000 less than in New York. There is no modern account of the frequency or distribution of rickets in this large country, so that we must have recourse to reports which were written in what we have termed "the early period" in the diagnosis of rickets, the period which took no account of roentgenological examinations of the bones or chemical analyses of the blood. In 1892, at a meeting at Dorpat, Kieseritzky called attention to the high incidence of rickets and its exceptional frequency among the Jews. This prevalence is not surprising in view of the congested life of the ghetto. At the Russian Congress in 1894, Bystrow reported an incidence of 60 per cent of rickets in a rural district to the south of St. Petersburg and 59 per cent in Kiew and in Moscow. In Riga, which lies on the Baltic, Mey stated in 1896, that 86 per cent of the infants under two years of age showed signs of rickets, in spite of the fact that almost all were nursed. This paper gives a good account of conditions in that city, and contains a rare appreciation of the influence of hygienic factors, especially of sunlight. About this time Kissel wrote an article on the frequency of the "englische Krankheit" in Moscow in children under three years of age. He found its incidence to be 80 per cent and that severe cases were exceptional in comparison to St. Petersburg which lies further north. He quotes Schukowsky as having found 95 per cent of rickets in the out-patient department there a few years previously. One of the latest reports of rickets in Russia is that of Joukooski who gave an address before the International Congress of Medicine in Paris in 1900, which he published in monograph form. It contains a good, short summary of the Russian literature. He examined 3225 infants from one month to six years of age and found 95 per cent of them afflicted with rickets; 35 per cent were severe. He tells us that in this same clinic some years earlier only 15 per cent were found. It is the same story everywhere. When rickets becomes the object of special inquiry by an interested and competent investigator, it almost always appears widespread. Joukooski states that he saw little rickets in the Crimea, the most southerly part of European Russia. It has been said that Asiatic Russia is free from rickets, but Joukooski informs us that conditions there are much the same as in other similarly located districts.

DISTRIBUTION OF RICKETS IN THE WEST INDIES.

In 1908 Vipond published an account of rickets among the colored children in *Kingston, Jamaica*. He examined some 200 infants and reported that it was rare to find rickets among them. The great majority of these babies are nursed, but are given starchy pap very early in life; although they have plenty of fresh air during the day, they sleep in poorly ventilated huts. In 1918, during the course of an investigation of "The Diet of the Negro Mother in New York City," I wrote to a number of physicians in the *West Indies* to ascertain the occurrence of rickets in these islands. The superintending medical officer at Kingston answered that "rickets as we know it in infants in large cities practically does not exist here in Jamaica." A physician who had been in the Health Department in the Canal Zone for many years wrote: "I have yet to see my first case of rickets in the West Indian negro child. My colleagues who have been here much longer tell me that West Indian children never have rickets." In regard to the Colonial Hospital at Port of Spain, Trinidad, one of the leading physicians reported: "You will be surprised to learn that during my twenty-four years in hospital practice in this colony I have not met a single case of rickets, although hundreds of children are treated in our children's ward every year."

In 1925, while travelling in the West Indies, I had an opportunity to investigate the question of rickets and to examine many infants personally. At Kingston among the children at the General Hospital, I found many suffering from mild rickets according to clinical criteria, although they did not present a rachitic appearance or pronounced bowing of the legs. This held true also for the children of the Babies' Welfare Clinic. Almost all the infants were colored. Congenital syphilis was not found as frequently as had been expected. I next visited San José, Costa Rica, and again found considerable rickets—some even of moderate degree—among the children in the hospital wards. In Panama the same was true of the children at the Santa Tomas Hospital and in the Ancon Hospital conducted by the United States Government. The radiographer of the latter institution showed me roentgenograms of rickets of mild and even marked degree which had developed in the Canal Zone. At a Babies' Welfare Clinic which is conducted for the white infants of employees of the Zone I found, much to my surprise, a large number of infants who presented signs of mild rickets. The babies were not as tanned as I had expected to find them, due possibly to the marked humidity of this region, the moisture tending to filter out the ultra-violet solar radiations. About a year later Dr. Knight, chief quarantine officer of the Canal Zone, sent to me about 100 radiographs of the epiphyses of children living

in this district. Sixty-two of this group were under eighteen months of age. Eight of these showed definite signs of rickets. From the fact that most of the lesions occurred in infants between the ages of four and six months, it is clear that had the entire group been limited to the first half year, the incidence would have been considerably higher. If we add to these undoubted cases 6 others under the age of seven months, which showed questionable signs at the epiphyses, the percentage is by no means negligible. Mention should be made of a group which showed hypercalcification at the epiphyses. There were 15 in this category, all over one year of age. At first this change was thought to have resulted from the healing of rickets. However, in the light of the recent observations of Dr. Lewis and myself in regard to the action of ergosterol in normal infants—hypercalcification of the epiphyses as well as hypercalcemia—I believe this radiographic picture to have had a similar origin, to have been the result of prolonged subjection to tropical sunlight.

In Trinidad, conditions were found to be much the same among the children in the General Hospital. Mild rickets was of common occurrence, but no case of severe rickets was seen. I examined the infants—all colored—at the Babies' Welfare Clinic on two occasions and found rickets in fully one-half.

It is evident that a mild degree of rickets is frequent throughout the cities of the West Indies, not only among negroes but also among the white infants.[1] At first this may seem surprising, in view of the fact that these islands lie in the subtropical or tropical zone. It should be borne in mind that the number of hours of sunshine which they receive is no greater, and frequently not as great as that recorded in New York and adjacent territory, although the distribution of this sunshine is entirely different. For example, the average number of days without sunshine at Ancon during the past twelve years has been about twelve days per year on the Pacific side and ten days on the Atlantic. Furthermore, the sun has far greater intensity in the tropics due to the decreased zenith distance. But even under favorable circumstances, unless the babies are taken out-of-doors, they do not receive sufficient ultraviolet rays to protect them against rickets. In Trinidad, which lies only 7° above the Equator and where, accordingly, rickets should be a disorder of the greatest rarity, it is the custom to keep

[1] In the official reports of the mortality in Porto Rico, tuberculosis stands first as a cause of death, with malaria and rickets following in the order named. For the fiscal year 1919–1920 the death-rate per 100,000 population in Porto Rico was 186 for tuberculosis, 121.2 for malaria and 108.9 for rickets. The last figure certainly needs explanation. In a bulletin published in 1923 by the Children's Bureau of the United States Department of Labor, it is explained that "rickets as it appears in the official statistics is not true rickets, but usually marasmus or malnutrition, the confusion arising from the popular use of the Spanish term 'raquitico' to include any wasting disease."

the infants indoors; it is only the little runabouts that we see outside the huts. The mothers work in the fields, and leave their babies at home.

DISTRIBUTION OF RICKETS IN MEXICO AND SOUTH AMERICA.

According to Torroella rickets does not exist in *Mexico*. He looked in vain for its stigmata among 6000 children and Carrillo supported his statement as the result of 4900 examinations of children. It is probable that conditions in Mexico in this respect are similar to those in other parts of the tropics, in other words that mild cases are not infrequent.

There is very little information of value in regard to rickets in *South America*. It is evident, of course, that this immense continent should not be regarded as a unit, for the climate in the north and the south, along the coast and in the interior differs markedly. Feer, in his monograph, states that although it was thought that rickets did not occur in Brazil, Moncorvo encountered it very frequently among the children in Rio de Janeiro. Rauenbusch wrote in 1910 that rickets was rare in Buenos Aires. He saw but 30 to 40 cases in the hospital every year, and these occurred mainly among Italians. The people spend a great deal of time out-of-doors, enjoying the mild climate; air, light and sun have free access to their homes. About four years ago I had the opportunity of examining some children in Caracas, Venezuela, and found many instances of mild and some of moderate rickets. In this respect conditions seemed to be similar to those in the Panama Canal Zone.

DISTRIBUTION OF RICKETS IN AFRICA AND THE FAR EAST.

In regard to *Africa* we have the statement of Dick, based on personal observation, that "even in the mildest form rickets is exceedingly uncommon in the immense elevated plateau of which the Karroo forms so great a part. This applies to native children and to the offspring of Dutch and English parentage alike." In response to an inquiry he was informed that in the Cape Colony cases of rickets are few and of mild type. However, it should be noted that one physician who had been in practice in this colony for a number of years replied that "it occurs fairly frequently in the poorer classes of white and occasionally among the well-to-do." There are many other reports of a general nature which might be cited in this connection but, as usual, it is difficult to know how much reliance to place on them. They may be found in the accounts of Hirsch and of Feer and refer to the incidence of rickets in Egypt, in Morocco, along the Gold Coast and elsewhere. Peiper has

written an interesting paper on "Rickets in German East Africa." He stated in 1912 that 60 per cent of the infants of this territory die during the first year. They are fed from the very first day with a thick boiled or unboiled cereal pap and die of digestive disorders. Nevertheless there is no rickets among these negroes; the diagnosis was based mainly on straightness of the legs. Peiper adds that no mention of rickets is found in the medical reports of the colony between 1903 and 1911. The interest in this account lies in the fact that these infants were fed on a diet exceptionally rich in carbohydrates. Another paper which may be mentioned in this connection, as it deals with unusual conditions, is that of Ebell, a Scandinavian who spent ten years in Madagascar. He found no rickets on this island. He cites Palm's article, published some eighteen years previously, and agrees that the lack of sunlight is the dominant etiological factor.

There is one modern paper on rickets in Africa—a thesis from the University of Algiers (1924). The author, Jean-Baptiste, concludes that "in Algiers, land of sunshine, rickets exists; it is infrequent in the country but frequent in the cities." He substantiates these conclusions by convincing radiographs. The author writes that among clinic patients rickets has increased rapidly and is present now in 1 infant among 3. In the quarter where the indigenous people live and observe the rite of seclusion (purdah) 75 per cent of the breast-fed infants show signs.

Turning to the Far East, we find that until recently the Orient was supposed to be entirely free from rickets. Palm received reports from various parts of the great Empire of *China*—Peking, Manchuria, Thibet, etc.—all to the effect that rickets practically did not exist in this country. From Shantung Province the report came back that "out of 4387 patients under treatment only 1 case of rickets had been seen and that not a well-marked case." In their book on the "Diseases of China" (1910) Jefferys and Maxwell make the interesting statement that "the most characteristic anomaly of infant disease in China is the rarity of rickets." "Bow-legs, knock-knees, square heads, beaded ribs . . . are frequently seen in Japan but rarely in China." A few years later, however, Harston writes: "Among native children rickets formerly was very rare; now it is of common occurrence, especially in south China." Strangely enough we have two up-to-date reports of rickets in China, emanating from the modern medical school in Peking, conducted according to western standards. One of these reports relates to the "Incidence of Rickets in Peking." It is by Tso who writes that he had seen 28 instances from April to August. This paper contains convincing radiographs and photographs which show that some of the cases were severe. The other modern account is by Suzuki and is entitled "A Study of Rickets in Cases of Breast-

fed Infants in Manchuria"—an account of an investigation carried out at Dairen. In view of this report a record of the amount of sunshine in this city has been incorporated in Table 1. It will be noted that the figure is high, due to the fact that there is hardly any rainfall; Dairen has somewhat more sunshine than New York City. Within a year Suzuki found 100 cases of rickets in this city, and substantiated his diagnosis by means of the Roentgen ray in 21 per cent of the cases. It is evident from these two accounts that in China rickets is of common occurrence and often of moderate degree. We should expect it to be milder in the southern sections.

There is surprisingly little information in regard to rickets in *Japan*. In his paper on Manchuria, Suzuki states, without giving the source of his information, that a few isolated cases of rickets were reported in Japan as far back as 1315, but that it was not until the beginning of this century that a considerable number were reported from any one place. These cases were noted in the Toyama prefecture. Baelz made the statement some years ago that rickets is practically unknown in Japan, but that a weakness of the thorax is observed frequently in the children of the well-to-do, a deformity resembling rickets. This dictum was accepted until the beginning of this century when gradually instances were reported from various parts of the country. The disorder was considered such a rarity that clinicians reported single cases from time to time. No pathological report on rickets appeared until 1903 when Fujinami described characteristic lesions of the skeleton in a boy about ten years of age. In 1890 Palm wrote: "During a service of over nine years in Japan, in the course of which several thousands of patients came under observation in dispensary and hospital annually, I am unable to recall a well-marked case of rickets, although some degree of pigeon-breast was occasionally met with. A degree of flabbiness of the muscles is not uncommon and the firm texture of a well-nourished child in England is not very often to be met with. A slight degree of bow-leg is also commonly to be seen among adults." There have been no recent reports from Japan and no clinical accounts fortified, like those from China, by radiographs or chemical examinations of the blood. There can be no doubt, however, in view of the climate of Japan, especially in its northern part, that rickets must be quite as common in this country as in the northern districts of the United States. It is probable that before long a modern and complete account will be published from one of the many medical centers.

We should expect to find almost no rickets in *India*. Palm tells us that Neve "seeing many thousands of patients annually in hospitals and dispensaries reports that he sees at Drogjum Hospital (Kashmir) on the average of 1 case of rickets per annum and at the city dispensary about 3 cases in six months." Neve himself, writing

almost thirty years later, states that there is almost no rickets in the city of Srinagar, Kashmir, in spite of the fact that the children are nursed two or three years and that conditions are filthy. "But," he adds, "there is plenty of sunlight all year." Among some 20,000 cases, he has seen perhaps half a dozen cases of rickets. It is probable that in southern India rickets occurs only under exceptional conditions when young infants are deprived of sunshine, and that it is generally of very mild degree, but that in the northern parts where the climate is cold and severe it is not uncommon. Castellani states that endemic tetany "is found in goitrous districts in the Himalayas where it is called 'turning of the hands.' This disorder is characterized by bilateral intermittent and usually painful spasms of the hands and feet and at times other parts of the body, and increased excitability of the nervous system." Later, in considering osteomalacia we shall find that tetany is of common occurrence among adults in India.

Davidson writing on "Geographical Pathology," stated in regard to *Java* that "rickets is a disease unknown among the natives but is occasionally met with in children of European parentage." In regard to *Borneo*, Nieuwenhuis writes: "I have still less doubt concerning the absence of rickets; during my sojourn on the island more than 5000 children up to the age of ten years passed through my hands in a state of complete nudity which allowed me to examine them readily. Among the well, as well as among the sick, I noted a complete absence of rickets."

It is difficult to understand to what pathological condition Poesch refers in the statement that in *New Guinea* he often saw bone diseases (among the Papuas and Melanese) resembling rickets—bowlegs and knock-knees.

DISTRIBUTION OF RICKETS IN AUSTRALIA AND NEW ZEALAND

Dick writes that "careful observations made at different periods during the last thirty years tend to show that rickets was not originally a serious factor in infant life in *Australia*, but that it is rapidly becoming one of great importance." "In South and West Australia rickets, as might be expected, is quite uncommon." These areas are sparsely populated and have a genial climate. The rickets in Australia, as well as in New Zealand, is generally of mild type and deformities of the pelvis sufficient to interfere with labor are of rare occurrence. Harper, writing in 1924, states that he examined 111 infants between the ages of one month and two years for rickets and found 14 cases. In a discussion of this paper Sutton stated that among 2000 school children in Melbourne 20 per cent showed clinical evidences of rickets—a surprisingly high percentage for children of this age group. It should be borne in mind that in Australia much

of the population is gathered into several very large cities, a condition which produces congestion and favors the development of rickets. In *New Zealand* social conditions are just the opposite. The cities are small and few, and the population mainly rural. From personal communications I learn that although rickets does occur in the cities of New Zealand, it is very mild in type and is not an important medical problem.

When we compare present opinion of the geographical distribution of rickets with that expressed by Hirsch in 1890, we find general agreement. The main differences concern countries where, as in China and the Faroe Isles, it was stated formerly that rickets did not occur—in other words, where rickets was thought to be absent, it has since been found. This same change in viewpoint holds true regarding the distribution of other diseases. It was believed that cancer did not occur in Japan, but since Japanese physicians have become more highly educated and trained, cancer has been found to be approximately as common in these islands as in Europe and in America. Cancer has been frequently reported as rare among the Eskimos, but a systematic inquiry in Greenland, conducted by the Danish Medical Association, showed that cancer is quite as common in this area as in Europe. We shall no doubt find that no country is entirely devoid of rickets, that it occurs sporadically throughout the tropics, when and where conditions prevail which render the surroundings similar to those of the temperate zones. *In general, a map of the incidence of rickets is the practical equivalent of a map of deficiency of sunlight.* On looking over Table 1, which gives the actual hours of sunshine in various parts of the world, we have an approximate picture of the geographical distribution of rickets. However, certain important qualifying factors must be emphasized. The most important of these is the degree of congestion of the population; whether in these areas the people are gathered together in cities or dispersed throughout the country in small towns and villages. In this way, industrialism plays an important rôle in the distribution of rickets; insofar as it has brought about the crowded city with its narrow sunless streets, it has led to the development of this disorder. But we must remember that even before the days of modern industry, people huddled together in small towns; the old cities of Europe still present innumerable evidences of the winding sunless lanes and alleys which were typical of the mediæval town. Indirectly industrialism has led to rickets by forcing the mother into the factory or shop and thereby depriving the infant of maternal care and supervision. These social conditions have led to his being kept indoors and being deprived of an adequate amount of fresh air and sunshine.

In a consideration of the distribution of rickets, a sharp distinc-

tion should be made between mild rickets, especially the incipient form which is readily recognized today, and moderate and severe rickets. As yet we do not know the medical or social significance of mild rickets, of the pathological lesions which can be diagnosed only by the trained clinician or by means of laboratory examinations. Whether such systemic and local alteration is fleeting and entirely innocuous, leading to no permanent damage, remains to be ascertained. It is still the moderate and severer forms in which we must be interested. These bring about deformities of the bones, especially of the lower extremities and of the bony pelvis, which are serious in their consequences. Moreover, they are often associated with a lack of vitality and resistance which constitutes one of the most important dangers of this disorder.

Interest in rickets is so widespread among physicians, health officials and laymen that before long much additional information will be available in regard to its geographical distribution. We may be able to make a topographical map of its incidence, and to compare this not merely with a similar chart of the actual hours of sunshine in various parts of the world, but with the intensity of ultra-violet energy in these localities. The area of distribution of rickets, especially of its severer forms, is becoming more and more circumscribed owing to the fact that we possess numerous specific measures to prevent its development. It is not too much to hope that the time is not far distant when in the civilized countries of the temperate zones—the stronghold of rickets—moderate or severe cases will be a rare disease and the milder forms far less frequent than at the present day.

CHAPTER III.

EXPERIMENTAL RICKETS.

The induction of rickets in animals is the very keystone of "The Newer Rickets." It is only ten years since a method was made available for the scientific and consecutive study of this disorder, but its use has spread to the laboratories throughout the world. As has happened so often, the ability to produce a disorder at will and under conditions subject to exact control has acted as a spur to investigation and led to a rich harvest. It should not be forgotten, however, that our appreciation of the specific value of ultra-violet light redounds to the credit of clinical and not of experimental medicine in the restricted sense of the term. In this respect the evolution of our knowledge resembles that of scurvy rather than that of beriberi. Although experimental rickets is of such recent date, its technique is well established and even standardized. It is suggestive, however, that a physical approach—the spectral absorption test—is now threatening to displace the biological method, although the final criterion of antirachitic agents is still the biological reaction of the experimental animal.

It was not until nearly two hundred years after Glisson described infantile rickets that an endeavor was made to induce this disorder experimentally in animals. The first attempt of this kind was made ninety years ago, in 1839, by the celebrated French orthopedic surgeon Jules Guerin, who fed some young puppies on meat and concluded that they developed rickets; the control animals which were suckled failed to develop it. The underlying principle was a deprivation of calcium, and therefore similar to the oft-cited investigation carried out by Bland Sutton some fifty years later on the lions in the Zoölogical Gardens of London. It is difficult to judge whether Guerin actually induced rickets or merely a disorder which resembled rickets. Tripier attempted to repeat the experiment in 1874, using dogs, cats and chickens, but was unable to do so; it should be noted, however, that the diet of his animals was not carefully supervised. A few years later Chossat, the French physiologist, endeavored to induce rickets in pigeons by feeding them wheat grains, a diet poor in calcium. As we should now expect, merely marked fragility of the bones resulted. The birds developed diarrhea which was attributed to a lack of calcium, a "diarrhée par insuffisance de principes calcaires." This calls to mind the observation

of Telfer (1922) that when the intake of calcium is reduced, infants develop diarrhea associated with a diminution of calcium soaps and an increase of fatty acids in the stools.

From 1871 to 1873 the physiologist Weiske reported a series of experiments which attracted considerable attention. Once again animals were fed on a diet poor in calcium. In the course of these studies chemical analyses for calcium were carried out, but gave negative results. It would seem that his animals were underfed, suffered from starvation and developed osteoporosis rather than rickets.

In 1880 E. Voit reported a careful investigation on "the importance of calcium for the animal organism." He fed meat and lard to puppies for several months. The animals were well-nourished and developed the typical appearance of rickets; the long bones became bent and beading of the ribs was visible. It is interesting to note that Voit realized that these signs developed in direct proportion to the growth of the animal, and that he, therefore chose dogs which were young and of a breed which grew to large size. Tenderness of the limbs also was manifested, due probably to the intercurrence of scurvy, a complication which calls to mind the early experiments of Mellanby some forty years later. Voit recognized the importance of a lack of phosphoric acid in the diet in hindering the formation of calcium phosphate in the bones. It is probable that he succeeded in inducing rickets in puppies, for the zone of proliferating cartilage was greatly increased, irregular in outline and there was marked overproduction of the cells. Two years later the well-known pediatrist, Baginsky of Berlin, repeated Voit's experiments and obtained similar results. In addition he tested the effect of giving lactic acid, a substance which Heitzman had stated was increased in the course of rickets and brought about dissolution of the salts of the bones. Two grams of lactic acid were fed daily and Baginsky concluded that the total ash of the bones was decreased to an extent greater than when the acid was not fed.

Mention should be made of an investigation which attacked the problem from a different angle, that of Stilling and v. Mering (1899) on "The experimental production of osteomalacia." They used a pregnant bitch to which they fed horse meat that had been cooked in water for two hours, then pressed and mixed with a small amount of fat. She had a litter of six, but none of the puppies showed any bony lesions when they died at the age of one month. However, when the bitch was killed four months after the beginning of the experiment, the investigators noted marked softening of the vertebral column and of the pelvis and extreme redness of the marrow—lesions similar to those occurring in osteomalacia of women. The description of the histological lesions is not given in

detail; it is stated merely that the osteoid borders of the trabeculæ were unduly broad.

A sharp distinction should be drawn between these investigations and those which followed. In 1885 Pommer established a new histological criterion for rickets. Before this time all studies, both experimental and clinical, were continually befogged by a lack of unanimity in regard to the conception of rickets and of its limitations. Although it was recognized generally that osteoporosis is a pathological disorder which differs from rickets, the main histological criterion of rickets was the width of the zone of proliferating cartilage. Pommer showed that the increased width of active cartilage cells is not distinctive of rickets and that the most reliable sign is an increase of the osteoid tissue which borders the bony trabeculæ and the periosteal walls. This interpretation which, some years later, gained general acceptance among pathologists, has cast doubt on most of the previous studies of rickets, so that we must distin- a *pre- and a post-Pommer period of experimental rickets*. In considering the pathology of infantile rickets we shall find that this demarcation holds to even a greater extent. However, from what we now know of the effect of diets, there can be little doubt that true rickets was induced by several investigators before 1885.

The first attempt to use chemical criteria to solve the problem of experimental rickets was that of Aron and Sebauer in 1908, who, in addition to the usual microscopic examinations, made careful chemical analyses of the bones. First, they used young rabbits for their experiments, but failed as the animals died from inanition; later they made use of young puppies and fed horse meat, corn, beef tallow and sodium chloride. As usual, satisfactory macroscopic lesions of rickets developed—enlargement of the epiphyses and beading of the ribs; photographs of dogs are appended which call to mind those of Mellanby's later investigations. The microscopic lesions of the bones were pronounced by one pathologist to be typical of rickets. However v. Hansemann expressed the opinion that they deviated somewhat from the characteristic appearance. In 1909 Goetting, in a report on the microscopic lesions of these dogs, stated that there was but a slight increase in osteoid tissue. The bones were found to be rich in water but poor in dry substance, which, in turn, was deficient in its mineral content. The calcium of the ash was but little diminished; in other words, the bones contained an excess of water, and organic matter which was insufficiently calcified.

Passing over Goetting's own experiments, which brought out nothing new, we come to the important studies of Dibbelt. The first of these was presented at the 1909 meeting of the German Pathological Society, which that year had rickets as its main theme. Schmorl, Stoeltzner and many others, who had devoted much

thought and energy to this subject, took part in this celebrated discussion. Dibbelt had fed dogs on horse meat and fat, or on horse meat, starch, sugar and sodium chloride. It will be observed that the foodstuffs which Guerin used in his pioneer experiments, carried out in the first half of the past century, formed the basis of the rations employed by subsequent investigators. The puppies which were fed fat as well as meat did not develop rickets, whereas those which received no fat showed "characteristic anatomical and chemical evidences" of this disorder. It would seem that this experiment resulted in a definite production of rickets in animals. In the following year Dibbelt pursued the subject further and reported on the importance of calcium salts during pregnancy and lactation—an experiment similar to that of Stilling and v. Mering. He fed a pregnant bitch on rice, horse meat and "fat;" this food was cooked and sodium chloride added. Rickets or osteomalacia was not induced; merely an osteoporosis of the bones of the mother which, according to Dibbelt, constitutes a predisposing cause of rickets.

Until this time attention had been focussed in all experiments on the calcium factor, an effort being made to induce rickets solely by a deprivation of calcium. In 1909 W. Heubner, the pharmacologist, published an account of experiments on the phosphorus metabolism of the growing organism. He fed two puppies on white of egg, rice, cane sugar, palmin, Na, K, Ca, Mg as chlorides, and saccharide of iron. Bowing of the legs and broadening of the epiphyses developed as evidenced by the Roentgen ray. Schmorl interpreted the histological changes, stating that there was no increase in osteoid tissue and that the lesions resembled those of Barlow's disease more closely than those of rickets. Heubner just missed producing rickets, although he fed a ration low in phosphorus. In the first place he fell into the error of conducting his experiment for too short a period—merely from weaning until the age of seven weeks—and secondly, he failed to render the diet complete by the addition of an antiscorbutic.

INFECTION AND BACTERIA IN EXPERIMENTAL RICKETS.

The subject of the rôle of infection and of bacteria in rickets will be discussed in the chapter treating of etiology, but a few of the experimental studies must be mentioned in this connection. The conception of rickets as due to an invasion of bacteria dates from 1902, when Morpurgo published a paper on malacic and rachitic skeletal changes induced in young white rats by means of infection. He injected a diplococcus—isolated from the feces of rats which had developed spontaneous rickets in the laboratory—subcutaneously into either new-born rats or those a few days old, and concluded that he had induced true rickets. He states that an increase of

osteoid tissue was present. It is quite possible that these rats developed rickets; however, a result of this kind has little etiological significance in view of the fact that no information is furnished in regard to their diet. A similar study was reported in 1911 by Koch, who injected rabbits with streptococci and believed that he had produced rickets by this means. From his account it is clear that vascularization and inflammation were brought about probably through the bacteria lodging in the terminal vessels of the epiphyses. In his conclusions he adopts the viewpoint of Kassowitz that rickets is an active vascularization of the epiphyses in childhood, the cause of which is not respiratory poisons or other indefinite substances, but bacteria. These experiments will be considered in detail elsewhere but, in passing, it should be observed that such a method of attempting to induce rickets is absolutely aphysiological. The recent experiments of Korenchevsky on the relation of infection to rickets are of importance because they were carried out on the rat, an animal which readily develops rickets, but more especially because the experimental diet was carefully controlled. He failed absolutely to induce rickets, whether the bacteria were incorporated in the food or injected subcutaneously.

In 1908 Findlay attempted to induce rickets in puppies. He fed one series a ration of cereals, bread and water, and another milk and porridge. The dogs which were kept in cages developed rickets, whereas those which were allowed to run about the laboratory failed to develop this disorder. The photographs illustrating the posture of the rachitic dogs and the beading of the ribs are typical. He concluded that "by confining young dogs and depriving them of exercise, rickets has been invariably induced," and that "confinement with subsequent lack of exercise is the main factor in causing the disease." Subsequent investigations have served to alter this conclusion.

VITAMINS AND EXPERIMENTAL RICKETS.

The *second period* in the attempt to induce experimental rickets is distinguished by an appreciation of the significance of the vitamins. Hopkins had suggested the importance of these nutritional factors as early as 1906 and Funk mentioned them in connection with the etiology of rickets in his book on "Vitamins," published in 1914. At that time he wrote: "It is very probable that rickets occurs only when certain substances in the diet essential for normal metabolism are lacking or are supplied in insufficient amount. The substances occur in good breast milk, also in cod-liver oil, but are lacking in sterilized milk and in cereals." It should be borne in mind that the fat-soluble vitamin or vitamin A had been discovered in 1913. The stage was set, therefore, for a study of the

relation of this nutritional factor to the etiology of rickets, and Mellanby, already actively engaged in an investigation of this subject, directed his experiments into this channel. Mellanby's work, published in 1919, almost eighty years after Guerin's first attempts, is the first important investigation of rickets from an experimental standpoint, not only because he took into consideration the rôle of the vitamins, but because his work was carried out with diets which were carefully constituted and controlled. The various rations which he used are as follows:

Diet I.	*Diet II.*	*Diet III.*	*Diet IV.*
Whole milk, 200 cc.	Whole milk, 175 cc.	Separated milk, 175 cc.	Separated milk 250–350 cc.
Porridge, oatmeal	White bread, *ad lib.*	White bread, *ad lib.*	White bread, 70%
Porridge, rice	NaCl, 1–2 gm.	(70% wheaten)	Linseed oil, 10 cc.
NaCl, 2 gm.		Linseed oil, 10 cc.	Yeast, 5–10 gm.
		Yeast, 10 gm.	Orange juice, 3 cc.
		NaCl, 1–2 gm.	NaCl, 1–2 gm.

It will be noted that there was a gradual development and improvement in the diets. Orange juice was introduced, as it was found that the early experiments were complicated by the development of mild degrees of scurvy. The quota of orange juice was increased later to 5 cc. and the separated milk reduced to a maximum of 250 cc. Mellanby sums up the underlying principle of his experimental method as follows: "This investigation carried out on puppies has consisted essentially in placing the animals on standard diets found to produce rickets and then adding to the standard diets other substances, in order to determine the effect of these on the development of the disease." The dogs were well cared for in a building, which (as it happened) was not well lighted, and were given a short run out-of-doors daily.

For the diagnosis of rickets the main dependence was placed on the radiological picture of the epiphyses and on the calcium content of the bones. Histological examinations of the epiphyses were made, but this part of the investigation was not so convincing, as few photomicrographs of sections were reproduced. However, there is no doubt that Mellanby not only induced, but controlled rickets by means of diet and that, in general, he drew the correct conclusions from his investigations.

In the course of his work Mellanby also demonstrated experimentally that cod-liver oil is an excellent antirachitic agent, incomparably superior to all other fats, whether animal or vegetable.[1] The

[1] A history of the vicissitudes of cod-liver oil therapy in infantile rickets may be found in the introduction to the chapter on Treatment.

substance next in order of potency was butter-fat, the activity of which was found to be somewhat unreliable. Suet also was potent. The vegetable oils ranged themselves in order of potency as follows: peanut, cocoanut, rapeseed, cottonseed and palm kernel oil. Olive oil and linseed oil were of no value and babassu oil was "the worst" of all. Bread was found to induce rickets; the more the puppies ate, the greater the intensity of the disorder, largely due to the fact that the bread led to a marked increase in growth. Meat exerted a mild antirachitic action. The tests with casein are of interest. Mellanby concluded that whereas alkaline casein has protective value, acid casein, made by the addition of hydrochloric acid to milk, tends to increase rickets and to depress calcification; the acid casein differed from the alkaline preparation in containing no calcium. This is not surprising in view of the fact that the rickets-producing action of Mellanby's standard ration depends on its deficiency of calcium rather than of phosphorus.

Mellanby believed and, for some years, clung to the idea that the antirachitic factor was probably identical with the fat-soluble vitamin A. In 1921 he wrote: "The action of fats in rickets is due to a vitamin or accessory food factor which they contain, probably identical with the fat-soluble vitamin." Subsequent investigation has shown that Mellanby was mistaken in this interpretation. However, the distinction between the two vitamins is so subtle that one could not expect it to have been recognized in a pioneer investigation.

This subject will be discussed in greater detail in the chapter on Etiology.

PHOSPHORUS AND EXPERIMENTAL RICKETS.

The third period of experimental rickets is distinguished by a shifting of the emphasis from a deficiency of calcium in the dietary to a deficiency of phosphorus. In view of the fact that it had long been recognized that approximately 95 per cent of the calcium in bone exists in the form of calcium phosphate, it is remarkable that greater attention was not devoted to the phosphate ion. The only previous investigation which considered this factor was that of W. Heubner, published in 1909. An important technical advance was also introduced into these newer investigations by the use of the rat as the standard animal for testing rickets and assaying antirachitic substances. As has happened so often in experimental medicine, the new method was announced almost simultaneously from different sources. Sherman and Pappenheimer, as well as McCollum, Shipley, Park and their associates, published reports in 1921, which showed that rickets can be brought about satisfactorily in rats by a ration in which phosphorus is deficient. The latter

group of investigators employed a ration composed either of rolled oats, flaxseed oil meal, sodium chloride, calcium carbonate and dextrin, or the flaxseed oil meal was replaced by gelatin. When a complete salt mixture, containing potassium phosphate, replaced the sodium chloride and calcium carbonate, the diets no longer induced rickets but typical osteoporosis.

Whereas McCollum and his associates emphasized the lack of the vitamin in the diet, Sherman and Pappenheimer laid stress on the deficiency of phosphorus. Their rickets-producing ration consisted of: patent flour, 95; calcium lactate, 2.9; sodium chloride, 2; and ferric citrate, 0.1 per cent. It led to the development of rickets almost without exception, but to osteoporosis as well, owing to the fact that it is inadequate in other nutritional factors—being highly deficient in vitamin A, in protein, and possibly in vitamin B. It contains about 76 mg. of phosphorus and 553 mg. of calcium per 100 grams of diet. This ration could be rendered rickets-protective by the simple replacement of 72 mg. or 0.4 per cent of alkaline potassium phosphate by an equivalent amount of calcium lactate. More recently (1925) Steenbock and Black have suggested a low-phosphorus ration composed of maize, wheat gluten, calcium carbonate and sodium chloride. This ration induces marked rickets as well as good growth, and is therefore very satisfactory.

During the years which have elapsed since the low phosphorus rations were introduced, a standardized technique has been developed for producing rickets in rats, and a great many series of experiments have been conducted with this animal as the test object. The great advantages of using rats rather than puppies are that they are more available, that they cost less initially and are less expensive to maintain, that the experimental period is only one-third as long, that there are not as marked differences in breed, and that a greater number of animals can be used to repeat and control the tests. Many years before, Morpurgo, Schmorl, Weichselbaum and Pappenheimer had reported characteristic rickets in rats and Erdheim gave a classic description of rickets in rats in connection with his experiments on parathyroidectomy. However, Erdheim gave little thought to the diet of the animals, stating merely that "the chemical composition of the ration of our animals was not determined. The diet consisted at all times of white bread and tap water." At first, investigations on rats emanated from the United States, but workers in England, Germany, France and other countries soon made contributions to our knowledge, using essentially the same technique. Some have preferred the curative and others the protective experiment. For the curative test the animal is placed on a rickets-producing diet and after the development of rickets has been established by means of the Roentgen ray, the test substance is added to the standard ration to ascertain whether

it brings about healing. Five to ten days later radiographs of the epiphyses at the knee-joints are again taken in order to note whether calcification has been brought about. A modification of this method, the "line test," was introduced in 1922 by McCollum and his associates, who describe it as follows:

"Rats which give a *positive 'line test'* differ from the controls in having a broad linear deposit of calcium salts on the metaphysial side of the epiphysial cartilage. The band, which may not be complete, is separated from the shaft of the bone by the depth of the metaphysis and from the nucleus of ossification of the epiphysis by the depth of the epiphysial cartilage. It can be seen on a freshly cut surface of an untreated bone as a yellow line which marks the epiphysial borders of the metaphysis. The deposit is blackened by 1 per cent silver nitrate in fresh gross specimens. It appears like a cross-section of a black honeycomb when it is examined with a binocular microscope. The metaphyses of these bones usually appear to be congested. The calcium salt deposit is in the proliferative zone of the cartilage. It may extend completely across the bone or may be interrupted or fragmentary according to the activity of the calcium-depositing substance. It is stained brown in permanent sections by silver nitrate, or an intense blue by hematoxylin."

In addition to the radiograph as a criterion of the healing or production of rickets in animals, estimations of the inorganic phosphorus of the blood are of value. The percentage of inorganic phosphorus in the young rat normally is about 6 to 8 mg. per 100 cc. of plasma. When rickets has developed this percentage decreases as in infants, and falls to about 4 mg. or even as low as 2 mg. In general it holds true for experimental, as well as for infantile rickets, that the reduction in inorganic phosphorus parallels the intensity of the rachitic process. Rats developing rickets on the Sherman-Pappenheimer diet, which is very incomplete, average about 3 mg. per cent of inorganic phosphorus, whereas those developing osteoporosis unaccompanied by rickets suffer only a moderate diminution of the phosphorus, percentages ranging from about 5 to 5.5 mg. When ultra-violet irradiation is given in conjunction with a marked rickets-producing diet, the inorganic phosphorus is maintained to a certain degree, but may still be within the rachitic realm, in other words, below 4 mg. per cent. This phenomenon indicates, as Gutman and Franz pointed out, that calcification is not controlled directly by the level of the phosphorus in the blood.

The crucial test of whether rickets has developed or healing has been brought about is afforded by a microscopic examination of the bones. It has become increasingly evident that all investigations must include a histological examination of the bones and should not be based solely on radiographic pictures of the epiphyses. It is

quite possible, as will be mentioned from time to time in the course of this work, that we may alter our conception as to the scope of the pathological changes which should be regarded as rachitic. Until such time, however, the classic microscopic lesion must be accepted as the final court of appeals.

It seems unnecessary to describe separately and in detail the histological lesions of the bones which develop in dogs or in rats in the course of rickets. These lesions resemble so closely those of infantile rickets that they may be regarded as identical, and as embraced in the description of the pathology of this disorder. An exceptionally detailed and painstaking exposition of the rachitic lesions in rats may be found in Erdheim's monograph, published in 1914. One of the histological criteria of rickets in the experimental animal is a marked increase in the width of the zone of preparatory cartilage associated with its irregular projection toward the diaphysis, and with a failure in deposition of calcium in this zone. The distinctive feature, however, is the marked increase in osteoid tissue, both surrounding the trabeculæ at the metaphysis, and along the shafts of the bones. The zone of preparatory cartilage is frequently 15 to 25 cells, instead of the normal 4 to 6 cells in depth; it is of an irregular outline and calcification of the matrix is either lacking or imperfect. The spongiosa adjacent to the cartilage may be composed almost entirely of osteoid tissue which is fringed with large, active osteoblasts; the osteoid margins along the shafts are likewise abnormally broad and the marrow spaces are narrow and the vessels hyperemic. There is a general swelling of the costo-chondral junction, over which the periosteum and perichondrium frequently are thickened.

Protective rather than curative tests may be employed. In our laboratory work, in the course of which many thousand rats have been used, the criterion generally has been protection. The technique is as follows: The rats are used as soon as they have been weaned, that is when they are four weeks of age; at this time they weigh about 40 to 50 gm. They are then generally placed on a standard low-phosphorus diet (Sherman-Pappenheimer), which is supplemented by the test material. After a period of twenty-five to twenty-eight days, they are radiographed, dental films being used for this purpose. Frequently blood is also aspirated from the heart for the determination of the percentage of inorganic phosphorus. The ribs are then removed, fixed for twenty-four hours in Müller formol, and decalcified in Müller's fluid for a period of five to ten days preparatory to being sectioned. In our opinion the protective is fully as reliable as the curative experiment, provided it is carried out with a sufficient number of control animals.

The main sources of error in this type of experiment are that one or more rats may have rickets in mild degree at the time the test

is begun or, on the contrary, that owing to an exceptionally liberal pre-experimental diet, they may fail to develop rickets in spite of the low-phosphorus ration. Such protection is most apt to occur if the mothers and young have been given cod-liver oil during the suckling period. The advantages of the curative test are that it is shorter, taking but seven to ten days, and that it requires a much smaller amount of test material, a factor which at times makes it the method of choice. For control, however, the curative test should not only be followed but preceded by radiographs of the epiphyses.

Animal tests in connection with studies of rickets should not be undertaken casually, for they are exposed to quite as many pitfalls as chemical tests. The age of the animals, their stock and previous diet, rapidity of growth or failure to grow in the course of the experiment, access of light, contamination of the cages with cod-liver oil, etc., may obscure the result. For example, some years ago we obtained rats from a dealer who fed his stock cod-liver oil. As the result of this supplement to the ration we were unable to induce rickets even when rigid rickets-producing diets were given. On the other hand, at another period, a series of experiments was confused and nullified by the fact that the pre-experimental diet of the rats had been such that the young developed a mild degree of rickets by the time they were four weeks of age. Recently some cages became contaminated with minute traces of activated ergosterol, which sufficed to protect the rats and to throw our experiments into confusion. These examples suggest the type of complication which arises from time to time.

DIET IN EXPERIMENTAL RICKETS.

Animal experimentation afforded an opportunity to investigate in detail *the influence of the diet during the pre-experimental period* on the susceptibility of rats to rickets. In an extended series of tests it was found by Hess and Weinstock that resistance is due to the previous diet of the animals rather than to peculiarity of strain or breed. A resistant condition could be brought about by a diet which had been exceptionally liberal during the first four weeks of life, or it could be overcome, in turn, and the offspring rendered more susceptible to rickets, by feeding both mother and young a less adequate dietary throughout the suckling period. Resistance could be broken down also by means of inadequate lactation during this period, by having a mother suckle young in addition to her own litter. Korenchevsky has laid emphasis on the importance of the fat-soluble vitamin and calcium in the diet of lactating animals and believes that the young may be protected against rickets by obtaining a liberal amount of these factors through the mother's

milk. These experiments imply the necessity of complete control of the ration of test animals throughout the pre-experimental period. To those actively interested in the clinical aspect of rickets they suggest that the diet of infants during the first weeks of life may play a rôle in susceptibility.

In connection with animal experiments, mention should be made of the observation of McCollum and his associates on *the effect of starvation* on the healing of rickets. It was found that when young rachitic rats were made to fast for periods of three to five days, receiving nothing but distilled water, definite calcification of the epiphyses resulted. It is important, therefore, in connection with curative experiments to note whether the animals consume their rations. But healing may occur also in rats which have not been starved but which, for other reasons, have not grown. Some years ago I noted "the spontaneous cure of rickets in rats" which had been on a standard low-phosphorus diet for a period of three months.

The thesis of Mellanby that rickets is due to a deficiency of the fat-soluble vitamin A was controlled and clarified by means of further experimentation which was carried out exclusively on rats. It soon became evident that Mellanby had erred in this particular and that animals do not become rachitic when deprived of this vitamin but develop a disorder of the eyes termed xerophthalmia or keratomalacia. The study of Hess, McCann and Pappenheimer (1921), as well as the investigations of others, left no doubt "that a lack of the fat-soluble vitamin in a dietary which is otherwise complete does not lead to the development of rachitic lesions in rats." It should be added that all of the rations fed by Mellanby contained vitamin A and that, accordingly, none of his puppies showed signs of xerophthalmia.

In 1920 Hopkins demonstrated that oxidation destroys vitamin A, that when oxygen was allowed to pass through heated butterfat, its vitamin A content readily was destroyed and lost the property of inducing growth and of curing xerophthalmia. This observation opened the way to the elucidation of the fat-soluble vitamin problem, which at this time had reached an *impasse*. Two years later McCollum and his associates showed that what was regarded as a single vitamin in animal fats consisted of a combination of at least two vitamins. These he separated by means of oxidation. After subjecting cod-liver oil to a stream of air bubbles, at the temperature of boiling water, for twelve to fourteen hours, he found that the oil no longer was able to cure rats of xerophthalmia but had lost none of its potency for rickets—in other words, that it still contained the antirachitic factor (which he termed D vitamin), but had been deprived of its fat-soluble or A vitamin. This demonstration was a marked step forward and clarified and coördinated many divergent views as to the action of the fat-soluble vitamin.

Goldblatt and Zilva soon confirmed McCollum's observations and showed that, in the presence of air, the growth-promoting and the antirachitic factors are inactivated at different rates by heat.

COD-LIVER OIL AND IRRADIATED ERGOSTEROL IN EXPERIMENTAL RICKETS.

Although it had been shown clinically that cod-liver oil is a specific therapeutic agent for rickets, the objective proof of this fact was first brought out in 1919 by Mellanby's experiments on dogs. Not long thereafter Shipley, Park, McCollum and their associates were able to demonstrate a similar phenomenon in rats. In no other province of rickets has the experimental method proved so fruitful in developing and clarifying our knowledge as in regard to the value of cod-liver oil and its various fractions.

In view of the fact that cod-liver oil had been found to act specifically in the prevention and cure of rickets both in animals and in man, experiments were undertaken to acquire fuller information in regard to the scope of its activity. From both a theoretical and a clinical point of view, it seemed of value to ascertain whether, when fed to pregnant animals, its active principle passes through the placenta and is transmitted to the fetus and, furthermore, whether the specific factor is secreted into the milk in quantity sufficient to protect the young. These experiments may be summed up by the statement that cod-liver oil, when given to the mother during pregnancy, cannot be relied on to protect the offspring from rickets, and that the active principle of the oil is not excreted in the milk in adequate amount. Rats receiving even large doses of cod-liver oil were unable to afford complete protection to their young, which were placed on rickets-producing diets after weaning.

On the other hand, cod-liver oil did confer subsequent protection when fed, during the latter half of the lactating period, to the young directly and not through the medium of mother's milk, thus demonstrating the essential difference between what may be termed direct and indirect nutrition. Although it cannot be taken for granted that these results are applicable to human rickets, it is probable that such distinction as exists is one of degree rather than of kind. An attempt to protect infants from rickets by giving their mothers liberal amounts of cod-liver oil during the last two months of pregnancy met with failure—a result quite in harmony with our animal experiments.

Irradiated ergosterol will be discussed in the chapter on Treatment. In this connection, however, it should be emphasized that it has been found to be a reliable specific for animals and that the result is effected by infinitesimal amounts. One hundred thous-

andths of a milligram suffices to protect a rat from rickets. It is protective or curative to a similar degree in rats, dogs and chickens.

Recently Kreitmair and Moll published a report showing that when toxic amounts are given—several thousand times the therapeutic dose—animals lose weight and may even die. The cat is the most sensitive; but white mice, rats and dogs react similarly. A most suggestive angle of this investigation is that sclerosis was noted in the larger vessels, as well as in the heart muscle, stomach wall, lungs and kidney. It would seem that such excessive doses furnish a means of producing and investigating arteriosclerosis. Hess and Lewis have found that, in the white rat, large doses of irradiated ergosterol, for example, 1 mg. daily for a period of a week or less, lead to marked hypercalcemia, concentrations of 16 to 18 mg. per 100 cc. of serum.

INFLUENCE OF FOODS ON EXPERIMENTAL RICKETS.

Although it seems unnecessary to review in detail the studies which have been made of the antirachitic value of various foods, it is important to have a clear understanding of the experimental evidence in regard to certain foods, especially of the leafy vegetable. There is a general impression among physicians, extending even to workers in the field of nutrition, that *the leafy vegetables, and more particularly spinach*, have a decided antirachitic value. This opinion prevailed before the new era or period of experimental rickets, and was intensified by Mellanby's investigation which claimed antirachitic potency for spinach and for cabbage. In 1920 Hess and Unger, in a study of the clinical rôle of the fat-soluble vitamin, reported that rickets persisted in an infant in spite of a diet which included 30 gm. of spinach daily and that such had been their experience with other infants. In 1923, Zucker attempted to extract and concentrate the active principle from spinach and carrots, using acetone, ether and alcohol. He concluded that "on this basis spinach or carrots, if they contain any antirachitic material, will require 4 kilograms to furnish as much as 1 teaspoonful of cod-liver oil." In other words, these vegetables were found to contain practically none of the antirachitic factor. McClendon reported that dried spinach did not protect against rickets, although it cured xerophthalmia. Zilva gave spinach to the equivalent of 30 per cent of the diet but found that it did not have the slightest effect in promoting calcium deposition. In 1924 Shipley, Kinney and McCollum, in the course of a series of tests of various vegetables, found that extracts of dried spinach, brussels sprouts, cabbage, celery, tomato, and sweet potato were without effect on the rachitic process in the bones. The most recent investigation of this subject is that of Chick and Roscoe (1926), who came to the conclusion that spinach

grown in the open, as well as that grown indoors, has little or no antirachitic properties; on the other hand, they comment on the marked difference in this respect between vegetables which had been grown in the sunlight and those which had been subjected to the radiations of the mercury-vapor lamp, which thereupon develop antirachitic properties. It would seem, therefore, to be proved beyond question that spinach and green vegetables have practically no antirachitic value and cannot be relied upon to any extent whatsoever in the preventive or curative treatment of rickets.

A few words must be devoted to the experimental evidence of the protective or curative value of *butter*. It is generally believed that butter is a specific for rickets, to be relied on only to a less extent than cod-liver oil. However, experiments of McCollum and others show that it is necessary to feed 15 to 30 per cent of butterfat in order to bring about even a faint calcification of the bones. Such tests indicate that although butter contains the antirachitic factor, it is present to a degree which renders it of little value from a dietetic standpoint.

For many years there has been a marked diversity of opinion among pediatrists in regard to the rôle of *eggs* in relation to rickets. This question has been satisfactorily answered by recent animal experiments. Mellanby has shown that the yolk of egg is of protective value for dogs, and Hess that it has similar value in connection with the rickets of rats and infants (Figs. 1 and 2). Boiling the egg for twenty minutes did not appreciably diminish the potency of yolk of egg. Recently Tso has reported that "egg yolk in small amounts furnishes a vitamin-like substance which enables the body to mobilize and utilize economically the apparently limited supply of calcium in the body." Drying the yolk and keeping it in a dried state, however, markedly reduced its antirachitic value. The yolk of egg was found also to confer protection when injected subcutaneously. On the other hand, the white of egg has no antirachitic activity whatsoever; indeed it tends to further the development of rickets and is incorporated in rickets-producing dietaries in order to intensify the disorder.

An entirely different form of rickets can be produced in rats—*a low-calcium rather than a low-phosphorus type*, by reducing the calcium and increasing the phosphorus content of the ration. This type of animal rickets was described in 1922 by Shipley, Park, McCollum and Simmonds and by Sherman and Pappenheimer. It is of particular interest, because it seems to be the counterpart of infantile tetany, which although not brought about by a deficiency of calcium in the diet, is intimately associated with a calcium deficiency, as indicated by the constant decrease in calcium content of the serum. The microscopic picture of this form of rickets differs from that brought about by a deficiency of phosphorus in

that the endochondral lesions are slight and the swelling of the epiphyses not marked. The zone of proliferative cartilage is not abnormally broad and the osteoid tissue, although increased in amount, does not attain the abnormal dimensions found in association with the low-phosphorus form of rickets. As we should

FIG. 1

FIG. 2

FIGS. 1 and 2.—Antirachitic action of *yolk of egg*. Fig. 1. Rickets induced by low-phosphorus ration. Fig. 2. Normal epiphyses of rat fed same ration to which 0.1 gm. daily of yolk of egg was added.

expect, in view of the slight endochondral changes of the epiphyses, the radiographic picture of the low-calcium rickets is not characteristic; in fact, very frequently no abnormal changes are evident, a state which may be interpreted as an absence of rickets.

Experiments showed that rickets likewise can be induced in

adult rats by means of diets deficient in phosphorus. The process develops more slowly and with less intensity than in rapidly-growing animals, but an increase in osteoid tissue comes about if the deficient diet is continued sufficiently long. As would be expected in animals in which active growth has ceased, changes in the epiphyses are absent. In this respect, the histological lesions resemble those which are characteristic of osteomalacia in man.

INFLUENCE OF ULTRA-VIOLET LIGHT ON EXPERIMENTAL RICKETS.

As is well known, the most significant advance in our newer knowledge of rickets is an appreciation of the importance of *ultra-violet light or energy* in connection with its etiology and cure. Our recognition of the rôle of the light factor did not, however, result from studies of experimental rickets, but should be credited to observations in the clinic. Huldschinsky, who first showed the curative effect of the rays of the mercury-vapor lamp, demonstrated this remarkable action by radiographs of the epiphyses of rachitic infants. Following this discovery, however, experiments on animals were of distinct service in giving us a fuller understanding of the factors involved. For example, had it not been for experiments on rats, many years would have elapsed before we should have known which wave lengths of ultra-violet light are endowed with anti-rachitic properties. We shall not consider in detail the animal experiments dealing with light, reserving a consideration of this aspect for the chapter on Etiology. Although from the outset it was surmised that the radiations, whether from the sun or artificial source, which possess antirachitic value, lie in the ultra-violet or invisible part of the spectrum, the proof was furnished by means of animal experimentation. It was shown not only that this potency is a quality associated solely with ultra-violet radiations, but—by means of filters of known transmissibility—that the "antirachitic zone" is sharply circumscribed and limited. In the solar spectrum, it consists of a small band which has its lower limit at 290 millimicrons, and its upper limit at about 310 millimicrons. Various other experiments, for example, those conducted to ascertain the transmissibility of clothing material for the antirachitic radiations were carried out by means of animals. This subject will be discussed in the chapter on Etiology.

The problem of the marked susceptibility to rickets of the negro infant and of the rôle of the pigment of the skin also was studied and elucidated by means of animal experiments. It was shown that there is a marked difference between the intensity of ultra-violet radiations necessary to protect black and white rats against rickets. The intensity of irradiation could be so regulated that all

of the white but none of the black rats were protected by the rays from the mercury-vapor lamp (Table 2). There is no doubt that pigment plays a similar rôle in relation to the action of ultra-violet light on negro infants, and is the greatest factor in their exceptional susceptibility to rickets. It should be added, however, that if the radiations are sufficiently intense, little difference will be noted between the effect on white and pigmented skin.

TABLE 2.

	Weight, gm.	Ultra-violet ray.	Diet.[1]	Roentgen ray.	Path.	Inorg. P.
White	70–70	1 min.	84	Neg.	Neg.	
White	58–60	1 min.	84	Neg.	Neg.	
White	60–70	1 min.	84	Neg.	Neg.	
White	62–70	1½ min.	84	Neg.	Neg.	
White	60–80	1½ min.	84	Neg.	Neg.	5.45
White	64–70	1½ min.	84	Neg.	Neg.	4.44
Black	50–60	1 min.	84	R.	R.	
Black	50–60	1 min.	84	R.	R.	
Black	60–58	1 min.	84	R.	R.	
Black	50–50	1½ min.	84	R.	R.	2.92
Black	48–54	1½ min.	84	R.	R.	
Black	60–60	1½ min.	84	R.	R.	3.00

[1] Rachitic diet, containing about 86 mg. per cent of phosphorus.

Ultra-violet irradiation, for this purpose the mercury-vapor and carbon-arc lamps were used, was found to be of value not only in the rickets brought about by a diet deficient in phosphorus but likewise in the type which follows a diet low in calcium. This result was to have been anticipated in view of the fact that ultra-violet therapy has been found to be of value both in infantile rickets and in infantile tetany, which is associated with and characterized by a decrease of calcium in the blood serum.

TABLE 3.

Weight of rats (gm.).	Diet.	Rickets.	Blood P. (mg. per cent).
50–76	Dry milk, 5 per cent	Moderate	
40–64	Flour, 90 per cent	"	
56–56	Salt mixture, 5 per cent	"	1.44
60–80		"	
56–76	Dry milk	No	
40–64	*(Irrad.)*	"	4.92
60–88		"	
42–68	Dry milk	"	
40–61	*(Irrad.)*	"	5.12
30–52	*Stored three months*	"	
34–55		"	
34–40	Dry milk	Slight	
24–40	*(Irrad.)*	"	4.56
30–54	*Stored twelve months*	No	
40–50		"	

At first it was supposed that the effect of ultra-violet light was to elaborate vitamin A, or to "mobilize the reserves of the fat-soluble vitamins." It was soon shown by Sheets and Funk that these rays are associated merely with the antirachitic factor and that they do not produce vitamin A, nor protect against the xerophthalmia which follows a lack of this vitamin in the dietary.

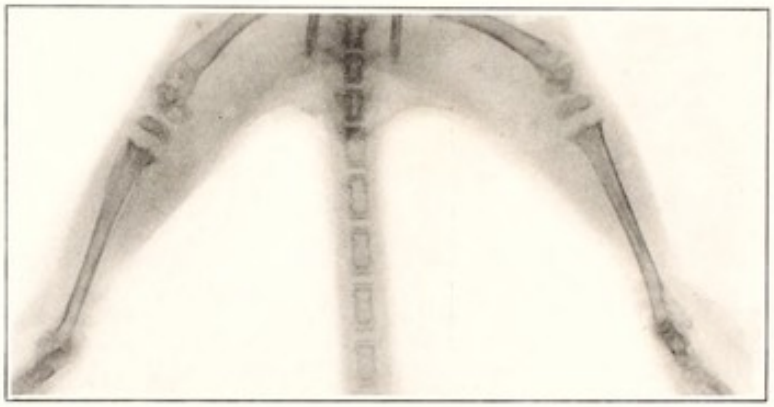


FIG. 3

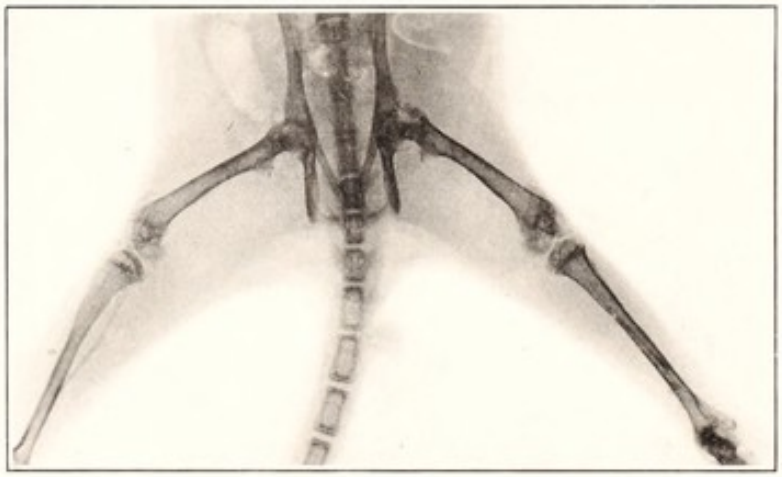


FIG. 4

FIGS. 3 and 4.—Antirachitic potency of *irradiated dried milk*. Fig. 3. Rickets induced by ration containing 5 per cent of dried milk. Fig. 4. Normal epiphyses of rat fed similar ration containing dried milk which had been irradiated.

Another and quite different aspect of the action of light was brought out by means of animal experiments. We have reference to *the specific activation of foods* which was demonstrated in 1924 by Hess and by Steenbock and their co-workers. As this subject will be considered more fully in the chapter on Treatment, it will not be taken up in detail in this place. It may be stated briefly that these investigations brought out the fact that vegetable oils, milk and other foods, which are ordinarily inert in relation to rickets, could be endowed with a high degree of antirachitic potency by means of exposure to the radiations of a mercury-vapor lamp

(Figs. 3 and 4). A further series of animal experiments showed that it is a sterol in these foods which is activated by these radiations. At first this was thought to be cholesterol, but more recently it has proved to be ergosterol, a closely related sterol. In all probability the marked antirachitic action of cod-liver oil is due to the same chemical substance which is formed as the result of irradiating ergosterol. The fact that Woodrow recently observed the characteristic absorption bands of ergosterol in a thin film of cod-liver oil bears out this point of view. Thus experiments on animals have served to coördinate two seemingly unrelated therapeutic experiences of the clinic—the action of ultra-violet irradiation and that of cod-liver oil, two specifics for rickets—and have shown that both depend on the same chemical factor, namely, activated ergosterol.

STRONTIUM RICKETS.

Mention should be made of an investigation which belongs entirely in the realm of experimental rickets. In 1908 Stoeltzner reported that feeding strontium to animals led to the development of a rachitic process characterized by an excessive production of osteoid. Since that time several similar investigations have been carried out confirming Stoeltzner's results. This experience, which naturally has no counterpart in clinical medicine, seems worthy of attention because at some future time it may be linked with the pathogenesis of infantile rickets. The most elaborate investigation of this subject was carried out by Lehnerdt on puppies and young rabbits. He made use of a diet which we now recognize to have been high in phosphorus, consisting of muscle and fat, to which was added strontium phosphate; he likewise reported the production of a marked excess of osteoid tissue in the bones. In addition to bringing about rickets in adult dogs, Lehnerdt induced the same pathological condition in the fetus *in utero* and in pups suckled by a bitch which had been given strontium. He termed this pathological condition "strontium sclerosis," a term which since has been applied to it. Many of the trabeculæ were surrounded by or composed entirely of osteoid tissue, others were calcium-free and the marrow cavity near the epiphyses was completely obliterated by these trabeculæ of osteoid. More recently Shipley and Park and their associates have conducted a study of the effect of strontium administration (2.2 per cent strontium carbonate) on the histological structure of the growing bone. In addition to corroborating the work of Lehnerdt, they observed that the abnormal histological structure could not be prevented by giving cod-liver oil. I may add that the animals cannot be protected by liberal amounts of irradiated ergosterol. In connection with this investigation it may be men-

tioned that many of the rats developed incomplete or total paralysis of the extremities, a condition which was partly controlled by cod-liver oil.

THE INFLUENCE OF ENDOCRINE GLANDS ON EXPERIMENTAL RICKETS

In considering the subject of experimental rickets some investigations on *the effect of removal of various endocrine glands* should be referred to, a subject which will be considered at greater length in connection with pathogenesis. The experiments of this kind have been many, but it is of little value to consider those undertaken without control of the diet. In 1923, Korenchevsky published an experimental study on the castration of young rats, and came to the conclusion that this operation brought about no essential changes in the bones, whether the animals were placed on a normal or on a rickets-producing diet. In the following year Hess and Jaffe published a short communication on "The effect of double adrenalectomy on the development of rickets in rats," a study which was undertaken in view of the importance which some investigators have attached to the secretion of the adrenal glands. No difference was found in regard to the development of rickets between rats in which the adrenals had been removed and control animals which had not been operated upon. Both groups were placed on a ration low in phosphorus, and both developed rickets of about the same degree. It was concluded that the functional activity of the adrenal glands is not an important or essential factor in the pathogenesis or cure of rickets.

Mellanby fed 5 to 30 grains of dried thyroid a day to puppies in order to ascertain whether this gland substance, by stimulating the rate of metabolism, would prevent the development of rickets. Notwithstanding a probable increase in metabolism, "no well-defined antirachitic effect" was evident.

THE RELATION OF RICKETS IN THE RAT TO HUMAN RICKETS.

We have subdivided experimental rickets into three periods, the first, the pre-Pommer period, embracing the years previous to 1885, when it was first recognized that an increase in osteoid tissue constitutes the essential pathological criterion of rickets; the second represented by the experiments of Mellanby, in which the diet was for the first time carefully controlled; and the third signalized by a recognition of the importance of phosphorus and by the employment of rations low in phosphorus in experiments on rats. Historically, experimental rickets may be regarded from a different point of view.

The earliest experiments were carried out in France during the first half of the past century; during the second half of the century investigations emanated from the various laboratories of Germany, whereas since 1918 their source has been mainly English or American. The reason why experiments on the rat were not undertaken in German laboratories was largely owing to the fact that leading German pathologists questioned whether the rickets induced in the rat was the counterpart of human rickets. It is, therefore, necessary to consider this question. The rachitic lesions brought about by the various rations which are low in phosphorus are characterized by an increased width in the zone of the proliferative cartilage and, a point of greater moment, by a marked overgrowth of the osteoid tissue investing the bony trabeculæ and the periosteal walls. Some histological differences between the rickets of rats and that of infants have been described, but it should be borne in mind that the pathological picture of rickets is one which is characterized by marked diversity and variability. The question of the unity of the disorder may be approached from the standpoint of response to therapy. These experiences may be summarized by the statement that it has been found that substances which exert an antirachitic action on the rat, exert a similar action on the infant. Cod-liver oil is a specific for both species and restores the mineral metabolism to the norm, whether there has been a deficiency of calcium or phosphorus. Furthermore, the same fractions of cod-liver oil have been found either inert or of specific potency both for infants and for rats. The same applies to the action of irradiated ergosterol and to various vegetable and animals foods activated by means of ultra-violet rays. Not only is this true, but the same wave lengths of radiations are found to be either specific or inert in animal and in infantile rickets. The question has been well summed up by Park in his recent monograph on the Etiology of Rickets; "The lesions in the skeleton, both gross and minute, are identical; the pathological conditions found to exist in the blood are identical; the rickets produced experimentally in animals may or may not be accompanied by the symptoms of tetany, exactly as rickets in the human being may or may not be accompanied by tetany; the same remedial measures are effective in both. Not the slightest doubt can exist that the rickets produced experimentally in animals and the rickets occurring in human beings is the same disease."

There is, however, one difference, which although by no means invalidating the identity of infantile and animal rickets, nevertheless clearly indicates that the metabolic processes brought about experimentally in the rat are not the counterpart of those associated with clinical rickets. Whereas rickets is induced regularly in the rat by a deficiency of phosphorus in the ration, a lack of phosphorus in the diet is rarely the cause of rickets in the infant. Cow's milk—

which forms the chief diet of infants—is exceptionally rich in its phosphorus content, containing three to four times as much of this element as human milk. Thus the dietaries of the laboratory are very unlike those of the clinic. This is true especially of the rat, in which it is not possible to induce rickets by a ration containing large amounts of milk; when we substitute more than 10 to 15 per cent of dry milk for the flour in the Sherman-Pappenheimer ration, it is found that rickets generally does not develop.

The same criticism is pertinent in regard to the induction of rickets in dogs. The diets which Mellanby used contained from 175 to 350 cc. of skimmed milk. When he substituted full milk and gave each animal 0.5 liter a day, rickets did not ensue. Contrast this result with what is known to be true of infantile rickets. It has been the experience of all pediatrists that the greater the amount of milk which is fed to an infant, the greater the likelihood of its developing rickets.

Although the pathological lesions of infantile and experimental rickets are essentially the same, it is evident that, from a metabolic standpoint, they are brought about in dissimilar ways. The difference may lie in processes which take place in the gastro-intestinal tract or in the intermediary metabolism of the infant and the rat. Whatever future investigation of this question may bring to light, it should not be forgotten that, under existing conditions, the metabolic processes associated with the development of rickets are totally different in the laboratory animal, fed a restricted ration, and in the infant fed an unlimited quantity of cow's milk.

EXPERIMENTAL RICKETS IN VARIOUS ANIMALS.

In treating of experimental rickets we have thus far considered its production in the dog and in the rat. *Rickets has been induced in other animals.* For example, the work of Elliot in 1922 and that of Zilva from 1921–1924 and their associates show definitely that typical rachitic lesions can be brought about in young pigs by dietary restriction. It has recently been demonstrated that rickets can likewise be produced in rabbits. Such experiments gain added interest in view of the fact that we are dealing with an herbivorous animal. Goldblatt and Moritz, in their investigation, used rabbits, aged four to six weeks, weighing 250 to 500 gm. They found it necessary to supply the animal with roughage in order to prevent diarrhea and gave them alfalfa for this purpose. Much of the food had to be given by means of a stomach tube. The lesions which were produced were characteristic of rickets histologically and were associated during life with a lowered content of inorganic phosphate in the blood. Furthermore, cod-liver oil added to the diet prevented the development of rickets. Another study of rickets in rabbits

was published in 1925 by Kawamura and Kasama. In this investigation the rickets was brought about not by means of a deficient dietary, but by feeding an animal parasite. They found that the young of rabbits afflicted with Schistosomum japonicum developed typical rickets, and that rickets can also be produced if we infect the young healthy rabbit with this parasite. Furthermore, the toxin of Schistosoma disturbs the calcium and phosphorus metabolism of the bone, especially during the period of vigorous growth.

There is no doubt that rickets can be brought about in monkeys. The recent report of Christeller on "Rickets in Apes" shows definitely that characteristic lesions of rickets and osteomalacia occur spontaneously in these animals. Many of the descriptions of rickets, including those of v. Hansemann, Christeller believes to have been fibrous ostitis or Paget's disease rather than rickets. It is impossible to interpret the nature of the pathological changes in the monkeys, lions and other animals which were described by Bland-Sutton almost fifty years ago, as histological details are lacking. It may be mentioned that Westenhoefer necropsied two lions, one one and a half and the other two and a half years old, which were supposed to have had rickets, but failed to find lesions of this disorder.

Although there are numerous reports of rickets-like disorders occurring in horses, cows, goats and sheep, no histological examinations have been made which clearly show whether these nutritional disturbances were true rickets. Most of these publications are illustrated by photographs of the animals and show merely marked deformity or abnormal posture.[1]

Whether typical rickets can be induced in chickens has been questioned. Numerous accounts have been published of rickets in young chickens, but only a few have been supported by histological evidence. A recent study by Pappenheimer and Dunn of "leg weakness" in chicks showed both atypical radiographical changes of the epiphyses and the histological changes of osteoporosis rather than of rickets. Nonidez has just published a paper in which he seems to have shown that in order to induce typical rachitic lesions the chickens should be reared in a normal environment for a period of four to five weeks before placing them on the experimental ration. If this method is followed, a lack of the antirachitic factor "leads to a disorder with all the essential characteristics of mammalian rickets." The advantage of using chickens as the experimental animal is that, like infants, they develop rickets in spite of receiving a diet adequate in phosphorus and calcium.

Several attempts have been made to bring about rickets in kittens, but they all have been futile. Tripier first carried out experiments of this kind in 1874. From an etiological standpoint, it would be of

[1] Hottinger told me that he found typical rachitic lesions in cattle which had died from a lack of phosphorus in the pasture lands of South Africa.

interest to ascertain the cause of the marked resistance of the cat to rickets.

In closing, it should be mentioned that although the induction of rickets in animals is almost invariable and can be relied upon, exceptions still occur from time to time, which cannot be adequately explained. For example, occasionally some rats from a litter will develop marked rickets, whereas others develop it to a mild degree, although all have been placed on an identical ration and have increased in weight to the same degree in the course of the test. Such biological inconsistencies are not confined to experimental rickets but hold true for the experimental production of other nutritional disorders, for example beriberi in pigeons and scurvy in guinea-pigs. They do not invalidate the conclusions drawn from experimental studies, but merely indicate that, in regard to rickets, there are still etiological factors of which we are not cognizant.

CHAPTER IV.

THE ETIOLOGY OF RICKETS.

THERE has been widespread interest in the etiology and pathogenesis of rickets on the part of the clinician and the pathologist ever since Glisson and his colleagues published their classic report in 1650. The interest has been spasmodic rather than sustained, as the theories were confusing in their multiplicity and, a point of greater significance, few of them were subject to verification. Their basis was almost entirely either hypothesis or general impression gained by clinicians in the course of their practice, so that the ingenious arguments upholding them were soon relegated to the pages of medical history. This situation has entirely changed during the past ten years, the period which we have termed that of The Newer Rickets. Largely owing to the fact that we now have at our service the experimental method, interest has once more become acute and activity intense, and our advance in knowledge has been greater during this decade than throughout the two hundred and fifty years preceding. This is true of etiology, whether considered from the broader standpoint, or from the narrower point of view of the individual dietetic or hygienic factors which play a rôle in its causation. It must be admitted that the lacunæ in this field of investigation are still numerous, but progress has been remarkably rapid, and the path seems open to further advance.

PREDISPOSING FACTORS IN ETIOLOGY OF RICKETS.

Heredity.—One of the oldest of these theories is that of heredity. During the past few years attention has been centered on the nutrition and environment of the infant rather than on that of the fetus. There have been some exceptions, notably the experimental investigations of Korenchevsky. The most ardent exponent of the rôle of heredity has been Siegert, who about twenty-five years ago made a careful study of numerous families, of parents as well as of children, in which rickets was notably present or absent. As the result of a thorough clinical examination of two generations, he came to the conclusion that heredity was "probably the most important etiological factor in relation to this disorder." This conception must presuppose a specific alteration in the germ plasm. Studies of this kind, in spite of their sincerity, can have little value at the present day if

only for the reason that the influence of sunlight was not suspected and therefore was entirely uncontrolled.

All clinical experience seems to be opposed to the dominant influence of heredity in rickets, if by this term we are to understand what Siegert did, namely, that the occurrence of rickets in a woman during infancy—quite irrespective of the diet or hygiene throughout later life, including the period of pregnancy—leads to the development of rickets in her offspring. In this connection, conditions prevailing among the negroes of the West Indies may be cited. As is well-known, rickets is of exceptional occurrence and of mild degree among these people—a fact which I was able to confirm by personal observation a few years ago. On the other hand, the testimony is practically unanimous that among the infants of the West Indian negroes, who immigrate to the northern part of the United States, rickets is unusually prevalent and severe. In the study which was carried out by Unger and myself among the negroes in New York City (a large proportion of whom came from the islands of the West Indies) rickets was found to be almost universal, even among the infants of the recent immigrant. Here is an instance where, had heredity played a dominating rôle, we should have expected to encounter a community singularly free from rickets. The same holds true in regard to the Italians. In southern Italy and Sicily, although rickets exists, it is mild and infrequent. On the other hand, it prevails to an exceptional degree among the offspring of these people in New York City and other large centers in the northern area of the United States. This is true even of the breast-fed infant, as pointed out many years ago by Snow of Buffalo, and has been corroborated by all who have considered the subject. It would seem, indeed, as if heredity exerts an influence in the opposite direction; that instead of rickets in the mother tending to induce the disorder in the offspring, just the reverse is the case, and that races which have not been subject to rickets are particularly susceptible when they migrate to a country in which rickets is prevalent. In the United States the negroes, Italians, Greeks and Syrians are most predisposed to rickets—all of whom, as mentioned in considering the geographical distribution of the disorder, rarely develop it in their native lands.[1]

In regard to the negro, there can be no doubt that the pigment of his skin markedly increases his susceptibility, owing to the fact that it filters out the specific ultra-violet radiations. Nevertheless, for a

[1] During the summer of 1927 I had the opportunity of examining many infants of American Indians living in the pueblos of New Mexico in the neighborhood of Santa Fé. In spite of the wealth of sunshine which this region enjoys, it was not uncommon to find rickets even of moderate intensity, as evidenced by craniotabes, beading of the ribs and bowed-legs. These infants are swaddled and strapped to boards during the first month of life. In this posture they are carried on the backs of their mothers and occasionally taken out-of-doors.

long time I have felt that in addition to this well-recognized factor, the negro may possess an inherent racial tendency to rickets—a tendency shared perhaps by other races. Some years ago a radiological study of the evolution of the carpal centers in white and negro new-born infants showed that these centers were developed

TABLE 4.—CARPAL CENTERS IN FULL-TERM NEW-BORN INFANTS.

Negro Infants.

Total				131
Male			69	
Female			62	
	Number of centers.			
	1.	2.	3.	
With centers				37
Male	6	6	0	12
Female	9	15	1	25
Without centers				94
Male			57	
Female			37	

White Infants.

Total				212
Male			119	
Female			93	
	Number of centers.			
	1.	2.	3.	
With centers				33
Male	6	6	0	12
Female	6	15	0	21
Without centers				179
Male			107	
Female			72	

TABLE 5.—CARPAL CENTERS IN PREMATURE AND SMALL INFANTS (LESS THAN 48 CM. OR 2.75 KG.).

Negro Infants.

Total		34
Male	15	
Female	19	
With centers		7
Male	5	
Female	2	
Without centers		27
Male	10	
Female	17	

White Infants.

Total		38
Male	11	
Female	27	
With centers		4
Male	0	
Female	4	
Without centers		34
Male	11	
Female	23	

far earlier in the negro babies. It was suggested that this precocious maturity of the negro might bear a relationship to his exceptional predisposition to rickets, especially in view of the well-known interrelationship of growth and rickets. It is in a generic sense such as this that heredity may play a rôle in races and in individuals, but the effect is subordinate and not dominant.

Age.—Age is one of the most important factors in the etiology of rickets—even as it is in infantile scurvy. In rickets this is due to the fact that the infant is less exposed to sunlight than the runabout child. The decreased incidence in scurvy comes about when the dietary of milk is enlarged to include vegetables and various fruits. Boerhaave appreciated the significance of age and in one of his celebrated aphorisms states: "Never congenital, rickets rarely occurs before the ninth month, scarcely ever after the second year." The latter part of this dictum is correct in principle as may be judged by the accompanying tables. In the first of these the significant feature is that the bones of almost 40 per cent of the infants under three months of age presented no microscopic evidence of rickets, and that this held true for 30 per cent of the children between three and four years of age. In the

TABLE 6.—DISTRIBUTION OF RICKETS ACCORDING TO AGE. BASED ON 386 NECROPSIES IN DRESDEN OF CHILDREN TWO MONTHS TO FOUR YEARS OF AGE. (SCHMORL).

No. of children.	Age (months).	Rachitic.		Non-rachitic.	
		Total.	Per cent.	Total.	Per cent.
33	2–3	20	60.6	13	39.4
34	4–6	33	97.0	1	3.0
53	7–9	50	94.0	3	6.0
75	10–12	73	97.3	2	2.7
59	13–18	58	98.3	1	1.7
33	19–24	30	90.9	3	9.1
65	25–36	57	87.7	8	12.3
34	37–48	24	70.6	10	29.4

TABLE 7.—DISTRIBUTION OF THE VARIOUS STAGES OF RICKETS ACCORDING TO AGE. (SCHMORL).

Age (months).	Beginning.		Florid.		Healing.		Healed.		Total No.
	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	
2	4	100.0	..	....	..	....	..	....	4
3	12	75.0	4	25.0	..	....	..	....	16
4–6	19	57.6	7	21.2	7	21.2	..	....	33
7–9	17	34.0	23	46.0	10	20.0	..	....	50
10–12	7	9.5	45	61.7	20	27.4	1	1.4	73
13–18	4	6.9	32	55.2	15	25.8	7	12.1	58
19–24	2	6.6	10	33.4	11	36.6	7	23.4	30
25–36	..	....	13	22.9	14	24.5	30	52.6	57
37–48	..	....	2	8.3	3	12.5	19	79.2	24

second table, which groups rickets into four categories—beginning, florid, healing and healed—it is noteworthy that beginning rickets was not met with in children over two years of age, and that healing was noted in a number of instances even before the sixth month of life. This summary furnishes a chronological picture of rickets from the pathological point of view, indicating that it is a disorder which begins at about the third month and ends at about the eighteenth month. There is no doubt that from a metabolic standpoint—the basic criterion of disorders of this character—rickets frequently begins during the first months of life. Indeed the recent investigations of Hottinger, which will be discussed at greater length in the chapter on Symptomatology, would lead to the conclusion that judged even by its microscopic pathology rickets is often demonstrable during the first few months of life. We have reason to believe that the newly-born infant brings with it into the world but little of the protective antirachitic factor, and that the disturbance in metabolism designated as rickets probably starts during the first weeks of life, its intensity and progress varying in the individual according to the interaction of a large number of determining factors.

In regard to the limitation of the age period of active rickets my clinical experience coincides with the necropsy report of Schmorl. Some years ago I carried out routine roentgenographical examinations, during the winter months, of a large number of institutional children between the ages of three and five years. No instance of rickets was discovered in the course of this survey. It is quite possible, however, that where hygienic and dietetic conditions are less favorable, the results may be different.

Sex.—Sex is not an established predisposing factor in rickets. There are no convincing statistics on this aspect and personally I have been unable to convince myself of a definite susceptibility of either sex. This is all the more notable in view of the striking relationship between sex and the development of late rickets, tetany and osteomalacia. According to Fromme the incidence of late rickets in males as compared to females is as 15 to 1. As will be emphasized in a subsequent chapter, tetany in infants as well as in adults, occurs far more often in males than in females. That there should be an etiological difference between infantile rickets and tetany is the more remarkable when we bear in mind that infantile tetany develops almost always on the basis of previous rickets. The subject is further complicated by the fact that osteomalacia, commonly regarded merely as the manifestation of rickets in the adult, is of such exceptional occurrence in males that single instances have been considered worth reporting. But it should be remembered that osteomalacia generally is brought about by the complicating circumstance of pregnancy. Most cases of osteomalacia have been

found associated with a disturbance of calcium rather than of phosphorus—a diminution of calcium in the blood.

It may be added that susceptibility to a deficiency of vitamin A, the other fat-soluble vitamin, has a definite sex linkage. Men develop night-blindness much more often than women. During the post-war period, Birnacher found this pathological condition in 105 men and only 2 women, and furthermore noted a definite and marked susceptibility during the years from fifteen to twenty-five, the period of maturation. Xerophthalmia likewise is more prevalent among males, especially in children under ten years of age.

All in all it would seem that sex may play a rôle in rickets, but that the endocrine factor manifests itself more particularly by disturbances of the calcium metabolism.

Pigmentation of the Skin.—A definite predisposing factor is the degree of pigmentation of the skin. As mentioned in the chapter on Experimental Rickets, this phenomenon was demonstrated some years ago by a simple test: Two groups of rats, one composed of white and the other of black animals (the melanotic form of the Norway rat) were fed on a standard rickets-producing ration, and were subjected to the minimal protective dose of ultra-violet light—exposures of one and a half minutes at a distance of 3 feet. It was found that although the rate of growth was about the same, the black rats developed rickets, whereas the white rats showed no rachitic lesions (Table 2).

This experiment has a direct application to the well-recognized susceptibility of negro infants to rickets. Some years ago in the course of a study of the prophylactic value of cod-liver oil on the infants of a negro district of New York, it was found that the majority of the breast-fed infants and almost all of the bottle-fed showed clinical signs of rickets. These babies received bottled milk from the same source as thousands of other infants in this city. The main distinction is—as demonstrated by the animal experiment—that negro infants require a greater intensity of the effective light rays than do white infants. This clinical observation does not imply that the increased susceptibility was the result solely of the greater degree of pigmentation of the skin, but rather that pigmentation is an important factor in determining the protective value of ultra-violet light. It has never been established whether, if white infants were deprived entirely of sunlight they would develop rickets to the same degree as negro infants placed under similar conditions. My personal opinion, as stated above, is that the negro, as well as some other southern races, evince a racial susceptibility to rickets when they migrate and live in a northern climate.

Growth.—Growth is still another factor which exerts its influence on the development of rickets. In my institutional experience those babies are most likely to develop rickets which are admitted

in a poorly nourished condition and which, subsequently, thrive and gain rapidly in weight. Almost 75 per cent of the cases belonged to this category, whereas about 25 per cent developed rickets while making subnormal gains. This observation can also readily be demonstrated by means of animal experiments. For example, if we give two sets of animals different types of rickets-producing rations, the ordinary standard diet and one which has been amplified so as to bring about greater growth, it will be found that the latter group cannot be protected by the minimal protective intensity of ultra-violet irradiation. Translating an observation of this kind into terms of clinical medicine, it signifies that the atrophic or marasmic infant—notably insusceptible to rickets—has a far less requirement of the specific light rays than the normal, rapidly-growing infant. This phenomenon is well illustrated by the relation of the cretin to rickets. It is a well-known fact that cretins grow slowly and rarely develop rickets. However, when they are given thyroid preparations, they not only increase rapidly in length but, unless protected by specific therapy, will most certainly develop rickets. This tendency was pointed out many years ago by the late Professor Thomson of Edinburgh, and carries with it a clinical precept. Whether the thyroid hormone has an effect on the epiphyses apart from its growth-promoting influence is a point worth bearing in mind.

In connection with a discussion of growth, the relation of rickets to *overfeeding* should be mentioned. This is an aspect which was first referred to by Glisson and emphasized more recently by Czerny and by Jundell. It should not be regarded simply as a corollary to growth, for in many instances it relates to infants who gain in weight disproportionately to length. Overfeeding leads to what may be classed as a definite clinical type of rickets—the overweight, well-nourished, bow-legged baby. Indeed, rickets is one of the greatest dangers associated with overfeeding. How rickets is brought about by this error of diet is not known, but it is clear that it cannot be due to any deficiency. From the point of view of pathogenesis, therefore, this subject is of special interest.

Congenital Factor.—The congenital factor has to be considered in relation to etiology quite apart from heredity. It is possible that, due to nutritional errors of the mother during pregnancy, the infant might be born with rickets or with a tendency to develop this disorder. Kassowitz, one of the keenest students of rickets, believed most cases to be congenital in origin, basing this opinion on the pathological changes in the bones. It is hardly necessary to analyze Kassowitz's evidence, as his histological criteria have been proved to be unsound. Schmorl's pathological investigations, to which frequent reference will be made, as they represent consecutive examinations made by one of the most experienced specialists in

bone pathology, must be weighed in this connection. In the course of a routine examination of over 100 full term and prematurely-born infants he failed to find histological lesions of rickets in a single instance. Pommer previously had come to a similar conclusion. Wieland observed that skull bones which show craniotabes at birth do not present the histological evidences, more especially increase of osteoid, which are regarded as characteristic of rickets. These reports must be considered of importance in judging of the congenital origin of rickets, but only insofar as the lesions are developed. It must be admitted that diagnostic criteria are not fixed and immutable, but change with new conceptions of disease—a principle which holds true for pathological as well as for clinical and chemical criteria. Were our conception of the pathology of rickets to broaden so as to include certain forms of osteoporosis, it would be necessary to reconsider the evidence from this new point of view.

The Roentgen ray, which has been so helpful in furthering our knowledge of rickets, has failed to disclose definite instances of congenital rickets. In the course of a roentgenological study of the epiphyses of 250 newly-born infants, carried out by Hess and Weinstock, none was found presenting a frank and unequivocal picture of rickets, although the ends of the ulnæ were suggestive in a few instances. However, as will be discussed elsewhere, a roentgenological diagnosis of rickets can be made only when the disorder is moderately advanced. Some years ago Ylppö carried out a roentgenological investigation of the bones and epiphyseal centers of newly-born premature infants, and studied their association with rickets. He believed that evidence of rickets was present in 5 of the 88 infants thus examined, that these lesions had developed during intra-uterine life, and that rickets is of fetal rather than of postfetal origin. Although well carried out, the study lacks the all important confirmation of histological examinations. It has been my experience, in the course of an examination of the epiphyses of a large number of newly-born infants, that peculiar and unexplained epiphyseal margins are evident occasionally—epiphyses which instead of being sharp are slightly frayed, with a tendency to cupping, such as might be termed incipient rickets in later months.

Nor have chemical analyses of the blood of the newly-born pointed to the occurrence of congenital rickets. No relationship was found by Hess and Matzner between the content of calcium or of inorganic phosphorus in the blood of the newly-born and the subsequent development of rickets. Some infants with a low percentage of inorganic phosphorus at birth failed to develop rickets in the course of the winter, whereas others with a high content of inorganic phosphorus were found to develop rickets during the first year of

life. It may be added that clinical signs are of very little value in judging rickets at this early stage.[1]

It is, indeed, remarkable that fully-developed rickets is not found frequently in the newly-born infant. When we reflect that two of the conditions that greatly favor its development are darkness and rapidity of growth, and that both of these conditions are present throughout intra-uterine life in extreme degree, it is surprising that rickets does not develop *in utero*—the period of most rapid growth, taking place in an environment absolutely devoid of light. That normal growth and metabolism can take place under such apparently adverse conditions may indicate the superior efficiency of placental nutrition to that carried out by way of the alimentary tract, or, on the other hand, that the bones are relatively insusceptible to rachitic changes during the period of fetal development.

It would be interesting to ascertain how often women suffering from osteomalacia give birth to infants with congenital rickets. Unfortunately, there are no data on which to base an opinion on this question. Fully developed osteomalacia occurs so rarely in Europe and America that it is difficult to obtain reliable information regarding mother and child in cases of this kind. A perusal of the literature as well as personal communications with physicians in the Far East have also been unsatisfactory in this regard. A consideration of the excellent reports on osteomalacia from Peking, which will be reviewed in detail in a subsequent chapter, seems to warrant the conclusion that were rickets frequent and severe in the districts where this disorder is prevalent, it would most certainly have been noted. It is quite possible that osteomalacia in the mother does not lead to rickets in the offspring. Quite apart from the fact that during fetal life there may be little tendency to develop rickets, it is well known that the effects of nutritional deprivation during pregnancy are visited on the mother rather than on the fetus. There are still a few centers where osteomalacia is endemic—notably certain districts in China, Japan, India and Persia—so that a study of this interesting question, especially a histological investigation, may still be forthcoming.[2]

The weightiest argument in favor of *a congenital factor* in etiology

[1] Beading of the ribs is not uncommon in the newly-born and therefore should not be accorded the significance which it possesses in later infancy. Bowing of the legs is also present frequently and, as stated elsewhere, softness of the skull at birth is not to be regarded as rachitic.

[2] The paper of Maxwell and Miles on "Osteomalacia in China" reproduces roentgenographs of the ends of the ulnæ of two fetuses born of osteomalacic mothers. Both show cupping similar to that which I have noted in a few instances in newly-born infants. The illustration of the microscopic appearance of the ulna of one of these infants is, as far as I know, the only one in the literature, and is therefore of especial interest. It is not, however, convincing in regard to the existence of congenital rickets.

is the well-established fact that rickets occurs with exceptional frequency and in exaggerated degree in premature infants. To such an extent is this true that cod-liver oil usually fails to protect such infants even when administered in the first weeks of life; although, it may be added, ultra-violet irradiation generally confers protection. It is impossible to give the percentage of prematurely born infants which develop rickets. Rosenstern's figures of 76 per cent do not seem to me an exaggeration. The disorder is somewhat atypical and characteristic, in that there is a peculiar tendency to enlargement of the head, associated with craniotabes and the development of frontal and parietal bosses. The proneness of twins to rickets, a susceptibility which, although definite, is far less marked, is another clinical phenomenon pointing in the same direction. Such instances of predisposition constitute an incontrovertible argument in favor of the occurrence of congenital rickets, if we include within this term a congenital tendency to rickets. If this holds true of infants born prematurely, it is quite probable that infants born at term suffer in some degree from the same tendency.

Some of the investigations on rickets in animals have been supposed to indicate the dominating importance of the congenital factor in rickets, notably those which Korenchevsky carried out for a number of years. I believe the results may be summarized fairly by the statement that it was found that when the diet of the animals contained an insufficiency of the fat-soluble factor and calcium throughout pregnancy, rachitic changes seemed to develop more readily in the offspring. Such results were not constant, however, and showed a tendency of the young to develop bone lesions similar to rickets rather than a frank development of the disorder. On the other hand, protection could not be brought about by enriching the diet and by giving cod-liver oil to the mother during pregnancy; the severity of the rachitic disorder merely was decreased by this means. Byfield and Daniels came to the conclusion that the effects of the rickets-producing ration do not become manifest until the second generation. In 1924 Miss Weinstock and I carried out an investigation on rats in regard to "Rickets as Influenced by the Diet of the Mother during Pregnancy and Lactation," and came to the conclusion that "rickets cannot be prevented by improving the diet of the mother (*a*) previous to pregnancy, (*b*) during pregnancy, and (*c*) throughout lactation, although it can be mitigated to a certain degree. Supplementing the diet of the mother for two generations also failed to render the young refractory."

A question such as this cannot be answered by experiments on animals, but must be decided by clinical observation on infants. At the same time we conducted a clinical test of the question by giving a series of women cod-liver oil during the last two months of pregnancy in order to ascertain whether the development of

rickets in the babies could be prevented in the course of the winter. The accompanying table shows that even under these favorable prenatal conditions rickets could not be warded off.

TABLE 8.—SUBSEQUENT DEVELOPMENT OF RICKETS IN INFANTS WHOSE MOTHERS HAD BEEN GIVEN COD-LIVER OIL DURING PREGNANCY.

Case.	Race.	Birthplace of mother.	Amount of cod-liver oil, ounces.	Age of infant, mos.	Nursed, mos.	Rickets.	
						Clinical.	Roentgen ray.
B. E.	Negro	British West Indies	16	6	3	R.	Slight.
R. D.	White	Greece	16	9	3	R.	Healed?
A. R.	White	United States	16	8½	8½	R.	No.
S. C.	White	Italy	16	10	10	R	Moderate.
A. F.	White	.....	16	7	3	R.	?
J. C.	White	.....	16	6	6	R.	No.
L. N.	Negro	British West Indies	16	8	8	R.	Moderate.
R. H.	White	.....	16	9	0	R.	Slight.
L. H.	White	.....	16	7	3	R.	No.
R. L.	Negro	United States	16	9	3	R.	Marked.
A. R.	Negro	United States	16	7	7	R.	Moderate.
B. C.	Negro	United States	16	5	3	R.	No.
C. B.	White	United States	16	9½	8	R.	No.
L. J.	White	United States	32	7	2	R.	No.
F. B.	White	.....	32	8	0	R.	Moderate.

Clinical experience furnishes strong evidence against the premise of Siegert and of Korenchevsky that the etiology of rickets is essentially prenatal. In the first place, rickets is far more common and severe among bottle-fed than among breast-fed babies; this is true throughout the world and among all races. Furthermore, pathologists and clinicians have demonstrated time and again that rickets has a seasonal incidence, with its peak in the winter and early spring and its ebb during the summer months. Both of these manifestations, the one dependent on diet, the other on climate, must be ascribed to postnatal factors. Neither can be considered as of secondary importance. The seasonal factor dominates the etiological picture to such an extent as to render active rickets practically non-existent during the summer months.

Reviewing the clinical and experimental evidence, I am of the opinion that congenital rickets is not of frequent occurrence, and is a minor factor in the incidence of this disorder. Probably it does occur occasionally. The fact that Schmorl encountered histological changes in rickets in an infant aged six weeks, and more recently that Dunham discovered an instance of well-advanced rickets in a prematurely-born infant aged only one month "makes me hesitate," as Park states, "to think that rickets cannot begin in intra-uterine life."

When we proceed a step further and consider the question of a constitutional tendency toward the development of rickets, rather than the actual development of rachitic lesions, it would seem that a congenital factor is at work—that babies do not enter the world with an equal susceptibility to this disorder. Recently I treated a pair of dissimilar twins, brought up in the same environment and nursed by the same mother, one of whom developed definite rickets with large head, beading of the ribs and bowed-legs, whereas the other showed no signs of rickets whatsoever. Probably there is a variability in susceptibility to be ascribed partly to hereditary circumstance, as is true of other metabolic disturbances, for example diabetes, and partly to intra-uterine factors. Nevertheless, in my opinion rickets must be regarded essentially as a disorder of postnatal life.

DIET IN THE ETIOLOGY OF RICKETS.

Milk.—In considering the etiology of rickets from the standpoint of diet, one must always bear in mind that milk is the universal food of infants—whatever may be the differences in preparation. The basic diet of every infant is either human milk or the milk of some animal. It is therefore of prime importance to have as complete an understanding as possible, based on investigation in the laboratory as well as in the clinic, of the relationship of woman's milk and of cow's milk, as well as of their constituents, to the development of rickets. Strangely enough studies of this kind are few in number, fewer, for example, than those concerned with the relationship of cereals and vegetables.

It should likewise be borne in mind that there is an essential difference between the reaction of the infant and the rat—the experimental test animal for rickets—in regard to calcium and phosphorus. Either or both of these constituents may be added *ad libitum* to the diet of the infant and still fail to prevent rickets, whereas if supplied in proper ratio in the dietary of rats, rickets will be prevented regularly. We do not know the phosphorus requirement of the infant. The very fact, however, that woman's milk contains only about one-fourth as much phosphorus as cow's milk, and that rickets is of far less frequent occurrence among nursing than among bottle-fed babies, indicates that phosphorus intake does not play the deciding rôle; even the extreme dilution of cow's milk by one-half does not reduce its phosphorus content to the level of woman's milk.

Although there is no unanimity of opinion as to which foods should be regarded as rachitogenic and, more particularly, as to what degree any of them tends to further rickets, all are in accord that woman's milk stands preëminent in the prevention of this

disorder. The incidence of rickets among nursing infants is universally less than among those brought up on cow's milk. On the other hand, woman's milk is far from being a specific. Some years ago (1922) in a study of this question in New York City, we showed that whereas approximately all bottle-fed infants developed rickets to some degree by the month of March, unless they had received specific therapy, one-third, and in the course of the subsequent winter, one-half of the breast-fed infants showed definite signs at the seasonal peak. These infants were well nourished and nursed by mothers who were getting a generous and varied dietary. These studies were carried out during the winter of 1920–1921 and 1921–1922. During the investigation of the "prophylactic therapy for rickets in a negro community," Unger and I reported in 1917 that almost all the negro infants developed rickets despite the fact that they were nursed. One of the most marked cases of rickets which has developed in my institution occurred in 1921 in an infant nursed by its mother; this woman lived on the premises and received an ample diet, including vegetables and over a quart of milk daily. The baby of another wet-nurse developed the type of rickets which is accompanied by fractures. At five months he showed signs of slight rickets and fractures of the radius and ulna, which were observed fortuitously in the course of routine radiographic examination. All these lesions responded rapidly to ultra-violet ray therapy. The mother of this baby had been receiving exceptionally large amounts of milk and vegetables.

There has been a tendency to exaggerate the protective value of woman's milk, probably on account of its undoubted superiority over cow's milk, and the fact that it furnishes practically complete protection against infantile scurvy. This tendency has been harmful, as it has led physicians to believe that it is quite unnecessary to prescribe cod-liver oil or other specific agents for nursing infants, whereas, under present conditions, all infants require protective therapy of some kind. It is by no means improbable that woman's milk may be fortified in this respect by the administration of an antirachitic to the mother, so that it will be unnecessary to supplement the diet of the infant. It is well to remember that during Glisson's time, the seventeenth century, all babies were nurtured at the breast, and that the employment of cow's milk for infant feeding was as yet unknown and that nevertheless rickets was widespread.

Recently (1927), in conjunction with Miss Weinstock, I carried out an investigation in the laboratory to ascertain whether the superiority of woman's milk was due to its greater *content of the antirachitic factor*. Much to our surprise we found that woman's milk contains very little of this specific factor, so that a rat of the usual age and weight could not be protected from rickets by a daily supplement

of 20 cc. of this milk. There can be no question as to the applicability of this result to the clinic, for the so-called antirachitic vitamin exerts a protective action on rats quite as effectively as on infants; in fact, the rat is the standard test animal for assaying the potency of antirachitic substances, such as cod-liver oil and irradiated foods and ergosterol. It is of interest to note that a few years ago Lesné and Vagliano found that the lipoid extract of woman's milk given to the amount of 5 per cent of the ration failed to protect rats from rickets, and that Outhouse, Macy and Brekke have found that even as much as 40 cc. of human milk contained an unappreciable amount of the antirachitic factor. Evidently the high protective value of human milk in infantile rickets cannot be ascribed to its content of the antirachitic factor. A more precise statement cannot be made at the present time, for we have no knowledge whatsoever as to the constituents which are responsible for its antirachitic potency. We can, if we care to do so, bolster up our lack of definite understanding with the attractive but highly speculative hypothesis that the favorable action is the result of the peculiar equilibrium of the various ions contained in woman's milk, a state which markedly furthers the absorption and retention of calcium and phosphorus.

Woman's milk can, however, be endowed adequately with the antirachitic factor by irradiating the nursing mother with ultra-violet light. Hess, Weinstock and Sherman (1927) showed that following irradiation of this nature, the milk had developed marked antirachitic potency, and furthermore that this property was due to an augmentation of the non-saponifiable fraction of the milk. In a clinical test Gerstenberger and his co-workers recently have reported that "human milk obtained from mothers who were exposed to artificially produced actinic rays gave evidence of possessing definite antirachitic properties in 2 cases of active non-healing rickets at the twentieth and thirty-second days of feeding." He could not bring about a similar enhancement of human milk by giving to nursing mothers 1 tablespoonful of cod-liver oil daily in addition to a satisfactory diet; in 3 cases of active rickets evidences of healing were not noted after an observational period of about two months. It is probable, however, that activated ergosterol would be effective when given in this way.

It is possible that milk may be rendered antirachitic by improving the ration or the hygienic condition of the cow, but as yet little has been accomplished by this means. It makes but little difference in the antirachitic titer of the milk whether cows are exposed to the sun or are confined indoors, but it has been shown that irradiation with powerful ultra-violet rays from artificial sources leads to the elaboration of the antirachitic factor and its excretion into the milk. Hart, Steenbock and their colleagues (1926), who conducted an experiment of this kind in June, concluded that "apparently summer

sunlight in comparison with the radiations of a quartz mercury-vapor lamp is feeble in its antirachitic properties when considered in relation to liberally milking animals."

Some years ago (1921) Unger and I carried out some clinical studies in an endeavor to interpret the nature of the peculiar seasonal incidence of rickets. With this in mind we placed under observation two groups of infants. To one we gave dry milk prepared during the previous summer from the milk of cows which had been out at pasture, and to the other we gave dry milk which had been obtained from stall-fed cows. The object was to discover whether a definite difference in the incidence of rickets could be noted between these two groups. No distinction was discernible. The ratio of rickets was the same among those fed what may be termed "pasture milk" and those which obtained the winter or "stall-fed milk." The logical deduction from this experience is that the milk of cows supplied with green fodder does not acquire antirachitic properties, and that rickets develops in infants during the winter months, whether given milk from pasture-fed or stall-fed cows.

Attempts have been made also to improve the quality of the milk in this respect by adding various amounts of cod-liver oil to the ration of the cow. Something has been accomplished by this means but not sufficient to indicate that this method will be serviceable in connection with infant feeding. Lesné and Vagliano found that 500 gm. of cod-liver oil have to be added to the daily ration of cows to give antirachitic properties to their milk. The effect on the milk of feeding irradiated ergosterol to the cow has not yet been tested.

It has long been thought that milk which is rich in fat has protective properties, whereas that which is poor in fat tends to induce rickets. There is some validity in this point of view, but hardly enough to be of clinical importance. In other words it seems to be of no consequence whether we give milk containing 3 or 4 per cent of butter-fat. However, animal tests showed that cream has a small degree of protective effect in rickets; this may be due in part to the calcifying properties of the fat-soluble vitamin which it contains. When skimmed milk is fed, the babies develop xerophthalmia and not rickets, as was demonstrated in Denmark during the World War.

Some believe that *condensed milk* tends particularly to induce rickets. This has not been my experience and there is no reason why such should be the case. Raw milk contains only a small amount of the antirachitic factor which is not destroyed in the course of the condensing process. Of course, if the baby gains abnormally in weight due to the sugar in sweetened condensed milk, there will be an increased tendency to develop rickets, but this cannot be ascribed to the condensation process.

Some years ago it seemed to me that *Eiweissmilch* (protein milk) predisposed to rickets. Why this should have been the case,

I do not know; it may be because it was given to young poorly-nourished infants and brought about rapid gains in weight. Since this time, the dietary in my clinic has been supplemented with cod-liver oil or other antirachitic agents, so that observations on this point could not be extended. It may be added that a dextrin-maltose preparation containing a high percentage of sodium chloride was added to the Eiweissmilch at the time of this observation, which may have contributed to the result.

It has been suggested that goat's milk and ass's milk are definitely superior to cow's milk in antirachitic properties. There are neither clinical nor laboratory studies to support such a contention. This idea is probably merely an outgrowth of the well-known fact that the milk of these animals more closely resembles woman's milk in its chemical constitution, and in some instances is better borne. For these very reasons it is possible that these milks may resemble human milk in relation to the development of rickets. The question is difficult to judge, as goat's milk and ass's milk are not used in countries where rickets is prevalent.

Butter.—At the outset of the experimental period of rickets it was thought that butter was a valuable antirachitic. This was the period of confusion between the two fat-soluble factors—the A and the D. At that time I attempted to prevent the occurrence of rickets by giving infants 2 or 3 teaspoonfuls of butter daily. The results were not satisfactory. In spite of the fact that butter is a rich source of vitamin A—comparing well in this respect to cod-liver oil—it proved ineffective in warding off rickets.[1] This is true likewise in the experimental rickets in rats. When 10 per cent of butter is added to a rickets-producing ration, no protection is afforded. Indeed the rachitic lesions are more marked due to the increment of growth which is brought about. When 20 per cent or more of butter is added, rickets develops to a less degree, but such a diet must be regarded as containing a percentage of fat which introduces other nutritional factors.

Vegetables.—Although it has been shown time and again during the past few years that vegetables have little or no value in protecting against rickets, physicians still prescribe *vegetables—more particularly spinach*—with this object in view. This practise is due partly to the precept of clinical teachers but quite as much to the early experimental studies of rickets. As a matter of fact, no vegetable, leafy or root, bears any relationship to the etiology of rickets, as it neither prevents nor induces it. All clinical and laboratory

[1] For example, a baby about one year old, weighing 12½ pounds, was given 15 gm. of butter a day from November to February. In spite of this fact the signs of rickets increased. It died of pneumonia in February, and marked rickets was found with no microscopic evidences of healing at the costo-chondral junctions.

conclusions are united on this point. In 1920 Hess and Unger in appraising the clinical rôle of the fat-soluble vitamin reported the occurrence of rickets in an infant which had received daily, for a long period, a diet containing a liter of milk and 30 gm. of spinach. Zucker and Barnett showed that even the concentrated (non-saponifiable) extract of spinach and carrots was devoid of the anti-rachitic factor. More recently Chick and Roscoe, in a paper which may be consulted for the complete literature of this subject, reported that "spinach grown in the open in winter, spring or autumn possesses no antirachitic properties" and "spinach grown in mid-summer has a slight but appreciable antirachitic value." This result should not be interpreted as meaning that "summer spinach" is of value in protecting infants against rickets; the amount ingested is far too small to have this effect. In this connection I may add that a leafy vegetable grown in the West Indies (Jamaica) showed no antirachitic potency when fed to rats in moderate amount.

Fruits, including tropical varieties such as the banana and the orange, likewise contain none of the antirachitic factor. It is true that oil prepared from the cocoanut may to a greater or less extent show curative properties if the copra from which it has been expressed was exposed to the sun in the course of the drying process; if, on the other hand, the copra had been dried in a kiln, it was found to be entirely devoid of the specific factor.

Cereals.—For many years cereals, more particularly cereal proprietary foods, have been thought by clinicians to exert rachitogenic action. In fact a particular type of rickets—the overweight, large, flabby infant, with knock-knees or bowed-legs—has been associated with this type of dietary. There is no doubt that this clinical picture not infrequently is brought about by overfeeding with cereal, but it is difficult to decide whether there is a factor at play other than the well-known predisposing factor of rapid growth. In 1921, in his monograph on rickets, Mellanby published the first experimental study of this question and came to the conclusion not only that carbohydrates induced rickets, but that oatmeal had a special tendency in this direction, although it contains less carbohydrate than wheaten flour or rice. Four years later he published a more intensive investigation of this subject and stated that among the numerous cereals tested, oatmeal had preëminently the worst effect on bone formation—maize, barley, rice and wheaten flour followed in order of deleterious action. The effect of the cereal was so diametrically opposed to that of the antirachitic factor that Mellanby suggested it might be due to an "antivitamin." The substance in oatmeal which led to an interference with the deposition of calcium in the bone seemed to be associated with the fatty acids. The clinical lesson drawn from this study was that

the ingestion of oatmeal during infancy leads to the development of rickets and during pregnancy and lactation does much harm to women. This is a novel etiological viewpoint, too new to be appraised at the present time. It should be added that Holst of Oslo came to a similar conclusion as the result of a study on rats which were fed a diet consisting exclusively of oatmeal. He also believed that the rickets was due to a toxic substance, stating that this rachitogenic factor could be extracted with hydrochloric acid. The rickets produced in this way could be prevented by adding calcium salts, but not phosphates, to the cereal diet. Although these results are of interest, one must be cautious in drawing inferences from experiments in which the diet was composed entirely of cereal. In connection with this consideration, it should be borne in mind that the majority of infants do not receive cereal additions to their diet until the sixth month or later, and even then the supplement is of small amount. Furthermore, in this country wheat rather than oat cereals are given most frequently, so that although oatmeal may play a rôle, it must be regarded as a secondary dietetic factor in the etiology of rickets.

Other Foods.—There is little that need be stated in regard to other foods. *Eggs* are protective, due to the yolk, as has been brought out in the chapter on Experimental Rickets. Egg-white has been found to increase the intensity of the disorder, perhaps because it increases the growth-promoting properties of the diet.

What is true of butter holds good for *beef drippings*, a food which is used extensively in England in the feeding of babies. At the same time that we tested butter clinically, beef drippings were given daily in 30 cc. amounts to a series of infants. It was at the time when it was thought necessary, in view of our lack of knowledge, to test the antirachitic activity of apples, cabbage, beef juice, beef extract, etc. None of these additions to the dietary prevented the development of rickets. The same was found to be true later of *beef marrow*, which Bosányi in animal tests found to be highly antirachitic. In a few instances the marrow seemed to have slight value.

The effect of *meat* has not, as far as I know, been tested, but under the circumstances can be of little etiological importance.

The influence of *sodium chloride*, table salt, is not known. For a long time I have felt that its addition is not immaterial, but experiments on animals and clinical observations did not definitely confirm this impression. The negroes in New York City add large amounts of table salt to their food, and the question arose, in the course of a study of rickets in the negro population, whether the high percentage of salt in their diet could play any part in the striking incidence of infantile rickets among them.

LACK OF EXERCISE AND OF FRESH AIR IN THE ETIOLOGY OF RICKETS.

For centuries, physicians have argued whether faulty diet or faulty hygiene is the dominant etiological factor in rickets. The pendulum has swung first in one direction, then in the other, swayed by the authority and prestige of individuals rather than by objective evidence. Today it inclines far toward the side of hygiene. However, defective hygiene is not an entity but has in turn been variously interpreted. For example, the Glasgow school, represented by Findlay, has laid the greatest stress on the importance of exercise. About forty years ago Kassowitz maintained that rickets came about in infants from breathing the noxious gases which accumulated in badly ventilated rooms. This conception is merely a variant of what more recently has been summarized by the designation "hospitalism," which we associate at present with the development of infantile marasmus or atrophy rather than with rickets. Von Hansemann laid the blame on "domestication," including under this broad term all the harmful influences which go hand in hand with modern civilization. More recently, as is well known, the deficiency has been focussed sharply on sunlight rather than on fresh air, the newer experimental technique making it possible to separate these two factors and to appraise their effect individually.

Lack of *exercise* is of but little moment in the development of infantile rickets. As previously stated, rickets is of frequent occurrence between the fourth and the sixth months of life; at this period, when the infant is as yet unable to stand, there can be little question of adequate exercise. Although exercise may tend to decrease the degree of rickets, judging from experiments on dogs, its rôle must be insignificant among the errors of hygiene which dominate the etiology.

The same holds true in regard to the influence of *fresh air*. This point can be illustrated by an animal experiment. As is well known, rats exposed to sunlight are protected from rickets. At first it was thought that this beneficent effect might be due to the purity of the air, perhaps to its oxygen content, rather than to the rays of the sun. A simple laboratory test showed that such is not the case. When a group of rats, fed one of the standard rickets-producing diets, was placed out-of-doors during the entire night, it was found that all developed rickets to the same extent as the control group which was kept indoors for the same period. In other words, the pure fresh air, unaccompanied by sunlight, was of no protective value. The remarkable results obtained in the poorly ventilated rooms of laboratories and clinics by the use of ultra-violet irradiation from artificial sources furnish undoubted evidence as to the factor which is responsible for the protective or healing effect of

out-of-door treatment. It is possible that humidity and atmospheric moisture exert an action apart from their influence in filtering out and nullifying the activity of the solar rays. Some believe such to be the case; but the studies on the incidence of rickets brought forward to support this viewpoint are as yet unconvincing. It is by no means unlikely, however—in fact there are some vague indications—that the ultra-violet rays are not the sole meteorological factor which exerts an influence on the development of rickets.

A remarkable phenomenon in connection with rickets and tetany was noted by Kassowitz forty or more years ago, namely, its marked *seasonal variation*, its frequent occurrence during the winter and early spring and its comparative infrequency with the advent of summer. Kassowitz realized the importance of this clinical phe-

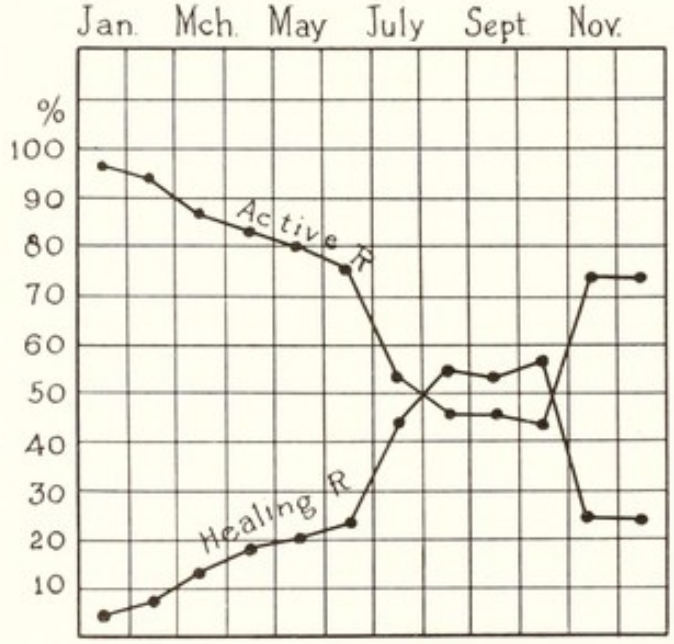


FIG. 5.—Seasonal incidence of rickets. Based on the histologic data of 386 consecutive necropsies. (Schmorl.)

nomenon but completely misinterpreted its true nature. He attributed the marked increment throughout the winter months to prolonged confinement of the infants indoors. It may be added that in judging of the curative effect of elementary phosphorus, his favorite child, he paid no attention to seasonal incidence whatsoever. So definite is the seasonal variation of rickets that it should have been realized long ago that this manifestation would provide the key for the solution of its etiology. Kassowitz's clinical observations were fortified by the extensive pathological studies of Schmorl, which comprised a continuous series of necropsies over a period of several years. These data are incorporated in the accompanying graph (Fig. 5) and show unmistakably, from a purely objective standpoint, the high incidence of rickets in the winter as well as

the paucity of acute cases developing during the summer. Even before this histological study, Palm, an Englishman, had concluded as a result of a study of the geographical distribution of rickets throughout the world, from Siberia to Africa, that the disorder came about as the result of a lack of sunlight. He pointed out that the important factor of the sunshine is "the chemical activity of the sun's rays rather than its heat," and recommended "the systematic use of sunbaths as a preventive and therapeutic measure in rickets." Little attention was paid to his thesis, however, as it was based purely on circumstantial evidence and not on clinical observation or on experiment.

In 1913 a very suggestive investigation was published by Raczynski, a study which I found several years later buried in an obscure society report. For some time it furnished the only definite chemical data demonstrating the influence of solar rays on the metabolism of inorganic salts. Raczynski's simple experiment consisted in taking two puppies of the same litter, both of which were being suckled by the mother, and keeping one in absolute darkness and the other in sunlight throughout the day. An analysis of their bodies showed that the one which had been reared in the sunlight contained 50 per cent calcium and 25 per cent phosphorus more than the other, but that on the contrary, it contained less than half the quantity of chlorine. It is open to question whether the dog with the insufficient phosphorus and calcium suffered from osteoporosis or from rickets, but the effect of sunlight on the bones cannot be doubted.

ULTRA-VIOLET RAYS IN THE ETIOLOGY OF RICKETS.

In 1919 Huldschinsky first demonstrated the calcifying effect of the ultra-violet rays in rickets, and it is his work which led to the long series of investigations, in clinic as well as in laboratory, of the relationship between these rays and calcification. He showed by means of roentgenograms that the epiphyses of rachitic infants undergo rapid calcification following exposure of their bodies to the radiations of the mercury-vapor lamp. The illustrations accompanying his report left no doubt of this action. In 1918 Unger and I, impressed by the striking influence of season, tested the effect of rays from this source on several cases of rickets. It was noted that the enlarged costo-chondral junctions became somewhat firmer and but little smaller, and therefore we judged the effect to be indefinite or slight. The healing process was not followed by means of roentgenograms. In 1921 we were able to show the curative effect of sunshine in cases of infantile rickets.

In the same year methods were developed for bringing about rickets in rats by means of a diet deficient in phosphorus, so that

the time was ripe to make an experimental test of the relation of ultra-violet rays to rickets. It was found by Powers and Park and their collaborators and by Hess, Unger and Pappenheimer that the radiations from the mercury-vapor lamp were quite as effective in preventing rickets in animals as they had proved to be in infants. Many refinements and variations of these experiments, which have been considered in the chapter treating of the experimental aspect of rickets, were carried out in the course of the next few years. That this specific effect of light is a chemical rather than a biological action was shown by Hess and Weinstock (1925) by means of a simple experiment. A section of excised human skin was irradiated in the usual manner by means of the mercury-vapor lamp and then fed in definite amounts to a series of rats. It was found to confer absolute protection against rickets. On the other hand, similar amounts of skin which had not been irradiated conferred no protection whatsoever. In other words, specific properties had been induced in the skin by means of irradiation, in spite of the fact of its having been deprived entirely of nerve supply and circulation. This experiment is significant as to the mode of action of the actinic rays and would seem to warrant the conclusion that a specific substance is formed *in situ* within the skin. At this time it was thought that this substance was an "activated cholesterol," but the results of investigations of the past year or two indicate rather that it is "activated ergosterol," another and closely allied sterol. Recently (1928), Falkenheim has extended these observations by showing in rats that areas of skin which are not directly irradiated likewise develop antirachitic potency following the use of the mercury-vapor lamp. The degree of ergosterol in the skin or in other organs of the body has not as yet been determined, but there is no doubt that within the next few years such quantitative estimations will be available. A consideration of ergosterol and its activation will be found in the chapter on Treatment.

In connection with the development of rickets, it would be of practical interest to know the extent of surface area which it is necessary to expose in order that protection be afforded. Under normal conditions in the temperate zone very little of the sun's rays are allowed to impinge on the skin of the baby. Even during the spring months, when rachitic lesions show rapid healing, only the face is usually exposed. From such clinical experiences it may be adduced that an exposure of only comparatively small areas is required. This assumption fits in well with our knowledge of the infinitesimal amount of irradiated ergosterol required in order to bring about calcification of the bones in infants and in animals.

Very little of "the antirachitic radiations" is able to penetrate clothing material. This question was put to the test of experiment in 1923 by employing as filters cotton and woolen goods of various

meshes and using the carbon-arc lamp as a source of ultra-violet rays (Table 9). It was found that if the cotton fabric was interposed between the animal and the lamp, three units of radiation were required to bring about protection, whereas if the material was somewhat heavier, and more closely knit, only slight protection could be brought about even with this intensity. Cotton and woolen stocking material, such as is worn by infants, permitted but a small degree of ultra-violet light to permeate unless a very large dosage was employed. White material allowed the passage of rays to a greater extent than black material manufactured on the same looms. It is clear, therefore, that the necessity of wearing clothing in the temperate zones deprives us of the benefits of a valuable section of the solar rays and is an important factor in the incidence of rickets.

TABLE 9.—PENETRABILITY OF VARIOUS CLOTHING MATERIALS (CARBON ARC IRRADIATION[1]).

Rat No.	Weights, gm.	Material.	Exposure.		Rickets.	
			Time, min.	Distance, feet.	Roentgenogram.	Microscopic examination.
1545	42–48	Thin cotton (nainsook)	10	3	Negative	None
1546	40–42				Negative	None
1547	40–50				Negative	None
1548	60–60				Negative	None
1549	40–46	Cotton stocking	10	3	Negative(?)	Slight
1550	28–28				Moderate	Moderate
1551	60–64				Rickets	Moderate
1552	28–26				Rickets	Marked
1659	70–66	Cotton stocking	30	3	Slight	Very slight
1660	60–54				Negative	No definite
1661	58–60				Negative	No definite
1662	66–60				Slight	No definite
1553	40–54	Woolen stocking	10	3	Rickets	Moderate
1554	60–60				Negative(?)	Very slight
1555	50–60				Moderate	Moderate
1556	70–68				Moderate	Moderate
1655	80–70	Woolen stocking	30	3	Slight	No definite
1656	50–40				Negative	Slight
1657	76–70					Very slight
1658	44–40					Slight

This seasonal variation of the ultra-violet radiations of the sun is well illustrated by the graph of Dorno (Fig. 6), a composite of many observations carried out at Davos, Switzerland. It shows the small amount of ultra-violet in the winter, its rather sudden

[1] Hess and Weinstock, Jour. Am. Med. Assn., 1923, **80**, 687.

increase during the late spring, its flood during the summer and its gradual fall during the autumn months. It is quite possible that other climatic factors and meteorological conditions play a rôle in rickets but they must be of minor importance. The similarity of this curve to the seasonal graph of rickets is apparent—the season with the lowest intensity of ultra-violet radiations corresponding to that of the greatest incidence of rickets. It may be added that in the days before antirachitic prophylaxis was carried out in a routine way, we found that three-quarters of the cases of rickets developed during the first half of the year and only one-quarter during the second half. These short rays constitute less than 1 per cent of the total solar radiations, and it is therefore all the more remarkable that they should prove to be essential to the well-being of man; the young, rapidly-growing infant thrives better when deprived of the visible rays than when deprived of the ultra-violet rays of the sun. It is an illustration in another field of what

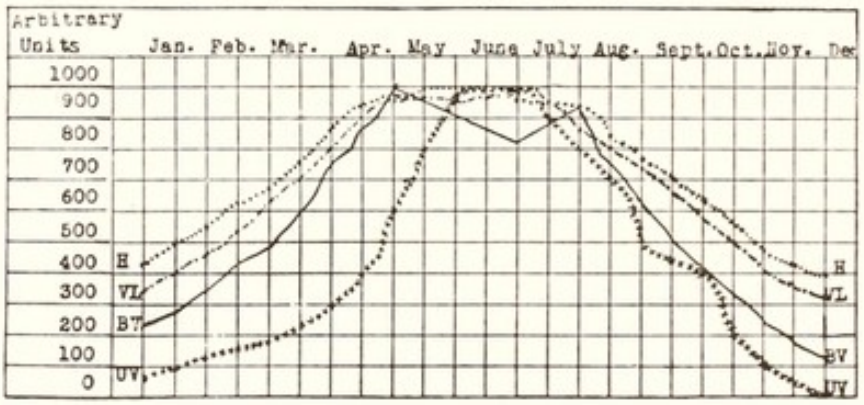


FIG. 6.—Seasonal variations of the sun's spectrum: *UV*, ultraviolet; *BV*, blue violet; *VL*, visible light; *H*, solar heat. (Dorno.)

we have recently become sensible of in regard to nutrition—the lack of relationship, one may almost say the inverse relationship, between abundance of supply and indispensability of food constituents. The vitamins furnish a striking example of this principle. The law of "the vital importance of the minimum" applies to the radiations of the sun—those rays which are furnished in smallest amount and in least intensity are nevertheless most indispensable.

In view of the marked seasonal variation of the ultra-violet rays as well as of the incidence of rickets, and bearing in mind the pronounced effect of ultra-violet radiations on the inorganic phosphate of the blood, Hess and Lundagen in 1922 investigated whether the transition of the seasons was accompanied by a periodic alteration in the phosphate of the blood. A seasonal tide of the blood phosphate, a summer flood and a winter ebb, was found to occur to a greater or less degree among well nourished bottle-fed infants in

New York City. These babies were out-of-doors every fine day for a few hours, although bundled up in the usual fashion, with but a portion of their faces exposed. The infants which were tested, month by month, were from six to eighteen months of age, living under excellent hygienic conditions and receiving a diet of high grade fluid or dried milk, as well as the usual amount of orange juice, the older ones being given cereal in addition. The graph of this "seasonal phosphate tide" (Fig. 7) bears a remarkably close resemblance to that illustrating the ultra-violet radiations of the sun. No doubt, the fact that most of the infants developed rickets to a greater or less degree during the winter accounted for the fall of the blood phosphate during this period, but when we consider that

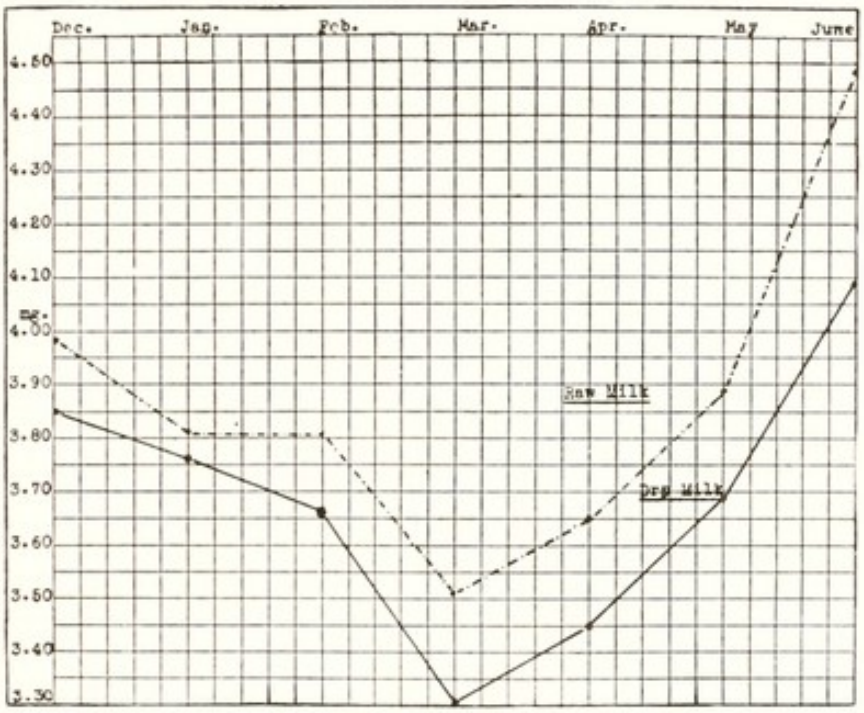


FIG. 7.—Seasonal tide of inorganic phosphorus of the blood in infants; diets, raw milk and dried milk. (Hess and Lundagen, Jour. Am. Med. Assn., 1922, **79**, 2210).

perhaps three-quarters of bottle-fed and one-third to one-half of the breast-fed infants develop rickets to some degree by the month of March, a reduction of inorganic phosphate of the blood must at present be regarded as the usual phenomenon of infants in the temperate zone. I believe that if a series of tests were carried out on a selected group of infants who showed no clinical signs of rickets, a similar seasonal variation in chemical composition of the blood would be found. Recently (1928) a test of this kind was carried out on normal adults by Havard and Hoyle, who found a concentration of 2.9 mg. of inorganic phosphorus in the winter which rose to 4.0 mg. in the summer.

In connection with a consideration of the geographical distribu-

tion of rickets (Chapter II) I compiled a table of the "Yearly Average Number of Hours of Actual Sunshine in Cities in Various Countries." It will be noted that Glasgow and London stand at the foot of the list, while Phoenix (Arizona) and Cairo (Egypt) stand at the head. Glasgow is notorious for the amount and intensity of its rickets and the disorder was first described in London by Glisson; in Germany it is still referred to frequently as the "englische Krankheit." In the tropics rickets is almost unknown, occurring merely in very mild form or in cases where the infant has been confined indoors for a long period. It will be found that the intensity of rickets

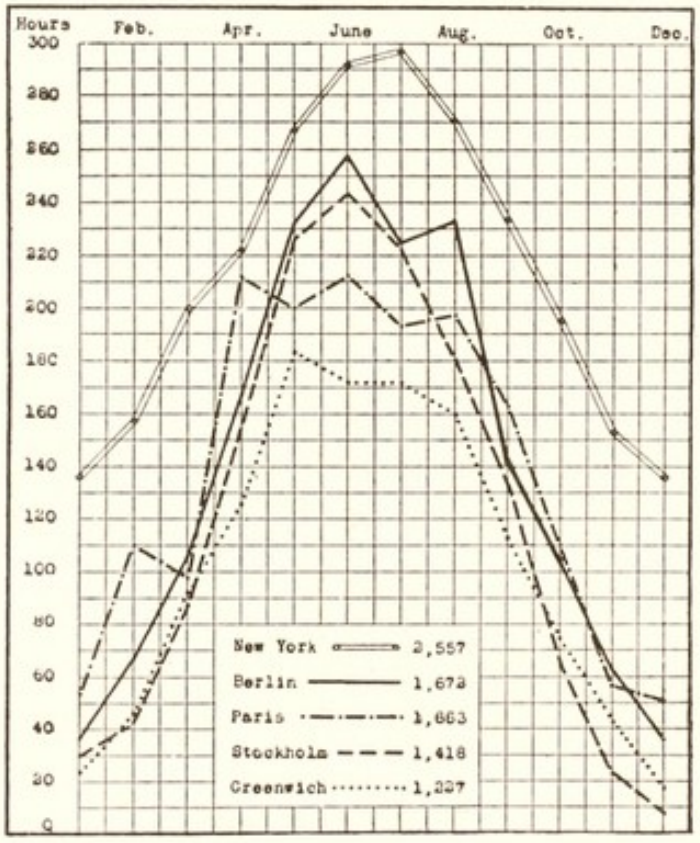


FIG. 8.—Amount of actual sunshine (yearly average) in five large cities in the temperate zone. (Hess, Jour. Am. Med. Assn., 1925, **84**, 1033).

throughout the world corresponds fairly closely to the amount of sunshine recorded in this table. When we bear in mind the varying diet of the peoples in the different parts of the world represented by these centers of population, the dominance of sunlight in the etiology of rickets is most striking. The fact that rickets, osteomalacia and tetany develop in India, where the women are deprived of the benefit of the tropical sunshine by observing the system of purdah, emphasizes still more strikingly the dependence of rickets and cognate clinical conditions on exposure to the sun's rays.

Fig. 8 shows the actual number of hours of sunshine yearly in some of the larger cities of the world, compiled from data furnished

by the U. S. Weather Bureau. It will be noted that New York has by far the greatest number of hours of actual sunshine and furthermore that this holds true for every month of the year. Greenwich, representing London, has the smallest total number of hours. But when we analyze the graph further, we find that New York has approximately the same number of hours of sunshine during the winter months of February and March as has London during the months of June, July and August. But rickets develops during the winter in New York, whereas it undergoes healing in London during the summer. In other words, about the same number of hours of actual sunshine induces rickets in New York during the winter as

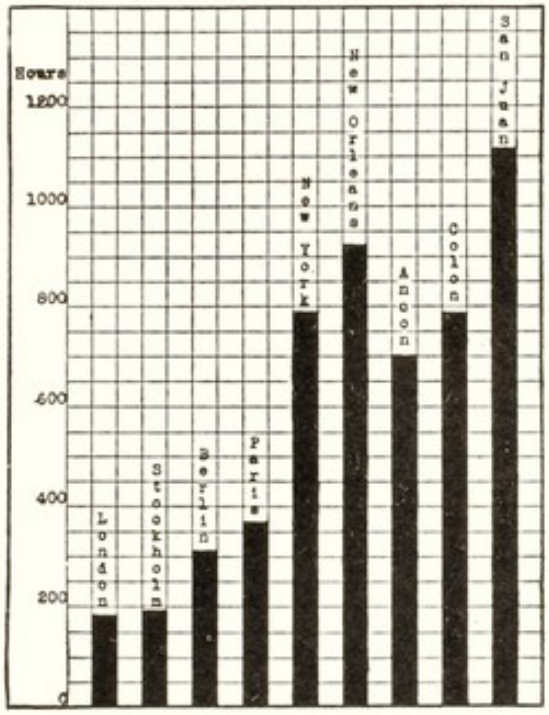


FIG. 9.—Amount of actual sunshine during the five winter months in cities of the United States and Europe and for five corresponding months in some cities of the tropics. (Hess, Jour. Am. Med. Assn., 1925, **84**, 1033.)

leads to the cure of rickets in London during the summer. This comparison makes it evident that the incidence of rickets and its seasonal variations cannot depend wholly on the number of hours of actual sunshine. If we construct a table giving the amount of sunshine only during the winter time, in other words those months which are associated with the occurrence of rickets (Fig. 9), it is found that the distinction between New York and London becomes still more pronounced. Whereas New York has approximately twice as many hours of sunshine as London throughout the year, it has more than four times as many during these five winter months. Now although rickets is of somewhat greater intensity and severity in London than in New York, the ratio is not 4 to 1 as these figures

would indicate. Evidently there is a factor involved in the etiology in addition to the amount of actual sunshine. Furthermore, this chart shows that some cities in the West Indies where rickets is mild and negligible, such as Ancon and Colon in the Panama Canal Zone, have even less sunshine yearly than New York.

The explanation of this seeming discrepancy is well brought out by a study of the figures of Dorno obtained in Davos, Switzerland. He showed by careful measurements that the sun's radiations are of a much shorter wave length in summer than in winter; in December the shortest radiations were somewhat more than 306 millimicrons in length, whereas in June they reached 298 millimicrons. Since New York is at about the same latitude as Davos there would be fully as great a difference in the quality of sunlight between the summer and winter. Indeed, the variation will be even greater since the atmospheric absorption, as well as its annual variation, increases with the decrease in altitude. It is the quality and intensity of sunlight in the West Indies which are superior to those in New York, this difference being due to the decreased zenith distance of the sun which has a smaller annual fluctuation in the tropics. The same is true, to a much less degree, in regard to the sunlight of London and of New York. *The dominant factor in regard to the antirachitic activity of the solar rays is not so much the number of hours of sunshine as its quality and intensity.* These properties go hand in hand.

These conclusions drawn from clinical observation are borne out by more exact laboratory experiments. In 1923 Miss Weinstock and I carried out "A Study of Light Waves in Their Relation to Rickets," employing a series of glass-filters of known penetrability. The results of this investigation may be summarized by the statement that in order to be of value in rickets, the ultra-violet rays must have a wave length not longer than 310 or possibly 313 millimicrons. Such being the case, sunlight which has passed through ordinary window-glass can have no therapeutic value—from the point of view of rickets it must be regarded as denatured. When we bear in mind that the shortest waves of sunlight that reach the surface of the earth are about 290 millimicrons and that, due to the effect of moisture, smoke and dust, rays shorter than 300 millimicrons rarely reach its surface, it is evident that the length of effective radiations is markedly circumscribed by nature and furthermore limited by natural and artificial meteorological conditions. These experiments served to emphasize the remarkable specificity of wave lengths of light in relation to rickets, and justified the conclusion that waves 324 millimicrons in length have little or no protective value, whereas waves of 302 millimicrons are of great value. The data, however, were not adequate, the analysis of the spectrum was not sufficiently precise to warrant a deduction as

to whether waves of 313 millimicrons contributed to the protection. The experiments did show, however, that a difference of 10 to 20 millionths of a millimeter in wave length sufficed to render ultra-violet light effective or ineffective. These results have been confirmed by the investigation of Luce.[1]

More recently Anderson and I have carried out a more refined study, using monochromatic light for this purpose. The main object was to ascertain the longest wave lengths of ultra-violet light which have an antirachitic effect. This study confirmed that previously carried out and was summed up as follows: "The activity at 313 millimicrons (3130 angström units) is very feeble so that this point must be regarded as the upper limit of the antirachitic field. The area of specific solar radiation is markedly circumscribed; a difference of a few millimicrons or millionths of a millimeter determines whether or not waves are effective. During the winter months, when the shorter ultra-violet rays do not reach the earth and the longer ones are less intense, the width of the antirachitic zone of sunlight is only about 5 millimicrons. These observations emphasize the danger of the small band of specific radiations being filtered from the atmosphere by moisture, dust, smoke and other foreign substances."

It may be added that it also was shown in this investigation that "ultra-violet radiations shorter than those of sunlight are more potent in healing rickets than the effective area of solar rays—a band comprising waves from 290 to 313 millimicrons." This result was anticipated in view of the pronounced effect of irradiation with artificial sources of light, such as the mercury-vapor lamp, which emits rays shorter than those of the sun, and in view of the comparatively short exposures which are required to effect protection and cure when such sources are employed. However, as Sonne and Rekling have shown in a study of monochromatic light, all the shorter ultra-violet radiations do not exert a marked antirachitic action. Whereas the region about 280 millimicrons is highly effective, the potency in the neighborhood of 248 and 240 millimicrons is inconsiderable.

Studies such as these show the intimate interrelationship between laboratory investigations and clinical procedure. My clinical experience with the protective and curative effect of sunlight in New York during the winter months has not been favorable and has coincided with the data obtained from the laboratory. It is true that during the months of January and February the sun exerts some antirachitic power, but it is so slight and the weather generally is so inclement at this season of the year that

[1] It should be remembered, however, that a difference of a few millimicrons in wave length is equivalent to a vast difference in wave frequency.

its action has proved most unreliable. Infants placed out on a veranda for several hours a day could not be cured of rickets during these months. No doubt if their entire bodies could be exposed, in other words if we had made use of a window-glass which filtered out but little of the antirachitic radiations, greater protection or cure might have been afforded. In experiments on rats I have found that the winter sunlight has a definite protective or curative effect. Recently (1927) Tisdall and Brown have reported that "the sun's rays during December, January and February in the latitude of Toronto produce a slight but definite antirachitic effect on rats fed on a rachitogenic diet." Fleming has come to a similar conclusion as the result of a study on rats in Washington, D. C. Furthermore, several investigators have reported the beneficent effect of winter sunshine in preventing the occurrence of leg weakness in chickens. But in interpreting these results on animals in terms of clinical medicine, it should be remembered, in the first place, that the entire bodies of the animals were exposed to sunlight, and secondly that for protection or cure they may require a smaller intensity of the specific radiations than infants.

There is not only the direct sunshine but what has been termed "*skyshine*," the sun's rays that are reflected from the sky and clouds in contradistinction to the rays received directly from the sun itself. Dorno reported in 1920 that when the sun is at its height, the reflected ultra-violet rays from the sky are 15 per cent greater in amount than the ultra-violet rays received from the sun directly. Tisdall and Brown have carried out on rats a study of the antirachitic effect of skyshine, and concluded that it "is approximately from one-half to two-thirds as great as that produced by what is ordinarily termed sunshine (rays from the sun plus the reflected rays from the sky)." It is due largely to the action of these reflected solar rays that infants are protected from rickets in spite of the fact that they are almost completely enveloped in clothing and sedulously screened from the direct sunlight.

From the first realization of the fact that ultra-violet radiations exert a specific effect in relation to rickets—a constitutional disorder—it has been difficult to harmonize this activity with the established teaching that these radiations have but slight power of penetration. Hasselbalch carried out an intensive investigation on the penetration of the shorter ultra-violet rays through the skin and concluded that they penetrate not deeper than about 0.1 millimeter. These results have in general been confirmed by other workers. Recent studies by Anderson and Macht have shown that there is a factor to be borne in mind which heretofore has not been considered, namely, that the shorter ultra-violet rays penetrate living skin much more readily than they do dead skin. By means of a spectrograph,

as well as fluorescence photometry, it was established that the penetration of these rays through the living skin of the rabbit was much greater than hitherto had been supposed. Transmission for a thickness of 1.2 millimeters was found to be 6 to 10 per cent for wave lengths as short as 2537 to 3000 angström units, in other words, waves shorter than those of ordinary sunlight. That the divergence between these results and those obtained by previous workers was due to the difference in experimental conditions was shown by spectrograms taken at intervals while the skin was gradually losing its viability—a phenomenon which ran parallel with a progressive loss of transmission of the ultra-violet radiations. These investigations do not alter the conclusion that the ultra-violet rays function by activating the sterol in the skin, but lead to the inference that they affect not only the epidermis but probably the blood lying in the deeper layers of the integument. It should be added, however, that the action of the ultra-violet rays on the skin is not yet well understood. For example, the white rat can withstand an intensity of irradiation from a powerful mercury-vapor lamp which would be most destructive to the skin of a human being; no redness or burn results from several hundred times an intensity which brings about a burn in the human being.

The knowledge of the relation of ultra-violet rays to rickets has changed our entire conception of this disorder and has necessitated a revision of our ideas as regards its etiology and treatment. Moreover, although it is certain that other solar radiations must have marked and definite effects on the human organism, at the present time we know of no specific action of these various radiations on the physiological processes of man excepting this peculiar and specific calcifying influence of this circumscribed band of ultra-violet rays. Physiologists and biologists have made antirachitic activity one of the criteria of the presence of these wave lengths. Rachitic animals, for the most part rats, are used as a test to determine whether, and in what intensity, antirachitic radiations are given off by sources of light. It seems most probable that this field will be extended and that before long we shall associate light of other wave lengths with definite disorders or at least with definite activities on the animal organism.

Our knowledge of the action of ultra-violet rays must still be regarded as empirical, in spite of the fact that the advances in this field during the past few years have been among the most marked in any province of the medical sciences. In general, the change in point of view may be summed up by the statement that now it has been actually proved, although it had been suggested previously by many, that actinotherapy is the result of a photochemical reaction upon a definite chemical substance.

THE VITAMIN FACTOR IN THE ETIOLOGY OF RICKETS.

As brought out in considering the history of rickets, a new era has come about through the appreciation that *a specific nutritional factor or vitamin* is vitally concerned in its etiology. The conception of a nutritional factor being a specific for a definite disorder was by no means new, having been suggested by physiologists from time to time and proved experimentally by Eijkman who, in 1897, in the course of experiments in Java, noted that fowl fed on decorticated rice became paralyzed and developed symptoms of beriberi (polyneuritis gallinarum), and that this paralysis or spasticity disappeared when rice polishings or their alcoholic extract was added to the diet. The subject slumbered for almost twenty years, until 1906, when Hopkins, the English biochemist, established it on a scientific basis by demonstrating that animals were unable to live on a dietary composed of casein, starch, lard, water and a mixture of inorganic salts after these ingredients had been carefully purified, but that this diet could be rendered adequate merely by the addition of a small amount of a natural food—a few cubic centimeters of milk.[1] The path was blazed as a result of empiric observation as well as carefully planned scientific investigation, and moreover as has happened so frequently in the past, alert empiricism prepared the way for and outran the more carefully planned laboratory experiment. Schaumann in 1910, as well as Funk, who was the first to classify our knowledge of the vitamins and avitaminoses, included rickets in the category of deficiency diseases, drawing their conclusions from analogy. The first, however, to attack rickets successfully from an experimental point of view was Mellanby, who as a result of an extended series of nutritional tests on puppies, came to the conclusion that rickets is a deficiency disease brought about by a lack of the fat-soluble vitamin.

[1] As early as 1905 Peckelharing stated: "When mice are fed on bread baked with casein, albumin, rice flour, lard and a mixture of all the salts which ought to be found in their food, while they are only given water to drink, the animals starve to death. During the first few days all is well. The bread is eagerly nibbled and the mice look healthy. But soon they get thinner, their appetite diminishes and in four weeks all the animals are dead. If, however, instead of water they are given milk to drink, they keep in good health, though the quantity of albumin, lactose and fat which they assimilate with the milk is quite negligible in comparison with what the bread on which they are fed contains. The element in the milk which keeps the animals alive also occurs in the whey from which the casein and fat have been eliminated. Till now my efforts constantly repeated during the last few years, to separate this substance from the whey and get to know more about it, have not led to a satisfactory result, so I shall not say any more about them. My intention is only to point out that there is a still unknown substance in milk, which even in very small quantities is of paramount importance to nourishment. If this substance is absent, the organism loses the power properly to assimilate the well-known principal parts of food, the appetite is lost and with apparent abundance the animals die of want. Undoubtedly this substance not only occurs in milk but in all sorts of foodstuffs, both of vegetable and animal origin."

Although his conclusions cannot be accepted unreservedly, this pioneer work has been invaluable and laid the foundation for much of the nutritional investigation which has followed.

At the present time it is clear that *the fat-soluble vitamin*, the so-called vitamin A, cannot be regarded as the antirachitic vitamin or factor, but a few years ago this question was by no means evident, in fact, it was one of the knotty problems associated with the elucidation of rickets. It may be well, therefore, to review cursorily the evidence on this point. From a clinical standpoint at the very outset it seemed impossible that rickets could be due to a deficiency of a specific factor which was present in milk in large amount. The very fact, known to all children's specialists, that rickets develops frequently when too large amounts of milk are fed, rendered this interpretation untenable. It was impossible at first (1920) to put one's finger on the weak spot in this theory, but it was clear that it did not conform to clinical experience. In the following year in considering "Newer Aspects of Some Nutritional Disorders," a report was made of two groups of infants who had been fed for a period of several months on two well-defined dietaries, one containing a minimum of the fat-soluble factor and the other a full quota of milk. "The fat-soluble minimal" diet consisted of 60 gm. of dried skimmed milk, 30 gm. of sucrose, 30 cc. of cotton-seed oil, orange juice, autolyzed yeast and wheat cereal. This diet was generous in every respect excepting for the fat-soluble vitamin. It comprised an adequate number of calories, a full amount of the water-soluble and antiscorbutic vitamin and an adequate salt content. After a period of six months only one of this group showed rachitic signs by physical examination or by the Roentgen rays. In one case, in fact, which was under observation for a period of eighteen months, it was noted that rickets existed at the onset and disappeared on this dietary.

At the same time as these clinical observations were being carried out, Hess, McCann and Pappenheimer conducted an experimental study on rats which was summarized as follows: "Young rats receiving a diet complete except for a lack of the fat-soluble vitamin invariably failed to grow and generally developed keratitis. The skeletons of such rats show no gross changes whatsoever. Microscopic examination of the bones of 22 rats on a ration of this character presented definite signs of a lack of osteogenesis but in no instance lesions resembling rickets. In view of these results and their conformity with our previous experience in regard to infantile rickets, we are of the opinion that this vitamin cannot be regarded as the antirachitic vitamin and that if the diet is otherwise adequate, this deficiency does not bring about rickets."

Clinical experiences emanating from various sources showed that rickets could not be regarded as due to a deficiency of the fat-

soluble vitamin A. As is well-known, xerophthalmia developed to a marked extent in Denmark during and immediately following the World War as a result of the excessive exportation of butter from that country. Bloch saw 77 cases of xerophthalmia, 65 of which were in infants three months to three years of age. In only 12 could the diagnosis of rickets be made and in these it was not severe. "The children which received for a long time as their sole food oatmeal and barley gruel had no rickets." In 4 children that died no rickets was found at necropsy. There were no signs of tetany; only 1 of the 65 children had laryngospasm. The incidence of rickets was much less than one would have expected to find during the winter. His report leaves the question of osteoporosis unconsidered. The results, however, show definitely that a lack of fat-soluble vitamin A leads to xerophthalmia and not to rickets. No doubt the decreased growth occasioned by the deficiency of the diet tended to diminish the incidence of rickets.

The experiences of Hutchison and Shah published in 1922, are highly interesting and confirmatory of this point of view. They showed that in a certain district in India rickets occurred almost exclusively among the well-to-do Hindus and Mahommedans—social classes which live on a diet far superior to that of the poor among whom rickets both of the early and late types is almost completely absent. The larger consumption of milk and ghee (melted butter) provides a greater supply of fat-soluble vitamin for the rich who suffer most from these disorders. The authors conclude that a deficiency of the fat-soluble vitamin A cannot be the principal cause of rickets. In this connection it may be mentioned that, during the past century, as England grew richer and the food of the general population became more abundant, rickets developed in greater frequency and severity. A corollary of this observation on the children of the well-to-do was expressed by Hutchison and Shah in regard to the children in a district which had been subject to famine. They write: "At the Bandardhara construction dam I examined 172 children most of whom were the children of agriculturists from the famine areas and I found only slight cases of genu valgum. Many of the children were under one year old. Though the dietary of the parents was in most cases destitute of animal food, these infants were plump and well-nourished."

The atmosphere was suddenly cleared when McCollum and his colleagues in 1922 showed by means of animal experiments that there had been a confusion in previous experiments, that the fat-soluble vitamin had contained two dietary factors—one the well-established fat-soluble vitamin which was readily oxidized, occurring particularly in animal fats and leafy vegetables and the other, comparatively stable to heat and not present, or present to only a slight

degree, in these foods. It was evident that previous discussions had been at cross purposes, that investigators had been referring to two distinct and quite different nutritional factors. It should be added, however, that some, notably Mellanby and Korenchevsky of the English school, still believe that the fat-soluble vitamin A plays a definite rôle in the etiology of infantile rickets. There can be no doubt that a lack of this vitamin leads to osteoporosis and it is possible therefore that it exerts an effect indirectly; that although this deficiency does not lead to the development of rickets, such lesions develop more readily in bones which have been partially deprived of inorganic constituents, especially if this deprivation is followed by a sudden increase in growth due to a more ample diet.

The antirachitic factor is characterized by its limited distribution in food. Whereas the water-soluble, antiscorbutic and fat-soluble vitamins are widely distributed in Nature, the antirachitic factor has been found in but few substances. It is present in greatest concentration in the liver oil of various fish, notably the cod, but also in many other species. It is not present in vegetables unless they have been subjected to sunlight and activated in this way. When butter contains it, this probably is the result either of irradiation of the cow or of the fodder. The only source, in addition to cod-liver oil in which it has been found unequivocably and in amount which gives it importance as a food, is the yolk of egg. The concentration in the yolk will vary according to the conditions under which the hens have been kept. If they have been given cod-liver oil or one of its concentrates, or have been exposed to ultra-violet light, the egg will be rich in this factor, whereas if they have been deprived of ultra-violet light or antirachitic supplement to their ration, the yolk will be comparatively poor in this factor.[1]

We may summarize our knowledge of the distribution of the antirachitic vitamin, from the point of view of infant-feeding, by the statement that it may be contained in minimal amount in the cream of cow's milk, in high degree in the yolk of egg and in still greater concentration in cod-liver oil. Whether we should regard cod-liver oil as a food is a matter of individual interpretation. It is evident that this nutritional factor does not conform, in its distribution, to the vitamins which previously have been described and investigated. It would be to no purpose to discuss whether, in view of its limited distribution among foods, the antirachitic factor should or should not be dubbed a vitamin. Personally, I have always referred to this calcifying agent merely as "the antirachitic factor." The question is one which is not essential and the answer should be postponed until we have fuller knowledge of the chemical nature of the entire group of vitamins.

[1] This specific quality of egg-yolk holds good not only for the hen but for the eggs of other birds, as well as for those of fish, such as the cod, and for the eggs of snakes, turtles and tortoises.

THE GLANDS OF INTERNAL SECRETION IN THE ETIOLOGY OF RICKETS.

The idea that one or more glands of internal secretion plays a rôle in the etiology of rickets has been suggested from time to time in various forms ever since Fehling in 1887 brought forward the theory that osteomalacia is due to an overactivity of the ovaries. It will be remembered that he believed that he was able to effect a cure in osteomalacia by means of extirpation of the ovaries. Opinions are still divided on this point. Recent experiments of Korenchevsky have failed to show, following castration, any chemical or histological changes in the skeletons of growing rats fed a normal diet. Nevertheless, as will be discussed in the chapter on Osteomalacia, there are several phenomena in connection with this point of view which have prevented it from being swept aside and left out of consideration. In the first place osteomalacia occurs almost entirely among women, and furthermore it is a disorder which is associated essentially with pregnancy. It may be mentioned also that osteomalacia develops frequently in the course of lactation, a type of the disorder which was termed by Trousseau "lactation osteomalacie." Another observation which to me seems to link the ovaries, or possibly the female sex organs, to the development of disorders of the skeleton is the occurrence of what Rehn many years ago called "infantile osteomalacia," a rare disorder which develops almost entirely or at any rate preponderatingly in female infants. This is the type of infantile rickets which produces such extreme degrees of softening and deformity of the long bones that its victims become monstrosities.

There are observations which point to a relationship between the *parathyroid glands* and tetany. This subject can merely be touched upon in this connection but will be taken up in detail in the consideration of tetany. In passing, it may be noted that tetany, both among adults and infants, has a distinctive sex incidence—it occurs far more often among males than among females. How this peculiarity is to be explained is not known, but whatever the interpretation, it seems to point to an involvement of one or more of the glands of internal secretion in the etiology. But we do not have to rely upon inference to prove that at any rate in one type of tetany the parathyroid glands are of essential importance. For years it has been known that when almost all of the parathyroid glands are removed, typical tetany develops accompanied by a low percentage of calcium in the serum. Furthermore it has been brought out by a number of investigators, more particularly by Collip, that in parathyroidectomized or in normal animals the serum calcium can be raised by injections of an extract of the parathyroid glands. Both Erdheim and Pappenheimer have reported enlargement of the parathyroid glands in rickets. Very recently a similar

change has been noted in connection with the development of leg weakness in chickens. It would seem therefore that where the calcium metabolism of the body and more particularly of the bones is concerned, a derangement of the function of the parathyroid glands must be considered.

Recent investigations of irradiated ergosterol have suggested a new point of view. In rickets, following the ingestion of a few milligrams of irradiated ergosterol, the calcium and phosphorus are raised, more particularly the former. Hess, Lewis, and Rivkin have shown that this increase, especially in normal infants, may reach abnormally high levels—the calcium in the serum rising to a concentration of even 15 or 16 mg. Accompanying this hypercalcemia there is a hypercalcification of the epiphyses of the long bones. The experimental aspect is also of interest. When irradiated ergosterol was fed in large amounts to animals suffering from the low-calcium type of rickets, the serum calcium promptly rose, but after the parathyroids had been extirpated, no benefit accrued—the signs of tetany were not allayed, nor was the calcium in the serum substantially increased. These observations suggest that irradiated ergosterol raises the calcium by stimulating the activity of the parathyroid glands, although it may function in other ways as well. This conception establishes a functional relationship between a vitamin and one of the glands of internal secretion. In view of the clinical and experimental evidence, it seems certain that the endocrine glands play an important rôle at any rate in the low-calcium type of rickets.

Investigators have associated numerous other glands of internal secretion with the etiology of rickets. Without going into detail, mention may be made of *the thymus*—of the extirpation experiments of Basch, Klose and Vogt, and of Matti as well as those of Park and McClure. Although there can be no doubt that some of the lesions which were brought about experimentally were truly rachitic in nature, it should be noted that they have been temporary and, a fact of much greater importance, that such experiments do not prove that infantile rickets is due to a similar cause.

Some years ago Stoeltzner claimed that adrenalin was of value in the treatment of infantile rickets, but extirpation experiments of the *adrenals* carried out by Biedl and by Hess and Jaffe, as well as the pathological studies of Schmorl, have failed to confirm this point of view.

There are various phenomena which lead to the deduction that endocrine glands may be concerned in pathological conditions of bone; for example, the fact that gigantism and acromegaly have been shown definitely to be associated with derangement of the *pituitary gland*. But, however attractive such observations, their lure must be resisted and they must be regarded merely

as preliminary in nature and quite insufficient to justify analogies in regard to rickets. In 1923 Jackson and Carleton published the weights of various glands in a series of rats in which rickets had been induced. They noted a progressive decrease of the thymus although marked individual variations occurred, and furthermore an increase in the weight of the suprarenal glands. No apparent changes of moment were observed in the head, ligamentous and cartilaginous skeleton, musculature, brain, lungs, liver, spleen, ovaries, testes and epididymes.

THE RÔLE OF INFECTION IN THE ETIOLOGY OF RICKETS.

It is not surprising that some should have suggested that rickets is due to an infection, to the invasion of microörganisms or to poisons which they elaborate. This point of view was strongly urged by the Italian physiologist Morpurgo on the basis of an experimental study on rats. He claimed to have brought about rachitic changes in a large proportion of rats by injecting cultures of diplococcus; he had previously isolated this organism from rats in which a spontaneous outbreak of late rickets had developed. It is difficult to interpret these results as we are not informed as to the ration of the animals and do not know whether it was deficient in calcium or in phosphorus. Some years later, in 1911, Koch came to similar conclusions, making use of dogs in his experiments and injecting a streptococcus longus. He tested a large number of animals, and gave a diet which was adequate, comprising milk, meat, potatoes and sodium chloride. The dogs became severely ill and developed swellings of various joints which were followed by deformities. Koch concluded that he had produced rickets and that this particular microörganism had an especial infectivity for the skeleton. The conditions of this investigation are so artificial, when compared with those underlying the natural development of infantile rickets, that the two biological processes cannot be compared. Doubtless the injected bacteria lodged in the terminal vessels of the epiphyses and brought about lesions at these sites, thereby impairing the normal processes of calcification. Such experiments, however, cannot be brought forward to prove the infective origin of rickets.

All clinical experience is absolutely against the point of view that rickets is the result of an infection. In my experience, and I believe in that of most others, the disorder develops quite independently of the infections which are common during infancy, for example the respiratory and gastro-intestinal disorders. During the summer when gastro-enteritis is prevalent, an acute onset of rickets practically does not occur, as proved by the pathological examinations of Schmorl and of others. Nor have I found, as claimed by Kassowitz, that one or more attacks of pneumonia, or other respiratory infections, tend to bring about rickets. I have

examined the infants in my clinic for several years, noting whether this supposed relationship exists, but have failed to observe it in long-standing infections, for example furunculosis or otitis media. Moreover, the fact that infections lead to a loss of weight and growth, argues against the development of rickets. In infantile scurvy, on the other hand, the relation of infection to the progress of the disorder is very definite, but even in this condition it is questionable whether the scurvy is intensified by an intercurrent infection or whether it is not rendered merely more manifest. It is certainly true, however, that an intercurrent infection, such as grippe, will precipitate the appearance of the signs of scurvy, more particularly of the petechial hemorrhages, and bring to clear view the hitherto undefined symptoms of latent scurvy. There can be no doubt also that tetany is induced to a certain degree by infectious diseases. The calcium in the serum may be decreased as well as convulsions precipitated. It has never been shown, however, that in rickets the inorganic phosphate of the blood is reduced under similar conditions.

For years it has been urged that *syphilis* is an important etiological factor in rickets. Many years ago Boerhaave took this point of view. More recently the French clinicians Parrot, Fournier and Marfan have urged the importance of syphilis in this connection. Marfan has formulated a syphilitic type of rickets, characterized by marked precocity of the symptoms, exceptional involvement of the cranial bones, anemia and enlargement of the spleen. It is true that syphilis brings about alterations in the bones with associated clinical signs which greatly resemble those of rickets. For a long period congenital syphilis and rickets were considered one and the same disease. Pathological histology has enabled us, however, to separate these two processes into two distinct categories and there can be no longer any confusion between them. Not only does the teaching of pathology argue against the etiological rôle of syphilis in rickets, but the fact that the Wassermann reaction is negative in rickets and, on the other hand, that cod-liver oil and ultra-violet irradiation are specifics, point against their identity. It must be admitted, however, that Marfan is quite right in his contention that the mere fact that a therapeutic measure, such as ultra-violet irradiation, cures rickets cannot be accepted as proof that the disorder is brought about by a lack of this activity.

What has been stated in regard to syphilis holds with equal force in relation to tuberculosis. Marfan believes that 25 per cent of rickets is tuberculous in nature, that this type of the disorder is associated with malnutrition, and occurs during the second half of the first year of life and may be accompanied by signs of scrofula. My experience does not substantiate this viewpoint; the great majority of infants which have developed rickets in my clinic have given negative tuberculin reactions.

THE RÔLE OF TOXIC PRODUCTS IN THE ETIOLOGY OF RICKETS.

Instead of the conception that rickets is brought about by the direct agency of bacteria, Marfan and others have suggested that it is due to toxic products, including those elaborated by bacteria as well as other poisons. They state the hypothesis as follows: "Toxi-infectious digestive-rickets" is a consequence of the reaction of the marrow and cartilage of infants to all chronic infections and intoxications which occur during the period of active osteogenesis. This tissue reaction extends to the lymphatic glands, adenoid tissue of the pharynx, tonsils and may involve even the thymus. It is always difficult to discuss the rôle of hypothetic toxins. The fact that one form of rickets comes about as the result of overfeeding, from the consumption of excessive amounts of milk, might be interpreted in this light. It certainly cannot be regarded as the reaction of the tissues to a deficiency of a food constituent. On the other hand, such overfed babies, especially those which are breast-fed, appear to be in other respects healthy and well, giving no evidence of indigestion, so that we should have to presuppose the participation of toxins of markedly circumscribed activity. It would seem wise, in view of the vagueness of our knowledge of this aspect, to pursue it no further, but to keep an open mind on the subject and await the development of further investigations. This point of view harmonizes in its main outline with that of Cheadle, who suggested many years ago that rickets is due to poisons elaborated from farinaceous food, and with that of Mellanby who observed harmful effects from feeding oatmeal or its extract to puppies. It should be remembered in considering this source of toxicity, that the majority of cases of rickets begin to develop in infants previous to the age when cereal is added to the dietary.

In considering the question of toxins there are some observations which should be taken into account, although their significance cannot be appraised at the present time. It has been shown by Lehnerdt and others that rickets can be brought about in animals by feeding salts of strontium; in contradistinction to the lesions of elementary phosphorus, the "strontium layers" are composed of tissue which is uncalcified. It is worthy of note, however, that strontium rickets cannot be cured by means of cod-liver oil or irradiated ergosterol. Furthermore, Buschke and his collaborators have published several reports to the effect that rachitic lesions develop regularly in rats which are given small amounts of thallium; hypothyroidism, alopecia, cataract and tumors of the stomach were also noted. Some years ago (1925) the Japanese investigators Kawamura and Kasama described "rachitic bone lesions in young rabbits injected with Schistosomum japonicum." Following the injection of the cercaria of the worms, beading of the ribs (an

overgrowth of osteoid), atrophy of the sex organs and hypertrophy of the pituitary developed. An investigation yielding such an atypical result should not be allowed to pass unconfirmed. In this connection it may be in place to add that there seems to be a definite tendency to rickets in association with diabetes—especially excessive beading of the ribs. That hypertrophy of the bone, quite apart from rickets can result from toxic processes, has been demonstrated by the bony enlargement associated with the cyanosis of chronic heart disease, of long-standing icterus, of phosphorus poisoning and the disorder which develops in workers with mother-of-pearl. These various experimental and clinical observations may have nothing in common and be devoid of etiological significance, but eventually must be adjusted to the histological concept of what we designate today as rickets.

THE MECHANICAL FACTORS IN THE ETIOLOGY OF RICKETS.

There is an entirely different aspect of the etiology of rickets which must be considered. It has been brought forward by Mueller in a series of most interesting papers and has been summarized in his recent monograph on the normal and pathological physiology of bone. Mueller believes that the changes in the epiphyses accompanying rickets are not specific of this disorder, but that they are the result of pressure, of an insufficiency of the bone to meet its functional requirements. The growth centers and sites of ossification, according to this hypothesis are peculiarly sensitive to *mechanical strain and pull*, and react to these influences by the formation of zones of cartilage and osteoid tissue. In order to prove this theory, Mueller resected in a number of animals a large part of the radius so that the weight of the body fell upon the ulna. It was then found that the over-burdened ulnar epiphysis hypertrophied and showed microscopically marked hypertrophy of the proliferating cartilage and an excess of osteoid tissue. The illustrations which accompany this work are convincing. Mueller accounts for the fact that late rickets preponderates to such a marked degree among males—according to Fromme the ratio of male to female adolescents is 15 to 1—to the heavy work and the mechanical factors involved in the occupations of the male. The singular development of enlargements of the epiphyses of the costo-chondral junctions may likewise be ascribed to mechanical causes, to the constant play at these sites incident to the respiratory movement.[1]

These experiments of Mueller are not to be interpreted as indi-

[1] Some years ago I attempted to test the effect of motility by constricting one side of the thorax with adhesive tape and noting whether any difference could be observed in the degree of the "beading of the ribs." A negative result was obtained, probably to be ascribed to ineffective mobilization.

cating that mechanical factors induce rickets, but rather that such incidents determine at what sites the disorder becomes manifest. Rickets is a constitutional, metabolic disorder and not simply a derangement of the histological features of the epiphyses. However it suggests, as a corollary, that there may be a form of rickets associated with but little deformity—a type quite as significant from a metabolic standpoint as that which is characterized by enlargement of the epiphyses, rosary and bony malformation. It explains satisfactorily, on the basis of experiment, the lack of bowing of the legs of the poorly nourished as compared to the overweight infant or one which walks at an early age.

Conclusions.—Although the etiology of rickets is not absolutely clear, it is much clearer than it was some ten years ago. Rickets is distinguished by the remarkable number of factors which seem to play a part in its causation. They are, however, of varying importance and may as usual be divided into those which predispose and those which actually give rise to the disorder, although this distinction cannot be sharply drawn.

Undoubtedly there is a constitutional factor; all infants are not predisposed to rickets to the same degree. It can be stated however that this variability is not due to differences in the store of the antirachitic factor which infants bring with them into the world. A recent (1928) experimental investigation of this question showed that the livers of new-born infants contain but a small amount of the antirachitic factor. It is probable that in this particular there is little distinction at birth between individuals. Nor was it found that the marked susceptibility of premature infants can be ascribed to an outstanding lack of the specific factor. Possibly individual differences in relation to the development of rickets are due to differences in the activity of certain endocrine glands. It is, however, premature to accept such a hypothesis; indeed the suggestion is warranted only in view of the definite relationship between tetany and the function of the parathyroid glands.

In general rickets may be regarded as a disorder of the first two years of life. Racial susceptibilities likewise must be considered in connection with etiology—not only the striking susceptibility characteristic of the negro in the temperate zones, but minor racial differences such as cannot be detected clinically, but are noted in the laboratory among animals obtained from various sources.

One of the most important predisposing factors is *growth-rate*—indeed, at times it is the determining rather than a predisposing cause. As has long been known, marasmic or atrophic infants rarely develop rickets, whereas the rapidly-growing baby, and more particularly the premature baby, which may show a growth-rate twice that of the infant born at term, is with great difficulty prevented from developing rickets. The importance of growth is well illustrated

in connection with the dosage of cod-liver oil for prophylaxis; rapidly-growing babies require fully twice as much cod-liver oil as those which are making small gains, and premature babies generally cannot be protected from rickets by cod-liver oil in any amount.

The diet is important in etiology. The very fact that there is such a marked difference in the incidence of rickets between breast-fed and artificially-fed infants compels this conclusion. We are at a loss at present to interpret this protective value of woman's milk. It can be definitely stated that this potency is not due to a comparatively high content of the antirachitic factor, for animal experiments show that in this respect it is not superior to cow's milk. Nor is it due to a superiority in respect to the ratio of calcium to phosphorus, for were we to make an appraisal according to this criterion, cow's milk would be the more favorable. Artificial foods should not be regarded as a unit in relation to rickets; there is no doubt artificial milk mixtures vary in this respect, some being more and others less rachitogenic. Whether these differences are attributable to their inorganic or organic constituents, or to more subtle variations in the menstruum, is a field which has not yet been investigated. In general, it may be stated that our understanding of the rôle of hygienic factors in the etiology of rickets has far outrun our understanding of the dietetic factors.

The dominant etiological factor is sunlight—a scientific truth which forms the hub of our newer conception of rickets. As stated, if we take a broad point of view and scan the incidence of rickets throughout the world, we find that its distribution parallels the amount of sunshine, that where there is little sunlight rickets occurs to the greatest extent and in severest intensity, and on the other hand that in the tropics it is a disorder which need hardly be considered. The same is true in respect to individuals. Other things being equal, the determining factor in regard to whether or not an infant develops rickets, is the intensity of sunlight which it receives. It is probable that if a full-term infant, nursed successfully at the breast, were kept absolutely in the dark for the first six months of life, it would develop rickets. In this respect it would react metabolically as did the puppies which Raczynski reared in the dark. Undoubtedly there are numerous qualifying factors in connection with the activity of sunlight. The one with which we are best acquainted is the pigment of the skin which leads to the susceptibility of the dark-skinned races. But probably there are others; perhaps the amount of ergosterol which is activated by ultra-violet energy may vary appreciably in the superficial tissues of different individuals. However, as Saleeby has stated, rickets must be classed as one of the "disorders of darkness."

CHAPTER V.

THE PATHOGENESIS OF RICKETS.

During the past decade the arena has changed from etiology to pathogenesis. Whereas advances in regard to etiology have been so great that they have brought about a new era, there has been but little advancement in our understanding of the pathogenesis of rickets. As has been the case so often in connection with the development of medicine, the forward march has been most irregular—the clinical phenomena of rickets were clearly outlined in the seventeenth century, its pathology was elucidated by Pommer some fifty years ago, and etiology and treatment given an entirely new direction within the past decade. Our comprehension of pathogenesis, on the other hand, has undergone little change since the days of Glisson, except that this aspect has been made the object of study from newer experimental points of view and accordingly that new theories have been advanced. All that can be stated at present is that these seem promising and may contain a kernel of truth.

The difficulty in comprehending the *modus operandi* of the etiological factors, in other words the pathogenesis, is that we still lack an understanding of *normal calcification* and of the physiological and chemical processes involved in ossification. As usual, our ideas are swayed largely by popular currents of medical science. Until recently the subject was considered as a more or less simple chemical reaction, but recently the newer concepts of physical chemistry have dominated the point of view.

It is generally believed that the inorganic material of bone is composed mainly of tertiary calcium phosphate and of secondary calcium carbonate. The phosphoric acid radical is present in far larger amount than the carbonic acid, the ratio being approximately 10 to 1. In 1910 Gassmann showed that the molar relationship of $Ca : PO_4 : CO_3$ is approximately the proportion $10 : 5.7 : 0.8$. These relationships are remarkably constant in bone, so that Gassmann suggested that the calcium is bound in a definite chemical complex with PO_4 and CO_3, and that the formula is that of apatite. Wells had found even before this time that the ash of various tissues which had undergone pathological calcification contained mineral constituents in approximately the same proportions as bone. He showed also by means of a series of ingenious experiments that cartilage, when implanted in the abdominal cavity, takes up a large amount of calcium, and that its phosphate and

calcium content approximate that of bone. Some years earlier Pfaundler had shown that cartilage absorbs calcium and suggested that one of its characteristics is this chemical affinity. Hofmeister likewise emphasized the elective affinity for the calcium ions as an important principle in connection with calcification. These various experiments are of interest as far as they go, but they fail to inform us as to the circumstances which favor or hinder calcification, and, of more importance, they do not furnish a clue as to the limitations which govern calcification in cartilage under physiological conditions. We have no knowledge of the solubilities of the salts nor of the reaction at the sites where they are being laid down. Recently Shear and Kramer have reported that $CaHPO_4$ and not $Ca_3(PO)_4$ is the important substance concerned with ossification.

There is just as much uncertainty in regard to the physiological activities involved in the process of calcification as in the chemical reactions. For example, some believe the osteoblasts secrete collagen and lime salts, and others that the lime is precipitated into the matrix as phosphate and carbonate or as a double salt. In other words, there is a cellular as opposed to a humoral theory. The most suggestive studies in this field have been carried out recently by Watt and by Lériche and Policard. Watt, who noted the behavior of calcium phosphate and calcium carbonate precipitation in various media, summarizes his investigations as follows: "(*a*) In the rapidly developing fetal skeleton the first appearance of bone in the matrix is in the form of fine granules or globules which quickly fuse or coalesce to form a homogeneous mass. This might be interpreted, according to the bias of the observer, as supporting evidence either of precipitation or of secretion of the salts into the matrix. (*b*) The view advanced by Barille and supported by Wells's work, that calcium is carried in the blood as tribasic calcium carbonophosphate, is probably correct, as it furnishes the bone salts in the proper proportion, but their view of its deposit in the matrix as a precipitate due to change in concentration of carbon dioxide does not appear correct in view of the fact that no precipitate of the bone salts is visible. (*c*) The theory that the salts furnished by the blood are taken by the bone cells and secreted by them along with the matrix seems reasonable in view of the condition found in the matrix. (*d*) The action of the osteoblasts seems to be reversible, they being able to absorb or take up the calcium salts again out of the matrix." He believes, following Gerhardt, that the matrix of bone is a constituent different from that of cartilage, that the former is crystalline whereas the latter is colloid.

Lériche's and Policard's conception of the process is original. According to these investigators, the inception of ossification is accompanied by a local edematous infiltration, composed possibly of collagen resulting from a modification in the circulation. The

osteoblasts tend to liquefy this medium and exert a mild osteolytic rather than an osteogenic action. These investigators express themselves strongly against the cellular theory of ossification which they believe has dominated histologists ever since the days of Gegenbauer. Osteoblasts are regarded not as cells with a specific secretion, but as aiding calcification merely as the result of their degeneration, much as is true of other cells in the body. Another point of interest in their conception is that of a local exchange of calcium from one part of the bone to another or from bone to adjacent periosteum—a conception which was promulgated by Ollier about the middle of the past century.

Rabl takes the humoral point of view. He criticizes many of the theories of ossification which have been advanced—more particularly that of Freudenberg and György—in that they regard calcium absorption or binding as the counterpart of calcification in an anatomical sense. Such an interpretation he believes to be impossible in view of the fact that the calcified tissues contain far more calcium than could be found chemically in a soluble form. With this idea in mind he carried out a series of ingenious experiments on human and pig embryos, using ammonium oxalate, which has the advantage of being soluble and at the same time of precipitating calcium, in a stable form, as the oxalate. His main conclusion is that calcification must involve calcium combinations which are water-soluble and which are either not at all or but slightly dissociated. This study, which was published in 1924, is highly interesting and should be repeated and either confirmed or refuted.

The physico-chemical theory of Freudenberg and György will be considered in connection with the pathological calcification which takes place in rickets. It is evident, however, from these diversified theories which stand isolated and uncontroverted, that we are quite at a loss to explain normal calcification. These theories in themselves are entirely unsatisfactory and are merely anatomical or chemical explanations of the process of calcification or ossification and leave quite out of account all physiological considerations. In order to gain a picture which is at all complete, we shall have to know the relation of the endocrine glands to the circulatory and nervous systems, in fact to the body as a whole. For example, what is the part played by the parathyroid and other glands in the process of calcification? What influence have nerve impulses on the process? We have long been acquainted clinically with the body changes which occur in association with various arthropathies. Recently Berg and Hess have shown that section of the abdominal splanchnic nerves regularly leads to a decrease of calcium in the blood stream. Bearing in mind the association between these nerves and vasomotor tonus, it would seem probable that this phenomenon may in turn involve the circulatory system.

In view of the uncertain state of our knowledge of normal calcification, it would seem wise not to enter into a detailed consideration of the various hypotheses which have been advanced to explain the abnormal calcification in rickets. They are being modified and cast aside so frequently, their life is so ephemeral, that it seems advisable rather to survey the field broadly. It is most probable that the many investigations of chemists, physicists and physiologists in this field will shed new light upon it in the near future. In general the theories may be arranged in the following categories: (1) Lack of calcium or phosphorus in the diet; (2) faulty absorption of calcium and phosphorus from the intestinal canal; (3) conditions in the cartilage or osteoid tissue which are unfavorable from the point of view of solubility or a physico-chemical state; (4) a deficiency of calcium or of phosphorus in the blood; (5) a combination of a deficiency in the blood and unfavorable local conditions.

When it was thought that rickets resulted simply from a lack of calcium in the body, it was quite natural to suppose that one of the factors which brought this about was *a deficiency of hydrochloric acid* secreted by the stomach. The literature of about fifty years ago contains numerous considerations of this point of view. Now that it is well-known not only that rickets is not due to a deficiency in the intake of calcium, but that on the contrary an additional supply of this salt may intensify the disorder, the conception of a diminished hydrochloric acid secretion loses its *a priori* foundation. This theory was never established on a basis of clinical or laboratory observations. Some years ago when Scheer first advocated the treatment of tetany with hydrochloric acid-milk, I made use of this preparation in the treatment of some cases of rickets. I soon found that instead of bringing about healing, it tended to intensify the rickets as judged by the roentgenological picture and the chemical examination of the blood. Wills, Sanderson and Paterson had similar experiences. They carried out a study of calcium absorption and found that "gastric acidity does not appear to be a limiting factor in the supply of calcium to the body." The problem is by no means so simple.

Ever since the subject of pathogenesis has been considered critically, investigators have been divided into two groups, those who believe that the lesions in the bones result from defective absorption of salts from the intestinal canal, and incidentally a deficiency in the blood, and those who attribute it to defective apposition of calcium and phosphate at the epiphyses. Strong proponents in the first group have been Findlay and Telfer of the Glasgow school, the former stressing more particularly the lack of absorption of calcium, the latter regarding rickets as of intestinal origin. At first thought it would seem that it should be easy to determine whether or not there is diminished absorption, and

therefore whether the lack of inorganic phosphorus in the blood in rickets and the deficiency of calcium in tetany are to be ascribed to this defect. The difficulty in interpretation is, as will be discussed more fully in the chapter on Metabolism, that some of the calcium and phosphorus is excreted through the intestinal wall and that there is no way of knowing how much of what is recovered in the feces has failed of absorption and how much been excreted into the bowel.

Some years ago Schabad showed that increased retention followed the giving of cod-liver oil and that there was a coincident clinical improvement associated with this increase—results which have been amply substantiated with improved methods by Grosser and by Telfer. Orr, Holt and their colleagues have obtained similar improved retention by means of treatment with ultra-violet rays. They state that "ultra-violet radiation causes large amounts of these elements to be retained in the body. Increased amounts of calcium and phosphorus are found in the urine after ultra-violet radiation, indicating an increased absorption from the intestine." But they add the comment that it is possible that these rays may act also by decreasing the excretion from the intestine. Undoubtedly such metabolism tests are in favor of the theory of a decreased absorption in rickets, but favorable results brought about by curative agents cannot be revamped and used as arguments in connection with the pathogenesis of the disorder. At present ultra-violet irradiation must be regarded as an activation of ergosterol and as similar to giving this sterol parenterally, although it may have additional action. It has not been shown that the body contains active ergosterol normally, and loses it in the course of the development of rickets.

In this connection it should be pointed out that cod-liver oil (which contains activated ergosterol) is of antirachitic value when given subcutaneously, as shown by the experiments of Hess, of Lesné and of Kramer, and that irradiated ergosterol also has specific value when given by this route. It is possible that such indirect measures may act by promoting absorption from the intestinal canal but we hardly are warranted in drawing this conclusion. An important investigation in this connection is that of Grosser who injected calcium as well as phosphorus subcutaneously and found that this did not lead to calcification but to an increase in the calcium and phosphorus in the feces, in other words that something more was needed than the mere introduction of these salts into the circulation. Many things point to the fact that from a functional point of view the calcium and phosphorus in the blood may be of two different kinds, one which may be termed "transitory," which is merely passing through the blood stream on its way to excretion, and another form which in large measure is of "permanent" value to the body. The inherent difference between the "transitory" and "permanent" calcium and

phosphorus salts, and their reaction to cod-liver oil or its active principle, are fields which are unknown and unexplored. It is evident that although a lack of absorption probably plays a rôle in the pathogenesis of rickets, it does not furnish us with the complete solution of the problem.

Ernst Schloss, who contributed greatly to our understanding of rickets, was the first to draw attention to the fact that the stools of rachitic children are generally of alkaline reaction and that in the course of the healing process, particularly under the influence of cod-liver oil, the reaction tends to change to acid. It may be added that subsequent investigation has shown that although there is a basis for this statement, the exceptions to the rule are not infrequent. A few years ago Zucker and Johnson reported that in rachitic rats the feces have an alkaline reaction which becomes acid in the course of treatment with cod-liver oil or ultra-violet irradiation. Recently this study has been amplified by Grayzel and Miller in experiments on puppies. They found the reaction of the entire intestinal tract to be acid and that when Mellanby's rickets-producing dietary was given, the reaction tended to become more alkaline; the addition of cod-liver oil to this dietary changed the intestinal reaction back to its normal range. On the other hand, still more recently, Shohl, Bennett and Weed have reported that in rats "when the same amount of phosphate is added to a high-calcium low-phosphate rickets-producing diet so that the resulting mixture is alkaline, neutral or acid respectively, cure of rickets results in all cases, according to histological studies. Analyses of the bones show the greatest ash deposition with the neutral diets, smaller with the alkaline diets and least with the acid diets." A complete bibliography of this aspect of experimental rickets will be found accompanying their paper. It is difficult to harmonize the results of these various investigations. It is to be noted, however, that the former study was carried out on puppies fed a low-calcium ration, whereas the latter was carried out on rats fed a low-phosphorus ration.

The point of view that the disturbance of calcification in rickets is due to a local disorder in the bone or cartilage is best represented by *the theory of Freudenberg and Györgyi* which has been accepted abroad more fully than in this country. These investigators criticize the preëxisting theories as being concerned too exclusively with considerations of solubility and replace them by one in which physico-chemical factors play the main rôle. The basis of their theory has been an intensive study of the binding power of animal tissues for calcium and other salts. According to this hypothesis, physiological calcification is subdivided into three definite phases. In the course of the first, the protein of the cartilage forms a combination with calcium. The reaction is therefore as follows:

Calcium + cartilage = calcium proteinate

It is conceded that this reaction does not proceed always at the same rate but may be hindered by various substances, for example, amino-acids, peptides, methyl guanidin, creatin—all products of normal metabolism. During the second phase, this calcium proteinate combines with phosphoric and carbonic acids to form a calcium-protein-phosphoric or carbonic acid molecule. The process may be represented as follows:

Calcium proteinate + phosphate = calcium protein phosphate
Calcium proteinate + carbonate = calcium protein carbonate

The third phase consists in the precipitation of the calcium phosphate and carbonate, thus setting free the protein to form new combinations. The equations are:

Calcium protein phosphate = protein + calcium phosphate
Calcium protein carbonate = protein + calcium carbonate

This is an interesting theory of calcification from a chemical standpoint. Freudenberg and György emphasize the importance of a normal reaction in order that calcification proceed physiologically. If the reaction is too acid, as they believe to be the case in rickets, the series of changes will be interfered with, as the increased acidity will prevent the precipitation of the calcium salts. In general, they believe that metabolism in rickets has a tendency to proceed in a direction which tends to abnormal acidity, owing to the fact that there is a lowered metabolism of the tissues. From this point of view the theory coincides with the old conception of rickets as resulting from, or being associated with, an increased production of acid. This physico-chemical hypothesis has been and probably will continue to be of value as a basis for discussion and experimental investigation. It should be borne in mind, however, that it has never been shown that in rickets the bones or the cartilage have an increased acidity. In fact Bosányi has stated (1927), as a result of colorimetric estimations, that the cartilage is more alkaline in this disorder, having found the pH to be 7.6 in rickets and 7.2 to 7.0 in normal cartilage. As mentioned above, the theory has been severely criticized by Rabl. It does not tell us how rickets develops, and even if we grant that the chemical process goes on in the three distinct phases which are suggested, it is clear that these equations leave the question of the underlying cause of the abnormal calcification entirely unconsidered.

According to the theory just outlined, rickets must be a disturbance of the first stage of the process, as we know that this disorder is characterized by a failure of the cartilage protein to become united with calcium. Within the past few years Robison and his collaborators have promulgated a theory to account for the lack of calcification on the basis of *a deficiency of a ferment—a phosphatase.*

This action, if adapted to the formula of Freudenberg and György, would take place in the second phase. Briefly stated, Robison believes that the precipitation of calcium phosphate in the matrix is due to a phosphatase which acts on the hexose-monophosphate of calcium and frees the PO_4 ions. He found a ferment of this nature in the epiphyseal junctions of bones, especially those in which calcification was taking place. Without doubt the determination of this ferment in cartilage is an interesting observation, especially as it presents a physiological point of view. It should be borne in mind that we have no knowledge of the substratum upon which this ferment acts. Furthermore, in view of the fact that Bosányi, as well as Robison himself, has shown that this phosphatase may be found in almost all tissues and that it is present in greater concentration in rachitic than in normal cartilage, it cannot be accepted as playing a determining rôle in the lack of precipitation of calcium in this disorder.

In this connection it may be mentioned that Bosányi (1925) hypothecates a deficiency in the cartilage of an antirachitic substance which is formed and contained in the marrow. He found this substance in the marrow of normal bone and failing to find it in that of rachitic bone, concludes that "this hypofunction is the primary cause of rickets." Without going minutely into the chemical constitution of this antirachitic factor, it may be stated that it is water-soluble and can be extracted from the spongiosa as well as from the marrow. Bosányi bases his claims on feeding tests on animals. Little can be stated in regard to the significance of this study before it has been confirmed by further investigators. It is, however, interesting in the light of Marfan's conception of rickets as being due to a lack of function of the marrow and associated with a disturbance in the formation of red cells and hemoglobin.

Iversen and Lenstrup in 1919 and Howland and Kramer somewhat later, showed for the first time that rickets is associated with a definite chemical alteration of the blood, that *the concentration of inorganic phosphorus is decreased*, the serum calcium being maintained approximately at the normal level. This fact must be regarded as one of the strongest arguments in favor of the theory that whatever may be the failure at the site of calcification, a systemic factor plays a rôle in the disturbance. Howland and Kramer suggested that the important factor in relation to calcification is not so much the concentration of calcium or inorganic phosphorus, as the product of these two factors in the blood. When this multiple is expressed in milligrams per cent, then, according to this theory, a product of 40 or more indicates that rickets is either absent or that healing is taking place, but when the product is 30 or less, the normal process of calcification has failed and rickets is developing. In general this categorical statement holds good, but it cannot be

accepted absolutely, for the rule is by no means without its exceptions. In the course of experimental rickets in which a large number of chemical analyses of the blood have been carried out, we have observed from time to time that rats which had received the Sherman-Pappenheimer low-phosphorus ration had "a product" characteristic of rickets, but that microscopic examination revealed osteoporosis and not rachitic lesions. Clinically I have met with a few similar experiences. The converse occurs more frequently. In other words, the "product" of Ca x P may be well within or even exceed the normal limits and a rachitic process nevertheless develop. About a year ago I had in my wards a case of this kind which was followed carefully for a period of months:

The baby was a triplet, aged two months, which was admitted without any signs of rickets. Within a period of two months, in spite of receiving cod-liver oil, it developed marked craniotabes, very definite beading of the ribs, and signs of mild rickets and osteoporosis by the Roentgen ray. At four and a half months of age it weighed $8\frac{3}{4}$ pounds (4 kg.), and at five and a half months it weighed about $10\frac{1}{4}$ pounds (4.7 kg.). In spite of the rickets, which showed no signs of healing until it was six and a half months old, the calcium concentration was 10.1 and the inorganic phosphorus 6.3 mg. The rachitic signs persisted until irradiated ergosterol was given, when the signs began to diminish, the craniotabes disappearing within a fortnight. This case is recorded in a recent paper on irradiated ergosterol published with Dr. Lewis.

Still more recently, I have observed a small series of infants who had received dried milk, which had been insufficiently irradiated, or inadequate amounts of cod-liver oil. Several of this group showed definite signs of rickets clinically, as well as by the Roentgen rays, but had normal concentrations of calcium and inorganic phosphorus in the serum.

The Ca x P multiple takes no cognizance whatsoever of the condition of the cartilage or of the bone trabeculæ. It also fails to take into consideration the state of the calcium and of the phosphorus in the blood—whether it is ionized or filterable to a greater or less degree, and whether it is transitory or permanent. Clinical experience has shown, however, that in the main it is a workable formula.

One of the most interesting advances in connection with the development of our knowledge of rickets has been *the in vitro calcification test* suggested by Shipley in 1924. This is a great advance over the early experiments of Pfaundler and of Wells in this field. This test may be stated to have demonstrated the ability of rachitic cartilage to calcify, provided a sufficient amount of bone-forming salts is furnished in the medium. It was found that when a section of epiphysis of a rachitic rat was immersed in serum and incubated for forty-eight hours, calcification came about

in the proliferating zone of cartilage if the concentrations of calcium and inorganic phosphorus were within normal limits. If, however, the product of the concentrations of these components was less than 35, calcification failed to come about. This method is interesting not only as visualizing a process concerned with fractions of a milligram of calcium and phosphorus, but provides a simple method of studying calcium precipitation from a biological point of view. In 1926 the method was extended by Shipley, Kramer and Howland, who showed that the same test could be carried out by employing a medium of bone-forming salts instead of serum, and that a solution of inorganic salts, artificial serum, either brought about or failed to bring about calcification according to whether or not conditions were favorable. One of these conditions is the reaction of the solution. The optimal pH is between 7.25 and 7.35; if the solution is too acid calcification does not take place, if too alkaline, precipitation instead of calcification occurs.

It would seem that an experiment of this description must be interpreted as showing that humoral factors play a rôle in calcification, for with this technique local conditions in the cartilage are maintained constant. There are, however, dangers inherent in *in vitro* tests which preclude their unqualified acceptance as the counterpart of biological processes. In this instance, it may be mentioned that the fact that calcium and phosphorus are absorbed by the cartilage at a restricted site, "the line test," and not laid down diffusely throughout the cartilage has not been satisfactorily explained. Ulrich has just published an interesting paper on pathogenesis, in which he attributes the phenomenon of the line test to artificial conditions, to the fact that the rats have been receiving rations which are exceptionally high in calcium. In a series of tests in which he noted "the avidity" of bone for phosphorus, by placing sections in a solution of sodium phosphate, he found that the bones of rachitic infants showed a distinct lack of avidity for inorganic phosphorus as compared to normal bones. In other words, they reacted quite differently from the bones of rats and showed a distinct local inhibiting factor.

Holt, LaMer and Chown, in a study published in 1925 claim that blood serum is supersaturated normally with tertiary calcium phosphate to the extent of more than 200 per cent and that this state has marked biological significance. In a paper published at the same time, Holt concludes that "the degree of supersaturation is a factor of the greatest importance in governing the deposition of $Ca_3(PO_4)_2$ from fluids containing the salt in solution. The reduced degree of supersaturation of the blood serum in active rickets is found so consistently and is of such magnitude, that it is difficult to escape the belief that this is the immediate factor which hinders the deposition of $Ca_3(PO_4)_2$ in the bones in rickets. On the other hand,

it should be emphasized that this is not necessarily the only factor influencing the deposition of this salt." However, Sendroy and Hastings have derived formulas from calculating the activities of Ca^{++}, $PO_4^{\equiv}$ and HCO_3^- from the solubilities of their salts at varying ionic strengths and reactions in aqueous solutions, and were unable to demonstrate the high degree of supersaturation of serum reported by Holt, LaMer and Chown, their values for the true activity solubility product of $CaCO_3$ and $Ca_3(PO_4)_2$ differing considerably.

It is possible that there may be not only stimulating but *inhibitory local factors*. As pointed out by McCrudden and others, magnesium is present in excess in the bones in osteomalacia. It is of interest in this connection to note that Kramer, Shelling and Orent have found that "magnesium ions exert an inhibitory effect upon calcification *in vitro*" and that "the increase in magnesium which suffices to inhibit *in vitro* calcification might conceivably occur in the body fluids." These experiments illustrate the possible action of both local and systemic factors in connection with calcification. Still more recent experiments of these investigators furnish further examples of such activity. They conclude: "We have shown that the reaction of the solution is one factor that determines calcification. There is an optimal reaction, that of normal blood serum. An increase in the total ionic strength of the solution, whether produced by increased amounts of sodium chloride or potassium chloride, inhibits calcification. This inhibition occurs at lower concentration of sodium chloride or potassium chloride if the concentrations of calcium and phosphate are also lower. Calcification occurs more readily in the absence of magnesium. The inhibitory effect may be due either to the toxic effect of magnesium ion upon cartilage cells, or the formation of an unionized magnesium compound."

In 1910 Lehnerdt published a monograph entitled: "Why Does the Rachitic Bone Remain Uncalcified?" After a full discussion of the subject, he could come to no conclusion. We are much in the same position today, in spite of the fact that we have at hand a large mass of data furnished by animal experiments. The outstanding observation in connection with pathogenesis is the knowledge that the inorganic phosphate content of the blood is almost regularly diminished in rickets. As stated, this fact does not give information as to whether the deficiency comes about as the result of lack of absorption or of increased excretion. But to some extent it does explain why we encounter rickets under certain conditions and not under others. For example, in osteoporosis, a disorder of bone closely allied to rickets, the percentages of calcium and of phosphorus in thes blood are approximately normal, and we now can understand why we meet with a different pathological picture. Unfortunately, a study of the blood does not inform us as to the underlying differ-

ences between the two conditions, as to why osteoporosis rather than rickets develops on a dietary deficient in lime. This information would be of great assistance to our understanding of rickets. Unless, therefore, we are to infer that the low percentage of inorganic phosphorus in the blood is of no moment in osteogenesis, we must conclude that there is a systemic factor in connection with the development of rickets. However, we must not be arbitrary in our interpretation of this phenomenon, for, as stated, there are undoubted cases where rickets develops in spite of the fact that the concentrations of calcium and phosphorus are normal and others where it does not develop in spite of the fact that these substances are markedly deficient. It may be that they are in an abnormal physical or chemical state, but of this we have no knowledge.

Although it seems evident that rickets cannot be explained merely on the theory of a local inhibition or retardation of calcification at the epiphyses—the conception of rickets as a general metabolic disorder, as well as the diminution of inorganic phosphorus in the blood, is quite out of harmony with such a restricted point of view—it seems to me that local factors at the site of calcification also come into play. The fact that rickets occurs in infants with a normal content of calcium and inorganic phosphorus leads to this interpretation.

The entire process of calcification, involving as it does so many factors which may be favorable or unfavorable—the action of various ions, the diffusion of different compounds of calcium and phosphorus, the important consideration of whether the atoms are free or bound, whether the salts are hydrolyzable or not, are only a few of the factors to be considered. Furthermore, there can be no doubt that the colloidal substratum is important in the process of calcification. Today a theory which is advanced by capable workers, and which for the time being seems promising is shown to be untenable tomorrow by other workers in the same or cognate fields. It seems the better part of wisdom to suspend judgment temporarily. Perhaps when we understand something of the way in which activated ergosterol and ultra-violet energy exert their protective or curative action, new light will be shed on this difficult problem. It is probable that before we reach an understanding of the pathogenesis of rickets and other pathological conditions of bone, we shall have to gain a fuller knowledge of the processes involved in normal ossification. However, events may prove otherwise. In the light of the experience of the past ten years it would be unwise to predicate the necessity of logical sequence in connection with the evolution of our knowledge of rickets. We have only to bear in mind our recent experiences in regard to ultra-violet light—the empiric demonstration that these rays are of specific preventive or curative

value was made without the slightest understanding of the mechanism of their action.

Possibly the whole question of calcification in relation to rickets will have to be considered from a new point of view. Today we regard rickets as a circumscribed and sharply-defined pathological entity. As will be brought out elsewhere from time to time in connection with the consideration of pathology, symptomatology and treatment, the question is by no means settled as to whether osteoporosis—to mention but one disorder of the bones—is a condition essentially different. Korenchevsky has pressed this broader point of view, believing that these two disturbances in bony structure are differentiated merely by differences in rate of growth. It will be remembered that the specific curative agents, ultra-violet radiations, cod liver oil and activated ergosterol, exert their specific action in both conditions. As stated at the outset, the field of pathogenesis is at present the most promising for the study and investigation of rickets. It is also the one about which we know least. Its ultimate solution rests in the hands of the trained clinician rather than in those of the biologist.

CHAPTER VI.

METABOLISM.

Investigations of the chemical disturbances involved in rickets date back to about the middle of the past century. It is true that various hypotheses of a chemical nature were put forward previous to that time, particularly the "acid theory of rickets" which held sway until the end of the eighteenth century and became well entrenched through the authority of the illustrious van Swieten, but these theories were based on chemical surmises rather than on analyses. The first scientific work in this field was carried out in Germany and is associated with the names of Bibra and Friedleben, just as the earliest studies of the microscopic pathology of rickets are associated with two German investigators, Koelliker and Virchow, who carried on their work at about the same period. The early chemical investigations were of a simple nature and consisted in an attempt to explain the evident differences in consistency between normal and rachitic bones. What was the explanation of the marked softening of the bones in rickets so frequently noted by clinicians or, as Friedleben framed the question for himself, what is the physical and chemical constitution of growing and rachitic bones in early childhood? Studies with these questions in mind have been carried out intermittently to the present day, and although a great deal of information has been collected during this period of about seventy-five years, there is still a lack of unanimity in respect to certain aspects of even this elementary problem. In general, it may be stated that we have a satisfactory conception of the crude chemical differences between normal and rachitic bones, although we have as yet no conception whatsoever of the form in which the chemical constituents are bound one to another, in other words, of the chemical combination in which they exist within the living tissue.

Attention was soon directed to a study of the calcium requirement of the normal infant, in order to ascertain the intake necessary to supply a sufficient amount of this salt to the growing bones. It was not, however, until about twenty years ago that investigations of the metabolism of the rachitic infant were undertaken, studies including estimations of the calcium content of the food, of the urine and of the feces. This period of metabolic study, begun in 1907 by Rothberg of Czerny's clinic, reached its height in Germany just before the World War. It is associated more particularly with

the names of Schabad, Schloss and Dibbelt, whose premature deaths constituted a severe blow to the advancement in our knowledge of rickets, of Orgler and of Stoeltzner, and is being continued at the present time by Telfer and the Glasgow school. Until 1910, when Schabad pointed out the importance of phosphorus in the metabolism of rickets, investigations were limited almost entirely to ascertaining the balance of calcium. Since that time a vast literature has accumulated, which is most involved and confused, the conclusions drawn from apparently similar investigations often being in flat contradiction to one another.

It is important to bear in mind that the bony skeleton contains approximately 97 to 98 per cent of the total calcium of the body. This means that net losses or gains of calcium correspond in general to similar alterations in the bones. Aron and Sebauer showed that this principle held true for animals fed on a diet deficient in calcium—the loss was almost entirely in the skeleton, the amount of calcium in the muscles remaining unchanged. A similar deduction does not hold, however, in regard to losses of phosphorus, of which about one-third lies outside of the bony frame—in the muscles, glandular organs, etc. This, however, is a crude conception of the chemistry of the body, for we know, from a physiological point of view, that the distribution and functioning of substances are of importance rather than their absolute quantities.

THE CHEMICAL CONSTITUENTS OF BONE IN RICKETS.

In investigations of the underlying changes in rickets it was but natural that attention should be directed first to the chemical constitution of bone. For many years such studies were confined to analyses of the total ash and of the amount and percentage of calcium in the skeleton. Some doubt has been cast on the reliability of these early analyses on the ground that the bones were incompletely dried or were subjected to a degree of heat which converted the organic into inorganic material, as well as that the entire bone was not analyzed but merely the compact layer. Phosphorus was left quite out of consideration. Subsequent studies have shown, however, that the relation of calcium to phosphorus in bone is practically constant under all conditions—whether normal, rachitic or scorbutic, in osteoporosis, in various diseases involving the bones and even in metastases. There is even no change in ratio during the course of starvation, which is associated with acidosis and a marked diminution in the ash of the bones. Schabad claimed that, relative to calcium, rachitic bones contained more phosphorus than normal, but this difference has not been found by other investigators; such a distinction would have marked chemical significance.

For the present it must be considered that in rickets the ratio of calcium to phosphorus remains constant and that figures for the one can be computed in terms of the other. Schabad gives the ratio of CaO to P_2O_5 as about 100 to 70 or 75. According to Gassmann not only is the relation between calcium and phosphorus constant but also that of $Ca:PO_4:CO_3$, a fact which would indicate that the inorganic chemical constituents exist in a similar complex in rachitic and in normal bone. This is one of the questions which requires further elucidation.

As is well known, *the fetus* contains very little calcium until the fifth month, and acquires its store during the last two or three months of intra-uterine life. This important phenomenon was brought out clearly some twenty-five years ago by Camerer and Soeldner and has been corroborated again and again. The rapid influx is well illustrated in the accompanying graph (Fig. 10).

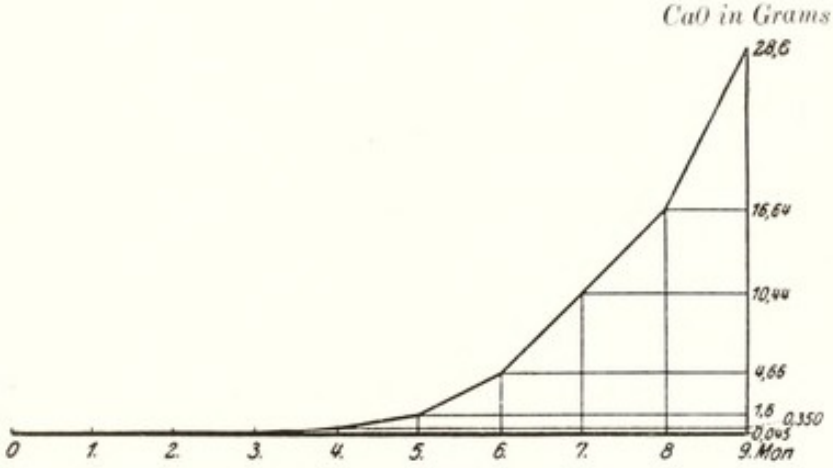


FIG. 10.—Calcium content, month by month, of the body of the fetus. (E. Schmitz, Archiv. f. Gynäk, 1924. Julius Springer, Berlin.)

Data in regard to the calcium content of the fetus are variable up to the fifth month and not of absolute value, but are fairly reliable after this period. It may be noted that at the end of the sixth month the fetus contains but 4.5 gm. of CaO, whereas at the end of the ninth month the total has risen to about 28.5 gm. The latter figure bears close comparison with Vierordt's approximation of 25 gm. and Brubacher's of 26 gm. CaO for the new-born infant. In terms of percentage we may accept Aron's generalization to the effect that the body of the new-born infant contains about 1.25 per cent of CaO and not less than 1 per cent.

Incidentally, this sudden accession of calcium toward the end of gestation suggests the importance of prematurity in the development of rickets. Although the marked susceptibility of *the premature infant* is not to be attributed solely to a comparative lack of

calcium in its skeleton, nevertheless there is no doubt that this deficiency at the seventh and eighth month is an important factor. Furthermore, calcium and total ash content run parallel. Where there is a decrease of the one, there is always a similar decrease in the other, so that a lack of calcium in the premature infant is associated with a comparative degree of osteoporosis. Camerer and Soeldner found the ratio of calcium to ash as 37.9 to 100, and Schmitz, on whose figures the accompanying graph is based, gives an average of 38.5 gm. of calcium per 100 gm. of ash.

In this connection it may be mentioned that the body of the premature infant is poor not only in calcium but in iron. Hugounenq found that during the last three months of intra-uterine life the fetus gains more than twice as much iron as during the entire previous period of its existence. This deficiency of iron is mentioned in view of the not infrequent association of rickets with anemia, as well as on account of the close physiological relationship between calcium and iron.

Not only is there a marked difference in the calcium content of the fetus at various months, but the amount in *the new-born infant* is subject to wide variations. This point must be emphasized, for many investigators, including Aron, Schabad and Dibbelt, have constructed tables of the calcium requirement of infants, basing their calculations on the existence of a constant level at birth. Camerer and Soeldner analyzed the bodies of 6 infants and found the CaO to vary from 0.70 gm. to 1.30 gm. per 100 gm. of body substance, which coincides very well with Hamilton's figures of 0.8 to 1.3 gm. per cent. Some of the variations in analyses are due no doubt to differences in the amount of fat in various infants. Orgler, however, calculated the figures in terms of fat-free dry matter and found them to vary from 4.74 to 8.04 gm., in other words, almost 100 per cent. Clinical experience teaches us that calcium cannot run parallel to body weight. The very fact that new-born infants vary so strikingly in the amount of subcutaneous fat, that some are long and thin and others short and plump, must indicate a marked difference in the ratio of the weight of skeleton to that of body weight. Not only does the calcium content of the infant vary greatly at birth, but this variation tends to increase owing to differences in diet, in the supply of the antirachitic factor and of light, in the assimilation of food, and other circumstances associated with the first year of life.

Analysis of the bones is a simple and valuable method for ascertaining the changes which have been brought about by rickets. The significant *characteristics of rachitic bones* are their relative increase in water, their decrease in total ash, and lessened content of calcium and phosphorus. Instead of ash in the dried bone bearing the normal ratio to organic matter of 3 to 2, the ratio may be reduced

to 1 to 4. All these changes are well illustrated in the accompanying table which was prepared by Orgler from the data of Schabad.[1]

TABLE 10.—ANALYSES OF NORMAL AND OF RACHITIC BONES (SCHABAD).

	Normal.		Rachitic.	
	Rib.	Occiput.	Rib.	Occiput.
Water	14.4–32.9	13.0–16.1	42.4–66.4	29.0–35.9
Organic matter	26.9–39.1	32.2–36.5	20.7–27.4	26.1–31.6
Ash	40.2–46.6	47.6–51.7	7.9–32.0	34.3–40.6
CaO	21.7–25.3	26.3–27.9	4.2–16.8	19.0–24.1
P_2O_5	12.3–18.9	18.1–20.7	3.3–12.8	13.7–17.8

Similar alterations exist in the cortex and spongiosa of the bones, as well as in the epiphyseal cartilages (Brubacher). No difference has been found in the potassium or sodium content of the bones in rickets. However, numerous investigators have reported an increase in magnesium. Gassmann, for example, gives the figure of 0.1 per cent for normal bone and 0.53 per cent for rachitic bone, and states that there is a similar increase in the teeth. In an excellent study on bone metabolism McCrudden reported an increase in magnesium in osteomalacia in contradistinction to rickets.[2]

There is little to add in regard to the calcium or phosphorus content of *tissues other than bone*. Some years ago Aschenheim and Kaumheimer reported a decrease of calcium in the muscles in cases of severe rickets. This result has, however, not been confirmed and therefore must await further investigation. Although the percentage of calcium in the soft tissues is comparatively small, it is highly important from a functional standpoint, as attested by the rapid development of tetany and muscular twitching following a decrease in the blood serum of 3 or 4 mg. per 100 cc.

THE CALCIUM REQUIREMENT OF THE NORMAL INFANT.

Instead of employing analyses of dead bone in order to gain an insight into the relation of calcium to bone formation and to rickets, balances of intake and output have been carried out to ascertain *the requirement and retention of calcium*. Such figures have been obtained for normal as well as for rachitic infants. To accomplish this task would not seem to be very difficult. As a matter of fact, although studies of this kind have been carried out for about

[1] Attention should be called to the marked latitude in the range of water content of normal as well as of rachitic ribs. It is probably due to this extreme variability that Gassmann found a comparative decrease, rather than an increase, in water in the ribs of a rachitic infant eighteen months of age. He found an increase of 5 per cent in the organic matter of rachitic bones.

[2] It is perhaps worth noting that in a case of osteogenesis imperfecta, Sindler found that the bones contained about three times as much magnesium (14.86 compared to 4.94 gm. MgO) and about fourteen times as much sodium (60.75 compared to 4.35) as the corresponding bones of a normal child.

thirty years, they have not yet yielded satisfactory results on account of the large number of complicating factors involved. One of the first inquiries, naturally, was in regard to the amount of calcium required by the normal infant to maintain equilibrium on a diet consisting of human milk or of cow's milk. Unexpected difficulties have been encountered even in this apparently clear-cut problem. More or less satisfactory data of this kind have been obtained in relation to woman's milk, but we still are lacking normal standards for a diet of cow's milk.

There is general agreement in regard to the calcium content of woman's milk, although it is certain that, for unknown reasons, this factor varies. Orgler gives figures of 0.35 to 0.4 gm. CaO per liter, Schabad 0.36 to 0.47 gm. Schloss found that the average amount of breast milk consumed contained about 0.3 gm. of CaO, the highest figures being 0.365 and the lowest 0.214 gm.[1] With the figures of 0.35 to 0.4 gm. as a mean, Orgler has estimated that *the average requirement of calcium of a breast-fed baby is 0.13 to 0.17 gm. CaO per day.* Schabad demands the higher figure, namely 0.17 gm. As a matter of fact, this standard must necessarily be elastic, as it is subject to a great many variables. For example, if the skeleton is insufficiently provided with calcium at birth, the requirement during the first months of life will be proportionately increased; a similar variability holds true in regard to growth in length—rapidly-growing babies necessarily requiring more calcium than those whose growth is less intense. There is the further factor of sunlight which until recently was unsuspected, but is now known to play such an important rôle in the retention of calcium and phosphorus that there can be no doubt that a baby which gets out-of-doors will retain far more calcium than one which is kept indoors. Furthermore, we now know that the correlation of the various salts, and probably of the organic substances as well, is an important factor in the utilization of calcium. If we bear in mind that there are various modifying factors, the extremes set by Orgler—0.13 to 0.17 gm. CaO—are sufficiently far apart to include most cases. In the course of these studies of the breast-fed baby, it has been found that about 70 per cent of the calcium of woman's milk is retained. Again this figure is subject to qualification, for retention will vary in proportion to the needs of the infant. If a large supply of milk is provided and comparatively little calcium is required for the bones, the percentage of retention will be considerably

[1] Berg states that women living in the country districts of Italy have an exceptionally large amount of calcium and phosphorus in their milk, and that this distinction obtains in general between the women of the city and those of the country. If this observation is correct, it is of significance not only in regard to rickets but as to the effect of urban life on function and metabolism. It may be added, however, that Telfer found in Scotland that the milk of the women in the rural districts contained a comparatively low percentage of calcium.

less than where conditions are reversed. Holt, Courtney and Fales give a retention value of 66.7 per cent, and Blauberg in his well-known case, which since 1900 has formed the basis of most calculations, found a retention of about 65 per cent.

The figures for the calcium content of woman's milk can be accepted only tentatively as the physiological norm, in view of the fact that breast-fed babies not infrequently develop rickets. In an investigation carried out some years ago I found that during one winter one-third, and during another even one-half of a group of well-nourished babies nursed by apparently healthy mothers developed unmistakable signs of rickets. It is in fact the overfed nursing baby, with a large intake of calcium, which most frequently develops rickets. We must always distinguish between the hypertrophic type of rickets occurring in the well-nourished infant, and the atrophic type which may be associated with osteoporosis. In this connection, it may be called to mind that the calcium content of woman's milk stands in an exceptional relationship to the total ash of the body of the infant. Bunge and Abderhalden have shown, that, whereas in the case of most animals, for example the dog, there is an approximation between the percentage of calcium and of phosphoric acid in the milk and in the bodies of the young, in man there is a marked deficiency in the milk—its calcium content per 100 gm. ash being approximately 14.8, and that of the offspring 33.5, the respective figures for phosphoric acid being 21.3 and 37.7.

When we turn to *the requirement of the artificially-fed baby* conditions become far more complicated. In the first place, the fact that cow's milk is not generally given undiluted renders interpretation difficult. In the various metabolic studies of normal babies, the diet has been by no means uniform. As stated, in almost all cases the milk has been diluted, in some instances with water, in others with cereal decoctions, to some formulas cane sugar has been added, to others maltose or milk sugar, and where "malt soup" has been fed the mixture included additions of flour and alkali. These supplements changed the chemical constitution of the milk, frequently altering its reaction, and must have affected absorption and retention. Moreover, the fat content of the diets varied greatly, even granting that the original milk was uniform in this respect. As will be discussed in detail elsewhere, calcium absorption is markedly influenced by the percentage of fat in the diet. But the difficulties in determining the calcium requirement extend beyond these various differences in the composition of the milk formulas, as even where undiluted milk was given, for some unknown reason, the retention of calcium was by no means the same. Let us take two cases, one of Blauberg and one of Cronheim and Müller, of infants of the same age, about six months—the former received approximately 2 gm. of calcium and the latter 1.5 gm. daily. Whereas

the former retained 0.92 gm. of calcium, the latter retained but 0.11 gm. It is evident that some important factor is left out of consideration in these metabolic tests. Orgler gives as the average normal retention 0.17 to 0.18 gm., demanding a retention of 0.12 to 0.13 gm. in order that rickets shall not develop, and believes that retention is the same in bottle-fed as in the breast-fed infant.

Schabad has placed retention at 30 per cent and Holt and his coworkers at 45 per cent. The latter figure, however, should be somewhat lower as no account was taken of the calcium excreted in the urine and as the 30 cases which comprised the group included 2 which were receiving cod-liver oil. In general, it may be stated that there are marked discrepancies in the figures and that averages have been computed from data which included retentions so low that, if we grant that rickets was not present, the figures must represent merely a temporary condition. If we accept the figure of 30 per cent, it means that the retention of the calcium of woman's milk is about two and a half times greater than that of cow's milk. As the latter contains about four times as much calcium, it would become, when diluted one-third, the equivalent of woman's milk.

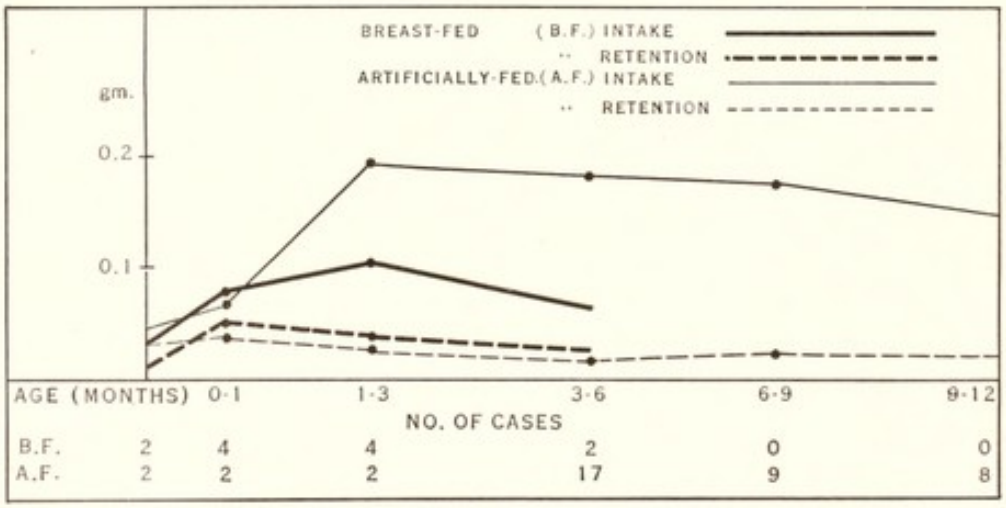


FIG. 11.—Average CaO intake and retention (per kilo body weight) of healthy infants, of various ages, fed on human and on cow's milk. (Findlay, Paton and Sharpe, Quart. Jour. Med., 1921.)

THE PHOSPHORUS REQUIREMENT OF THE NORMAL INFANT.

Before considering the phosphorus requirement of the normal infant, it should be borne in mind that 25 to 30 per cent of the phosphorus of the body is contained in tissues other than the bones, which implies that the phosphorus which is excreted may originate from the soft tissues, and in turn that phosphorus which is withdrawn from the skeleton may be taken up by the muscles and glandular organs.

As in the case of calcium, the phosphorus requirement must be considered separately for the breast-fed and the bottle-fed infant. Studies of the former date back to the earliest period of metabolism in pediatrics, to the case which Blauberg reported in 1900. This baby was aged five months and received 0.203 gm. P_2O_5 in its food and retained 0.093 gm. or about 46 per cent. The same year Keller reported a study which included the case of a breast-fed infant aged two months, weighing 4350 g. On an intake of 0.325 gm. P_2O_5 daily, 81 mg. P_2O_5 (35 mg. P) per kilogram of body weight, 54 per cent was retained. A report by Tobler and Noll should be mentioned as it is frequently cited on account of the exceptionally large retention on a small intake of phosphorus. The baby was breast-fed, aged two and a half months, and received only 0.051 gm. P_2O_5 (0.022 gm. P) per kilogram body weight. Of this amount it retained 56.5 per cent. It may be added that Michel has published data of new-born infants in which retention was as high as 87 per cent. Such high percentages are to be expected where the intake is exceedingly low.

Turning for a moment to the artificially-fed infant, we find irregularities in regard to phosphorus similar to those encountered in connection with the requirement and retention of calcium. For example, in 1907, Bruck published an account of two infants, one aged three months and the other aged eight months. The intakes of phosphorus were respectively 0.212 and 0.260 gm. P_2O_5 (0.093 and 0.114 gm. P) per kilogram body weight. Of these amounts 23.5 and 26.3 per cent were retained. The calcium retention was 45 per cent. It should be mentioned that the periods of collection were only three and four days in this study and that the diet consisted of milk, gruel and malt. Another report on artificially-fed infants is that of Birk (1909), carried out as controls in connection with his well-known study of phosphorized cod-liver oil. The 4 infants each received the equivalent of over 4 gm. of phosphorus a day, and were followed for periods of three days. The retention of phosphorus was 21, 18, 32 and 17 per cent, that of calcium 43, 20, 44 and 24 per cent. Birk concludes that 20 to 30 per cent of the intake of phosphorus is retained in the artificially-fed baby. Retention occasionally may be beyond these limits as in a case reported by Keller which showed 37 per cent retention. In valuable observations on 3 infants which were breast-fed and later received the same quantities of cow's milk which had been diluted with two parts of water, Keller (1899) showed that the loss of phosphorus during the second period was quite out of proportion to the higher content of phosphorus contained in the cow's milk. *The phosphorus in human milk is retained far better than that in cow's milk.* It has been shown, however, by Blauberg and by others that if a large amount of phosphorus is given in the form of cow's milk, the absolute retention,

in contradistinction to the percentage, is greater than can be brought about by feeding woman's milk.

The path of excretion of phosphorus is of special interest. In this same paper, published thirty years ago, Keller observed that the path is different in the breast-fed from that in the bottle-fed infant. The urine of the healthy, breast-fed infant contains almost no phosphorus. Moll, who later greatly extended these observations, stated that the normal amount varies between 10 and 20 mg. of P_2O_5 in twenty-four hours and that higher figures are to be regarded as pathological. The excess in the bottle-fed baby is beyond what can be accounted for by the relatively large amount of phosphorus contained in cow's milk. It has been suggested that it is derived not from the phosphorus of the food but from the proteins of the body, the intestinal secretions and the bones, and that it runs parallel to the nitrogen excretion.

THE CALCIUM AND MAGNESIUM METABOLISM OF THE RACHITIC INFANT.

When we turn to a consideration of *infants suffering from rickets,* we are presented with a mass of material which it is impossible to appraise. Until 1908, when the paper of Cronheim and Müller appeared, no study on the metabolism of rickets included a full report of the phosphorus exchange. It was deemed sufficient to determine the output of phosphorus in the urine. In view of the fact that a large part of the phosphorus is excreted in the feces, such studies are of little value in determining the phosphorus retention. The first step is to attempt to cull the cases of active rickets from the large number where there is a possibility that healing was taking place. Future investigators will have an advantage in selecting their cases; they will be able to subject them to the control of radiographs and chemical examinations of the blood. There are hardly any such studies available at the present time. Recently Hoag, Rivkin and their collaborators carried out chemical tests of the blood and took radiographs in some cases in which they were investigating the effect of parathyroid extract on metabolism. In the study of Telfer, one of the very few in which radiographs were taken, the two cases which appeared normal by the Roentgen rays gave low balances of calcium and phosphorus and three months later were found to have developed rickets. Such a mishap is not surprising, for radiographic changes of the epiphyses demonstrate rickets only after it is well developed. It indicates that, in the future, greater reliance will have to be placed on the percentage of inorganic phosphate in the blood than on the radiographic picture. This inherent difficulty in studies of metabolism was recognized by Schabad, Dibbelt, Schloss and others, who met it as best they could

by discarding such control cases as showed an abnormally low retention, attributing the deficient balance to unrecognized incipient rickets—a procedure which can hardly be regarded as scientific. Greatest weight must be given to balance tests of infants between three and nine months of age, as beyond this period healing is apt to begin. Furthermore, all metabolic tests which were carried out during the spring and summer months raise the question of a disturbing action of ultra-violet light. A table, replete with data, covering all metabolic investigations of healthy as well as of rachitic infants to 1921 may be found in a paper on "Metabolism in Rickets," published by Findlay and his associates.

TABLE 11.—CALCIUM METABOLISM OF RACHITIC INFANTS ON A DIET OF WOMAN'S MILK. (AFTER ORGLER.)

Author.	Infants. Age, mos.	Infants. Weight, gm.	CaO (gm.). Intake.	CaO (gm.). Urine.	CaO (gm.). Feces.	CaO (gm.). Balance.
Peiser	1½	3850	0.270	0.029	0.238	+0.003
Schloss	1¾	3200	0.214	0.014	0.168	+0.032
Peiser	3	4300	0.335	0.036	0.287	+0.012
Schloss	3	4000	0.365	0.027	0.126	+0.212
Schloss	3	3870	0.278	0.012	0.165	+0.101
Schloss	4	4270	0.265	0.013	0.149	+0.103
Schloss	4	3650	0.282	0.017	0.196	+0.069
Schloss	4¼	4200	0.359	0.019	0.195	+0.144
Schloss	4½	3580	0.269	0.017	0.180	+0.072
Birk and Orgler	4½	3440	0.210	0.009	0.130	+0.071
Schabad (*a*)	5	5870	0.345	0.014	0.185	+0.146
Schabad (*b*)	6	6410	0.324	0.014	0.226	+0.084

Calcium metabolism in the course of rickets is well illustrated by the accompanying tables, which were compiled by Orgler. Table 11 shows the balances in infants under six months of age who were receiving nothing but woman's milk. It will be noted that in none of the cases was there a negative balance, merely an insufficient retention. The Table 12 comprises data concerning infants under nine months of age who received various preparations of cow's milk. Some of these did show a negative balance, more especially those who were fed a milk preparation rich in fat. The Table 13 of this series depicts the well-known case of Birk and Orgler, one of those rare clinical coincidences which is met with from time to time. These investigators were studying the metabolism of an apparently normal premature infant, aged one and a quarter months, and found that in spite of the large content of calcium in the food it showed a negative balance of calcium. There were no symptoms of rickets. They carried out two further metabolic periods and noted the development of signs of rickets between the second and third period. The case is interesting in view of the fact that it is perhaps the only instance in which the evolution of rickets has been followed from a metabolic standpoint, as well as because the balance of

calcium was less—in fact it was negative—before the symptoms of rickets had developed clinically than in the later period when it was apparent.

TABLE 12.—CALCIUM METABOLISM OF RACHITIC INFANTS ON COW'S MILK, ETC. (AFTER ORGLER.)

Author.	Infants.		Nature of diet.	CaO (gm.).			
	Age, mos.	Weight, gm.		Intake.	Urine.	Feces.	Balance.
Peiser	2¼	4500	"Eiweissmilch"	0.714	0.052	0.813	−0.151
Schloss	3	4180	"	0.800	0.055	0.616	+0.129
Schloss	3	4350	"	0.800	0.050	0.678	+0.072
Schloss	3¼	4900	"Fettmilch"[1]	0.426	0.015	0.351	+0.060
Schloss	3½	4820	"	0.521	0.016	0.490	+0.015
Schloss	3¾	4960	"	0.432	0.009	0.438	−0.015
Schloss	3¾	5260	"	0.545	0.028	0.636	−0.119
Schloss	4	5500	"	0.578	0.023	0.691	−0.136
Peiser	4	5000	"Eiweissmilch"	0.874	0.050	0.894	−0.070
Freund	4	..	Milk, "Mehlsuppe"	0.652	0.024	0.596	+0.032
Rothberg (*a*)	4	3800	Skimmed milk	0.847	0.016	0.729	+0.102
Rothberg (*b*)	4¼	3950	½ milk, ½ "Mehlsuppe" + malt	0.462	..	0.514	−0.052
Schloss	4½	5150	"Fettmilch"	0.573	0.019	0.694	−0.140
Schloss	4½	5160	"Eiweissmilch"	0.800	0.040	0.774	−0.014
Schloss	4½	4560	"	0.800	0.078	0.760	−0.038
Schabad	5	4300	⅗ milk, rice gruel	0.914	0.015	0.788	+0.111
Cronheim and Müller	6	4000	¾ milk, water	0.912	0.020	0.643	+0.249
Orgler	6½	6030	⅔ milk, ⅓ "Mehlsuppe" + 5 per cent sugar	1.041	0.014	0.765	+0.262
Dibbelt	7	4800	Buttermilk	1.107	0.009	1.437	−0.339
Birk	8	4020	½ milk, ½ "Mehlsuppe" + milk sugar	0.472	0.009	0.456	+0.007
Birk	8	5700	Ditto + once solid food	0.543	0.004	0.584	−0.045
Schabad	8½	7200	⅔ milk and rice gruel	0.792	0.005	0.884	−0.097
Rothberg	9	6200	⅔ milk, water	0.765	0.032	0.707	+0.026

[1] Gaertner's "Fettmilch" contains about 3 to 3.5 per cent of fat.

TABLE 13.—METABOLIC STUDY OF INFANT DURING THE DEVELOPMENT OF RICKETS. (AFTER BIRK AND ORGLER.)

Metabolic period.	Age of infant, mos.	N.	CaO.
I	1¼	+0.465	−0.187
II	2½	+0.344	+0.079
III	4½	+0.325	+0.071

The most striking feature of rickets is the loss of calcium from the body. This increased excretion occurs mainly through the feces, in fact excretion generally is decreased in the urine due to a lack of absorption from the intestine. The urinary path plays a compara-

tively small rôle in the excretion of calcium in the bottle-fed infant, 90 per cent passing out by way of the bowel; the breast-fed baby excretes normally a very much larger proportion through the urinary path. An observation of Findlay's to the effect that excretion of calcium in the stool varies practically with the weight of the dried feces is of interest and might well be of practical value to the clinician. One of the greatest contributions of metabolic studies to our knowledge of rickets is the demonstration that the disorder begins at a far earlier period of infancy than we had imagined, an observation which has been amply confirmed by careful clinical examination, and especially by chemical analyses of the blood. The chronological relationship between variations in calcium retention and variations in the concentration of inorganic phosphate in the blood has not been investigated, but would make an interesting study from the standpoint of pathogenesis. As far back as 1881, Uffelman reported a daily loss of 0.6 gm. calcium; Dibbelt had a similar experience with a three months-old baby; Birk and Orgler reported a negative balance (—0.177 gm. CaO a day) in a baby aged one and a half months, an instance that is frequently mentioned in the literature. These losses in breast-fed infants are probably due to the fact that woman's milk furnishes an amount of calcium which is only just sufficient to fulfil requirements and that slight disturbances in the metabolic balance suffice to bring about inadequate retention. Only exceptionally is the balance of calcium in rickets negative, it is what may be termed "subnormally positive," a state which persists with fluctuations for many months. Metabolic studies have been able to show likewise that an increase in retention begins before the first signs of clinical improvement. By the time convalescence sets in, in other words by the time healing is definitely recognizable by ordinary clinical methods, the retention of calcium may exceed the normal two or threefold and constitute 60 to 80 per cent of the ingested amount. This improved retention is due to a cessation of the marked excretion through the bowel, in fact the excretion by the urine becomes increased rather than decreased, following a better absorption of calcium through the intestinal tract. The convelescent period is gradually succeeded by that of complete recovery, when calcium retention becomes somewhat less and steadily falls to normal.

This is the metabolic picture of the average case of rickets. In the exceptionally severe case the calcium balance may be negative to a greater or less extent. The fact that more calcium is being lost from the body than is being taken in with the food, must indicate in these instances that osteoporosis is taking place and that Virchow's conception of rickets, as due solely to a lack of apposition of calcium, cannot be insisted upon too rigidly.

This question of *osteoporosis*, which is so difficult to define in

connection with the pathology and pathogenesis of rickets, presents similar difficulties in the realm of metabolism. Naturally, when a diet markedly low in calcium has been fed for a long period, as carried out experimentally by various investigators, for example by Dibbelt, a loss of calcium results. But such studies can have but little significance for clinical pediatrics. As stated, a condition of this kind may occur, to a very limited extent, in the nursing baby when insufficient milk is provided. We meet with it occasionally in the bottle-fed infant, although by no means so frequently nowadays as some years ago when the fear of cow's milk protein was rampant and it was the vogue to dilute the milk excessively. Schabad reports a case where rickets developed in the infant of a wet-nurse whose milk was markedly deficient in calcium, containing only 0.023 per cent. Great care must be exercised in interpreting the instances of "pseudo-rickets" in the literature. For example, we cannot accept the case of Tobler and Noll, which has become almost a classic, of a baby, aged two and a half months, which retained only 0.05 gm. of CaO daily and showed no signs of rickets at seven months; for not only was the metabolism test conducted for only six days, but there was "a severe intercurrent bronchitis and otitis media with fever lasting for weeks," and the baby was flabby and its general condition somewhat poor—a state which is opposed to the development of rickets and favors osteoporosis. Dibbelt has reported a metabolism study, which is frequently cited, of a seven months' infant which evidently was suffering from scurvy. The baby was fed on prepared buttermilk and had a positive balance of P_2O_5 of 0.0123 gm. and a negative balance of CaO of 0.0704 gm. per kilogram body weight. The nitrogen as well as the phosphorus balance was positive and the negative balance of calcium became markedly positive merely by changing the food. But we note that four weeks later "the urine was hemorrhagic and contained red cells and blood casts," in other words suggested scurvy, so that Dibbelt changed the diet from the prepared food to raw milk. Thus it is with many similar cases. But even in osteoporosis due to calcium deficiency, we have no means of judging whether the condition has resulted from a lack of absorption of calcium, or indeed whether this factor has played any rôle whatsoever in its causation. *For, as is well-known, calcium is not only absorbed from the intestinal canal, but is excreted into it.* It is evident, therefore, that the calcium in the feces represents not only calcium which has failed to be absorbed, but likewise that which has been absorbed and not utilized. We have no means of separating the two fractions and do not know even approximately the percentage of calcium which is normally excreted through the intestinal wall. In view of this situation, it is clear, especially as the alimentary tract constitutes the main path both of intake and output of calcium, that we are in no position to study the

question of absorption of calcium. A corollary of this proposition is that the calcium content of the urine is not a reliable indicator of the absorption of calcium.

The marked tendency of calcium to be excreted through the intestine rather than through the kidneys is illustrated by Grosser's study (1920) which showed that, even when calcium is injected subcutaneously, it is excreted mainly by the bowel; under similar conditions it was found, on the other hand, that phosphorus was passed in the urine, no increase being noted in the feces. This investigation was corroborated and amplified by the experiments of Salvesen on dogs (1923). He injected 3 dogs with a 10 per cent solution of calcium chloride and found that "there was excreted an amount of calcium corresponding to the amount injected, but more than nine-tenths was excreted in the feces and less than one-tenth in the urine:" *These investigations illustrate the marked divergence in the paths of excretion between calcium and phosphorus.* On the other hand, in extreme pathological conditions, for example, in some cases in adults of wasting of the bone resembling osteomalacia (Chapter XIII), such large amounts of calcium may be passed in the urine that they are evident to the naked eye and have been termed renal sand.

McCrudden and others have claimed that a retention of *magnesium* takes place in osteomalacia and Schloss has reported the same to be true in rickets. This view is supported by the analyses of Gassmann, who found an increase of magnesium in the bones of rachitic infants. There are very few data on this point, as most metabolism studies do not include an estimation of magnesium. Furthermore, the magnesium content of cow's milk is so low, about one-eighth that of calcium, and its retention only about one-tenth, that there is great danger of error in the analyses. Schueler has just published an interesting study of this question in which he discusses 13 instances of normal and 12 of rachitic infants where the magnesium, as well as the calcium balance, was determined. He is inclined to take the view of Birk that calcium and magnesium have a tendency to go in a parallel rather than in an antagonistic direction. The fact that in 4 cases of severe rickets, where the calcium balance was negative, the same held true for magnesium, is against the theory of a replacement of the losses of calcium in the bones by a deposition of magnesium. Birk's observation that in cases of rickets cod-liver oil led to retention rather than to a loss of magnesium is also against this point of view. This work has been confirmed by the recent study of Telfer (1926), who showed not only that cod-liver oil increased the retention of magnesium, but that its output in the urine was increased very considerably. However, the question cannot be regarded as settled, for the studies are too new and the evidence conflicting.

THE PHOSPHORUS METABOLISM OF THE RACHITIC INFANT.

One of the most significant changes in viewpoint has been the recognition of the importance of *the metabolism of phosphorus* as well as that of calcium. This advance is due largely to the work of Schabad and must be regarded as perhaps the greatest contribution metabolic studies have made to our knowledge of the chemical processes associated with rickets. As is true of calcium, the excretion of phosphorus is markedly increased. This is especially noticeable in the breast-fed infant which may excrete twice as much phosphorus as under normal conditions; the phosphorus in the urine at times may even exceed that in the feces. A sharp distinction must be made between the absolute amount of phosphorus excreted in the urine and its ratio to that excreted in the feces. The absolute quantity passed in the urine may remain unchanged or even become lessened, so that the normal excess of phosphorus in the urine is changed to an excess in the feces, the figures varying markedly according to the intensity of the rachitic process. As rickets develops, the excretion of calcium and phosphorus increases concurrently. There is the distinction, however, that the amount of phosphorus excreted exceeds the equivalent of the calcium accompanying it, as gauged by their well-known ratio in bone, so that the soft tissues must also be involved in its loss. As convalescence begins, there comes about both an absolute and a relative decrease in the total excretion of phosphorus, as well as an absolute and relative increase in the amount passed in the urine. The relation between the excretion in the urine and feces, which is such an important mechanism, becomes normal once more; we may have a hyperphosphaturia, in spite of the fact that there is a diminution in the total excretion of phosphorus from the body. This paradoxical phenomenon may be compared to the conditions which are typical of the active stage of rickets where, in spite of an increased excretion of phosphorus, there is a diminished amount in the urine, in other words a hypophosphaturia.

According to Schabad the characteristic metabolic feature of the active stage of rickets is the excess excretion of phosphoric acid in the stool compared to that of calcium. Under physiological conditions, fecal calcium is always greater than fecal phosphoric acid, for the calcium is bound not only to the phosphoric acid but also to the fatty acids with which it forms soaps. In the breast-fed infant Schabad found that after the phosphoric acid in the stool was fully saturated, from 35 to 77 per cent of calcium remained over, and in the artificially-fed infant, over 22 per cent on an average. In rickets, on the other hand, the phosphoric acid in the feces not infrequently exceeded its equivalent of calcium. This observation led him to conclude that the prevailing opinion that phosphorus

excretion depended upon the increase of calcium in the feces, which served merely to bind and neutralize the phosphoric acid, was a misconception, indeed a reversal of the true state of affairs. This point of view has been borne out by chemical analyses of the blood in rickets, which, as is well known, show an almost normal percentage of calcium and a marked diminution of inorganic phosphate. But this change is probably not primary, for animal experiments have demonstrated that there is no parallelism between the decrease of blood phosphorus and the intensity of the rachitic process. By a suitable arrangement of the diet rickets can be brought about with a phosphorus concentration of the blood no lower than that encountered in nutritional disorders of a non-rachitic nature. It is evident, therefore, that a lack of phosphorus is not at the root of the metabolic disturbance.

THE EFFECT OF FAT ON CALCIUM AND PHOSPHORUS METABOLISM.

Some of the earliest metabolic studies in regard to calcium and phosphorus concerned themselves with *the rôle of fat in the diet.* The first investigation of this aspect was carried out about thirty years ago by Keller of the Czerny school. He showed, what has since been substantiated by numerous investigators, that the addition of fat increases the excretion of phosphorus in the urine, decreasing it in the stool; this partition is brought about by the formation of fatty acids which combine with calcium to form soaps. The calcium is excreted in the stool as phosphate and as calcium soaps, mainly as calcium oleate, for the formation of which about 1 part of CaO is required to 10 of the fatty acid. This absorption of the calcium by the fatty acids sets free the phosphoric acid and allows it to be absorbed by the intestine, as is evidenced by its increase in the urine. In other words, the addition of fat to the diet has just the reverse effect on phosphorus as on calcium. These basic facts were substantiated a few years later by Freund[1] and are of the greatest importance for an understanding of some of the metabolic processes underlying rickets, both as to the effect of diet on calcium absorption and as regards the pathogenesis of the disorder.

The pernicious effect of an excess of milk fat on calcium retention was brought out in 1907 by Rothberg, also of the Czerny school, who clearly demonstrated that a positive balance on a diet of skimmed

[1] Freund found that sesame oil was an exception to other fats, and that it led to retention of calcium and phosphorus. This observation has not been confirmed by subsequent workers. In view of our present knowledge, the question may be raised as to whether the sesame oil which he used had not been activated by the solar rays, in a manner similar to the activation of cocoanut oil, which takes place in the course of drying the copra under the tropical sun.

milk could be converted into a negative balance by the substitution of whole milk. This important phenomenon has been frequently confirmed by subsequent metabolic tests and clinical observations. It is, however, contrary to the teachings of the older clinicians, who taught that one of the main etiological factors of rickets is a deficiency of fat in the diet. Perhaps, as Orgler states, there is an individuality in regard to the effect of fat in relation to rickets, its harmful influence on absorption holding true only for certain infants. Clinical experience bears out this observation, which indicates that there are reciprocal factors. With some of these we are conversant. For instance, the reaction within the bowel, as will be discussed later, plays an important rôle in calcium absorption, as does constipation, which tends to a loss of calcium by furthering the formation of soaps.

The consideration of milk fat raises the question of the action of butter fat. As mentioned in considering etiology, Mellanby and others believe that butter fat has a specific antirachitic action. In view of the fact that his pioneer investigation was published some ten years ago, it is surprising that more metabolic studies have not been carried out in order to substantiate this viewpoint. Recently (1926) Telfer published a test of this kind on an infant, aged ten months, to whom an unspecified amount of butter fat was given emulsified in the milk. The mineral retention remained unaltered as did the ratio between the urinary and fecal phosphorus. It should be added that when cod-liver oil was substituted for butter fat in the same amount, definite improvement resulted. Clinically it has been my experience that no reliance can be placed on the preventive or curative action of butter fat in doses which are practical from a dietetic standpoint. Telfer also carried out a test with olive oil added to the diet of a twenty month-old infant. This addition led to a fall in the retention of both calcium and phosphoric acid; the ratio of urinary to fecal phosphorus was as 2 to 2.4 before, and as 1 to 3.4 after the oil was given. According to this test, olive oil has a deleterious effect and leads to a greater excretion of calcium than does butter fat.

The complexity of this entire question becomes evident when we consider that woman's milk, which contains approximately the same percentage of fat as cow's milk, is not associated with rickets to nearly the same extent. Although, according to Holt, Courtney and Fales, 90 to 99 per cent of the fat in woman's milk is absorbed, a certain amount remains in the bowel unabsorbed—enough to constitute as much as one-third to one-half of the dried feces. Of this total fat, 43 per cent was in the form of soap which, as we know, leads to an excretion of calcium. Probably this is an important factor in the development of rickets in the breast-fed infant, an occurrence which, as we have recently come to realize, is by no means exceptional.

EFFECT OF COD-LIVER OIL ON METABOLISM.

The discovery that *cod-liver oil exerts a specific effect on phosphorus and calcium metabolism* in rickets was a notable achievement. As will be discussed in connection with its therapeutic use, cod-liver oil, although appreciated by some of the medical profession, was until recently regarded by pharmacologists and physicians merely as a highly digestible form of fat. It was first shown in metabolic experiments, undertaken by Schabad in 1909 and 1910, in connection with the study of fats in relation to rickets, that it possesses peculiar properties in regard to the utilization of calcium and phosphorus. How this activity is exerted is still a moot question. Metabolic studies were not, however, unanimous in according cod-liver oil specific calcifying properties, and it was not generally accepted as an antirachitic until some years later, when its virtues could be demonstrated objectively by means of roentgenograms of the epiphyses of animals and infants suffering from rickets.

TABLE 14.—CALCIUM AND PHOSPHORUS BALANCE OF RACHITIC INFANT. I. DIET OF BREAD AND MILK. II. COD-LIVER OIL ADDED. III. PHOSPHORUS AND "ORDINARY OIL" SUBSTITUTED. (SCHABAD.)

	I.	II.	III.
Intake (CaO)	1.404	1.072	1.260
Urine	0.0	0.0	0.0
Feces	1.337	0.607	1.388
Balance	+0.067	+0.465	−0.128
Intake (P_2O_5)	1.956	1.522	1.780
Urine	0.572	0.714	0.562
Feces	1.268	0.391	1.266
Balance	+0.116	+0.417	−0.048

When cod-liver oil is given to a rachitic infant, one of the striking changes is a return of the normal excess in the percentage of phosphorus in the urine over that in the feces. The total excretion of phosphorus from the body becomes even subnormal. These underlying phenomena were brought out by Schabad in his two classic studies. The action is therefore just opposite to that of milk fat, as is well illustrated in the accompanying table which depicts a case where the calcium and phosphorus balances, which were low on a milk diet, were markedly increased when cod-liver oil was added and became negative when "ordinary oil" and elementary phosphorus were substituted for the fish oil. As stated, this specific effect on retention has not been found uniformly, which holds true likewise for clinical observations in regard to the favorable action of cod-liver oil. Birk has shown that if the rickets is at its height and progressing, although cod-liver oil may improve the calcium balance, it is unable to raise it to the normal. Such failures may be inter-

preted in many ways—to an insufficient dosage of oil, to the lapse of too short an interval for its action to become manifest, to a comparatively inert preparation of oil, or to associated conditions of the diet or in the intestinal canal which robbed it of its efficacy.

Peculiarly enough, rachitic infants which are breast-fed do not improve as readily as those which are on a diet of cow's milk. This diminished activity is probably due to the comparative deficiency of calcium in woman's milk. In a balance experiment carried out by Schloss on a breast-fed infant, it was found that after the calcium balance had been unfavorably influenced by the addition of cod-liver oil (containing phosphorus), the calcium as well as the phosphorus balance were rendered positive by adding calcium acetate. In this connection Berg's statement is of interest, to the effect that if the calcium intake is very small, a decrease in retention may follow the use of cod-liver oil, but that if the diet contains an excess of calcium, excretion is diminished, especially the elimination by the kidneys. Schloss, who carried out an immense number of metabolic tests in connection with rickets, published similar unfavorable reports in regard to the action of cod-liver oil and, on the other hand, of the favorable retention brought about by adding calcium to the oil. It is difficult to account for these discordant results; they are, however, differences in degree rather than in principle. It is clear, however, that if we should not be arbitrary as to the invariable specificity of cod-liver oil, it would be still more unwise to attempt to generalize in regard to the manner in which it influences the paths of excretion of calcium and phosphorus; this phenomenon is very delicately balanced and is found to vary under conditions which are apparently identical. In 1926 Telfer published a study which brings out sharply the change in the path of excretion of phosphorus brought about by cod-liver oil. For example, in the case of an infant fourteen months old, which was receiving undiluted milk, the ratio of urinary to fecal phosphorus was as 1 to 1.7 before cod-liver oil was given; in other words, an excessive restriction of phosphorus to the intestinal tract. After cod-liver oil was given for a period of seven days, the ratio was almost inverted, becoming as 1.5 to 1. The change may well be illustrated by the following formula:

		Before cod-liver oil.	After oil.
Urinary phosphorus / Fecal phosphorus	=	1 / 1.7	1.5 / 1

In another instance where 6, instead of 3 teaspoonfuls daily of cod-liver oil were given, an even more striking alteration was brought about in this ratio, namely $\frac{1}{3.4}$ to $\frac{4.6}{1}$. The excretion of phosphoric

acid in the feces was reduced to about one-half that of the lime, the latter being excreted as calcium soap as shown by the great rise in the combined fatty acids. The effect of cod-liver oil in relation to the mineral elements was quite different from that of butter fat or olive oil.

For some years there was a lively discussion as to whether cod-liver oil acted by preventing the formation of soaps in the intestine and consequent loss of calcium. This would seem logical, in view of the fact that cod-liver oil tends to diminish the formation of the soap stool. It was ingeniously shown by Schabad, however, that only one-tenth or one-fifth of the calcium in the feces is bound in this way, that phosphoric acid binds the calcium to a far greater extent and that only the moiety which fails to be bound to phosphoric acid is united to the fatty acids. When cod-liver oil is given, the calcium which is bound to the fatty acids often increases while the calcium bound to phosphoric acid decreases. The soap in the stool may increase both absolutely and relatively and nevertheless be associated with a decreased excretion of calcium. Schabad and Sorochowitsch illustrated this in their study on the comparative merits of white and yellow cod-liver oil. The following are the data concerning an infant one year old suffering from rickets and tetany. It will be noted that cod-liver oil caused a diminished excretion of calcium in the feces, but at the same time an increase in the amount of soap:

	CaO.	Soap.
No treatment	1.724	2.73
White cod-liver oil	1.109	3.34
Yellow cod-liver oil	1.419	7.50

At the present time several preparations of *the unsaponifiable fraction* of cod-liver oil are being used for the prevention and cure of infantile rickets. As yet no metabolic tests have been carried out which enable us to compare the action of this fraction to that of unfractionated cod-liver oil. It should be mentioned that Hart, Steenbock and their co-workers recently found that when the unsaponifiable fraction was fed to lactating goats, it did not further calcium assimilation, but that when it was given dissolved in corn oil, a marked improvement in lime assimilation resulted. Daniels and Brooks report similar results in connection with curative experiments on rachitic rats. These studies raise the question as to whether the action of the unsaponifiable fraction is not enhanced by a menstruum of fat.

Nothing has been stated as to the site or mode of action of cod-liver oil. Some believe that its specific function is carried out within the intestinal canal by bringing about an improved absorption of calcium and phosphorus, whereas others are of the opinion that it acts on the intermediary metabolism. According to the latter

interpretation, the oil brings about calcification of the epiphyses either by direct chemical action on the bone and cartilage or through some intermediary mechanism. It is premature to discuss this question as we have not sufficient data on which to base an opinion. It may be mentioned, however, that Gutman and Franz found that following the use of cod-liver oil in animals, healing of the bones was evident before an increase in the inorganic phosphate of the blood came about. Furthermore, Hess and Weinstock demonstrated that both cod-liver oil and irradiated cholesterol (ergosterol) have a markedly antirachitic action, even when injected subcutaneously. Although this observation does not prove that the specific factor of cod-liver oil functions quite apart from the alimentary tract, it points in this direction. In my opinion, although cod-liver oil and the active principle which it contains, may increase absorption of calcium and phosphorus in the intestinal canal, its main activity is exerted in the intermediary metabolism.

EFFECT OF IRRADIATED ERGOSTEROL ON METABOLISM.

Metabolic studies on the effect of irradiated ergosterol are few and we have but little information in regard to its therapeutic action on the normal or rachitic infant. From the recent study of Warkany it would seem that this specific factor is able not only to augment the inorganic phosphorus of the blood but to bring about a most rapid absorption of phosphorus from the alimentary tract. Fig. 12 reproduces an experiment which illustrates this important phenomenon. It shows the intestinal absorption of Na_2HPO_4 a few hours after it has been given by mouth to a series of infants. It may be seen that whereas there was very slight absorption in the rachitic infants which had not received irradiated ergosterol, there was not only marked but rapid absorption of the sodium phosphate in those which had been getting this medication from one to three weeks; in the course of an hour the concentration rose from less than 6 to over 10 mg. or from about 6.5 to 13.5 mg. This exceptionally rapid absorption of phosphorus reminds us of another investigation, that of Murdoch, which indicates the marked absorption of acid sodium phosphate in cases of healing rickets. After 4 gm. of this salt were given, the inorganic phosphate in the blood rose in an hour from 5 to 10 mg. per cent. The nature of the treatment is not stated. There is no study, however, which gives us data in regard to the action of therapeutic doses of irradiated ergosterol on the excretion of phosphorus or calcium in the urine and feces in cases of rickets. As yet we have merely analyses of the blood.

Hottinger has just published an interesting study on the calcium and phosphorus metabolism following *large doses* of irradiated ergosterol. He found a decided difference in this respect between

normal breast-fed or artificially-fed infants and those suffering from rickets. The normal infant reacted with a loss of calcium by way of the urine, which resulted in a negative balance; the same was true to a less degree of phosphorus. This alteration in the path of excretion of calcium held true for infants convalescent from rickets. On the other hand, the rachitic infant responded with a retention of calcium, a diminished excretion in the urine and stool. The phosphorus balance was improved, but more slowly. Cases of

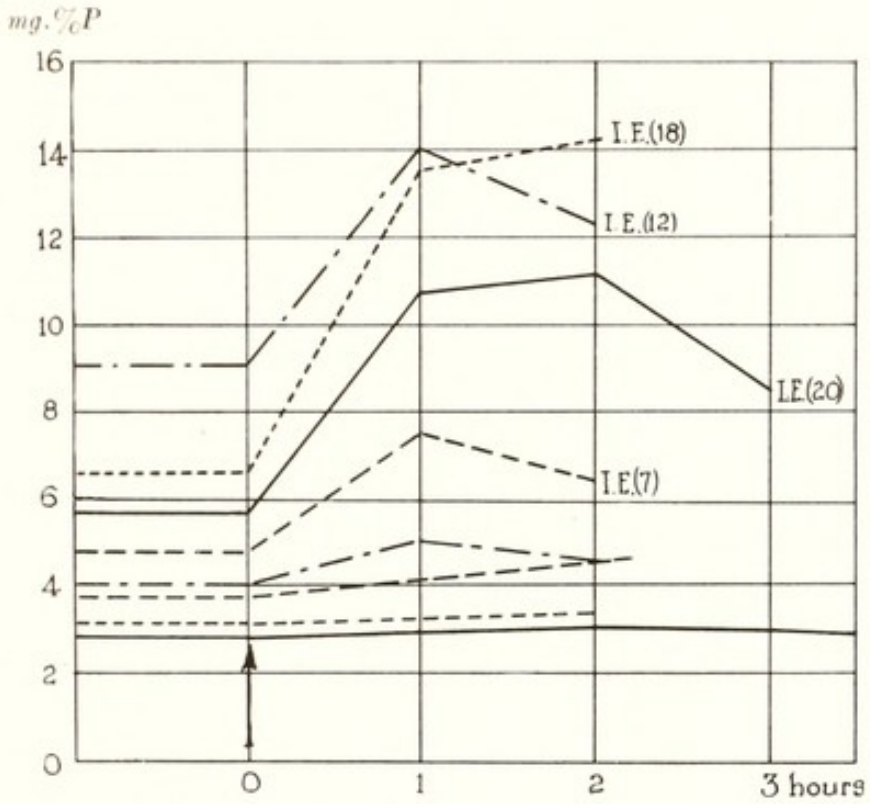


FIG. 12.—Showing the effect of irradiated ergosterol on the intestinal absorption of phosphorus in a rachitic infant. The arrow indicates the giving of Na_2HPO_4 (0.5 gm. per kg.) by mouth. I. E. signifies irradiated ergosterol, and the bracketed numerals the number of days it had been taken. No irradiated ergosterol was given where there are no numerals and the lines are almost flat. It may be noted that giving irradiated ergosterol for one to three weeks caused a marked and rapid absorption of phosphorus. (J. Warkany, Zeitsch. f. Kinderh., 1928, **46**, 1. Julius Springer, Berlin.)

tetany responded in a way similar to rickets, phosphorus being retained to a less extent. From studies on dogs, I can confirm this sudden and remarkable excretion of calcium by way of the urine. It should be remembered that Hottinger's investigation dealt with the effect of large amounts of irradiated ergosterol and cannot be considered to hold good for the action of small therapeutic doses on normal infants.

Recently Hess and Lewis have shown that large or occasionally even moderate doses of irradiated ergosterol may lead to a hyper-

calcemia, the concentration rising to more than 16 mg. per 100 cc. of serum. At times the inorganic phosphate is raised to abnormally high levels. Both of these effects are much more likely to occur in the normal than in the rachitic infant and may be accompanied by signs of hypercalcification of the epiphyses as noted by means of the Roentgen rays. From the standpoint of metabolism the interest is not so much in the fact that irradiated ergosterol is able to increase the calcium or inorganic phosphorus of the blood, as in determining the mechanism by which this action is brought about. Although the phenomenon of hypercalcemia is not understood, it should be

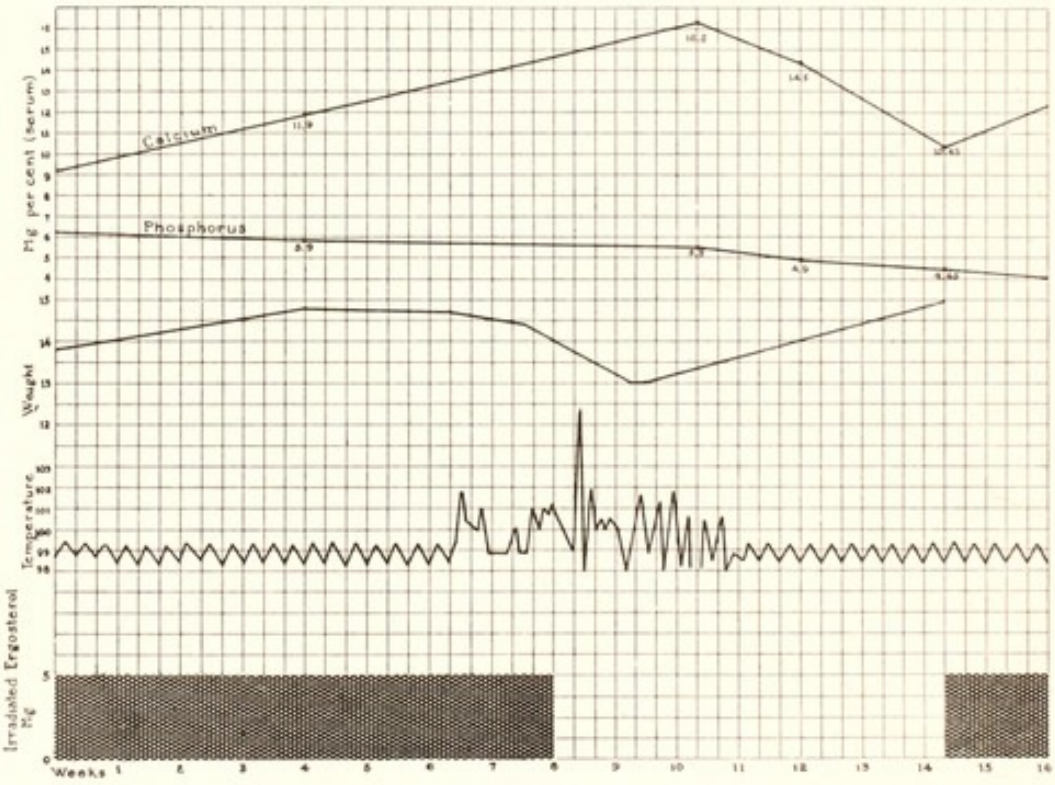


FIG. 13.—Hypercalcemia in normal infant. Note maintenance of excessive level of calcium for several weeks after irradiated ergosterol was discontinued, and its rise when the drug was begun anew. (Hess and Lewis, Jour. Am. Med. Assn., 1928, **91**, 783.)

noted that where it took place the level tended to remain abnormally high for some weeks after the irradiated ergosterol had been discontinued. The accompanying graph (Fig. 13) well illustrates this point. In this connection, it will be remembered that the hypercalcemia which follows the giving of parathyroid extract is temporary and of short duration. Preliminary experiments would seem to indicate that the hypercalcemia induced by irradiated ergosterol, given either by mouth or subcutaneously, is *associated with the activity of the parathyroid glands.* The following experiment is suggestive:

In a monkey in which latent tetany was induced and had been maintained for several months by means of a diet low in calcium, large amounts of irradiated ergosterol given by mouth promptly raised the serum calcium to a normal level. After the parathyroid glands had been removed, the calcium fell once more and could not be raised by repeated doses of irradiated ergosterol. The level was raised, however, by injections of parathyroid extract. During the past year we have carried out numerous similar experiments on dogs and monkeys, a short account of which has just been published (1929).

Daniels and her collaborators have recently shown that *irradiated milk and irradiated olive oil* definitely increase the retention of calcium and of phosphorus. This paper may be consulted for data in regard to the retention of these ions by infants fed pasteurized or boiled milk. It includes some seventy-four metabolic studies.

EFFECT OF ELEMENTARY PHOSPHORUS ON METABOLISM.

There is still no unanimity of opinion in regard to the effect of elementary phosphorus on metabolism. At first it was believed that this form of phosphorus led to a decided retention of calcium. However it was soon evident that Kassowitz's exaggerated claims for phosphorus could not be supported either by clinical or metabolic studies. Schabad concluded from his analyses that although phosphorus in itself was inactive in promoting calcium retention, when combined with cod-liver oil it enhanced the effect of the latter. Further experiments will have to be carried out in order to prove this point. It should be remembered that even a demonstration that phosphorus brings about increased calcium retention would not be proof that it possesses antirachitic potency. Tests which will be referred to elsewhere (page 194) showed that although phosphorus increased calcification of the epiphyses, as evidenced by the Roentgen rays and the microscope, the calcification did not take place in the rachitic zone but formed a distinct "phosphorus line" in the metaphysis. In other words, there seem to be distinctions in the metabolism even of such an apparently uniform structure as compact bone, which, from this point of view, cannot be regarded as a unit.

THE RELATION OF ACID–BASE EQUILIBRIUM TO RICKETS.

Although *acidosis* in relation to rickets has been discussed for a great many years, no complete study of metabolism has been carried out to ascertain the existence of this condition. This is surprising when we consider that it has long been known that any disturbance of the acid-base equilibrium must alter the metabolism of the inorganic salts—of calcium and phosphorus—and thus have

an effect on the development of rickets. Not only have such studies not been carried out in connection with rickets, but Shohl recently has stated that "only 5 cases of normal infants contain data sufficiently complete to permit discussion of the acid-base relationship." According to his calculations "the metabolism in infancy results in a base retention per kilo per day of 10 to 15 cc. 0.1 N." As is well known, one of the most important mechanisms for regulating the acid-base equilibrium of the body is the excretion of phosphate by the kidneys. It is here that we have an indication, in fact the only indication, of a disturbance of the acid-base relationship in rickets. In 1921 Hodgson pointed out that there is an increased acidity of the urine in rickets, as shown by the difficulty in reducing its acid reaction by feeding bicarbonate of soda, and that in addition the excretion of ammonia is increased. This important observation was confirmed a few years later by György, as well as by Burgess and Osman. It should be mentioned, however, that György noted exceptions to the rule, that in some cases although there was an increase in the NH_3 output, the urine was neutral or alkaline. He found that treatment with cod-liver oil or with ultra-violet light generally brought about a decrease in the excretion of acid in the urine. As mentioned elsewhere, these findings were interpreted as indicating an increased intermediary formation of acid, a trend of the metabolism toward the acidotic direction. There have been no further metabolic data to support this important conclusion. Rickets has been given a contraposition to tetany which is associated with a metabolism tending toward alkalosis, and, as is well known, can be checked by giving various acids. The comparison is attractive but we must bear in mind that infantile rickets cannot be checked, similarly, by the addition of alkali to the diet.

THE RELATION OF GASTRIC SECRETION AND INTESTINAL REACTION TO RICKETS.

Another subject which must be considered in this connection, although it has been discussed in relation to pathogenesis, is the rôle of the hydrochloric acid of the gastric juice in calcium metabolism. Some recent metabolic tests of Wills, Sanderson and Paterson have shown that when hydrochloric acid milk, containing 20 per cent of $\frac{N}{10}$ acid, was fed, the calcium retention was decreased and the balance became negative; ammonium chloride also failed to improve the balance. Shohl and Sato gave 250 cc. of $\frac{N}{10}$ HCl and found that the amount of calcium increased in both the urine and feces. These results coincide with clinical observations. Some years ago, when Scheer first recommended HCl for tetany, I used his preparation of milk for the prevention and cure of rickets. In every instance it tended to intensify the process, as judged by the clinical, radiological

and chemical criteria. That hydrochloric acid should fail to be of curative value is not surprising, as gastric acidity is not the limiting factor in the supply of calcium to the body, nor is rickets regularly associated with either an increase or a decrease in the secretion of hydrochloric acid. Indeed, some observations would seem to point the other way. For example, the path of excretion of calcium and phosphorus in rickets resembles that brought about by alkaline rather than an acidotic condition; the stools have a tendency to become alkaline rather than acid. Many years ago Gerhardt and Schlesinger showed that when sodium bicarbonate is given, the calcium is decreased in the urine and increased in the feces, as happens in the course of active rickets. On the other hand, when acid is added, the excretion of calcium is directed to the kidneys and less is excreted by the bowel. This phenomenon was clearly demonstrated by Zucker in experiments on man, carried out by feeding HCl and $NaHCO_3$.

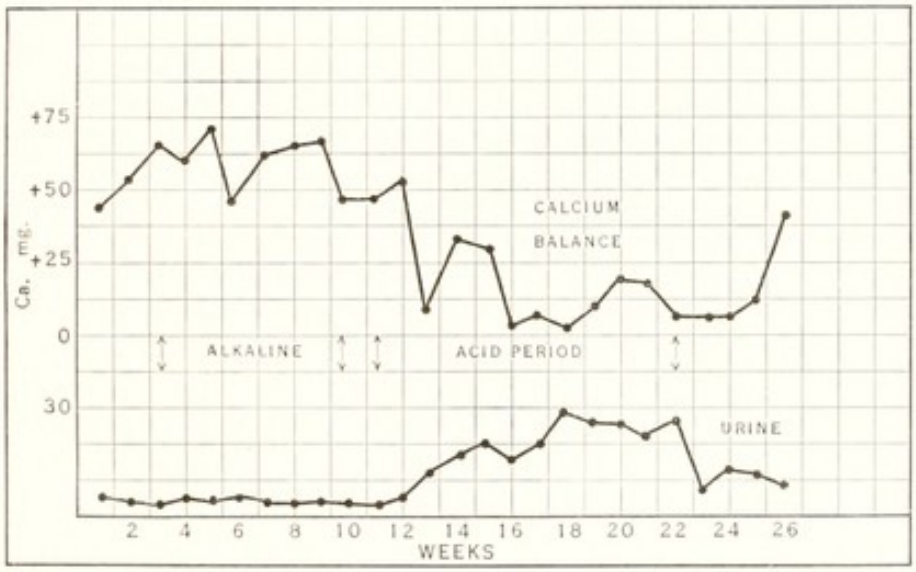


FIG. 14.—Showing the decrease in the balance of calcium which results from an addition of acid (1.0 M NH_4Cl) to the dietary, as well as its increased excretion in the urine. (L. T. Fairhall, Jour. Biol. Chem., 1926, **70**, 495.)

In judging this complicated question, one must bear in mind that the result will vary a great deal according to the degree of acidity or basicity of the diet, and that marked or weak concentrations of either may direct the metabolism into opposite paths. Furthermore, there are many uncontrollable conditions at work within the gastro-intestinal canal—for example, bacterial action. During the past few years studies on the acid-base equilibrium, carried out in large part in this country, have demonstrated the delicacy of this phenomenon and the large number of factors which are able to swing it in one direction or the other. As Berg, who has done so much work in this field, states: "In no realm can one generalize less than in that of mineral metabolism."

THE RELATION OF CARBOHYDRATE METABOLISM TO RICKETS.

The relation of carbohydrate metabolism to rickets has been vaguely considered for a great many years. For generations, clinicians have contended that foods rich in sugar and starches are especially prone to induce rickets. There is as yet no scientific support for this contention, but, it should be added that it has not been tested from a metabolic point of view. There can be no doubt that the increase of weight which is so readily brought about by the addition of carbohydrates to the dietary tends to the production of rickets. As mentioned elsewhere, for many years lactic acid was associated with the pathogenesis of rickets and it was surmised that this acid was increased in the blood and tissues. There is no basis for this supposition; in fact, recent investigation has tended to show that the lactic acid is decreased rather than increased. In 1922 Dodds reported an increased excretion of diastase in the urine and suggested that this increment indicated an inadequate function of the pancreas. This observation has such important connotations that it should be confirmed by several investigators before being definitely accepted. The recent work of Koenig and Lenart points in this direction. Following the ingestion of large amounts of sugar in rickets, they noted higher values for blood sugar, which also were unduly prolonged.

Freudenberg and Welcker recently reported that glycolysis is diminished in the blood of infants suffering from florid rickets and that it can be brought back to the normal by means of ultra-violet irradiation. A communication by Brock and Welcker has just appeared from the same clinic, stating that a similar diminution, associated with a decrease of inorganic phosphorus in the blood, has been found in rats in which rickets has been induced. A decrease of lactic acid in the blood has likewise been noted. It is too early to attempt to assess the value of these studies. They have an added interest owing to the fact that they tend to confirm clinical observations that carbohydrates play a rôle in rickets, observations which have been persistently brought forward for a great many years.

THE RELATION OF NITROGEN METABOLISM TO RICKETS.

Very little can be stated in regard to the relationship of nitrogen metabolism and rickets. Metabolism studies have failed to associate either losses or increases in retention of calcium with similar variations in nitrogen. Gassmann found the nitrogen content of rachitic bone the same as that of normal bone, in other words, 5.8 to 6.01 per cent. Some years ago Meyer reported that calcium retention was retarded by adding casein to the diet. Tests of this kind have not

been repeated, but this conclusion would fit in well both with biological tests carried out on rats fed a low-phosphorus ration, and with clinical experiences with a diet rich in casein.

THE RELATION OF ULTRA-VIOLET IRRADIATION TO METABOLISM IN RICKETS.

One of the newer aspects of metabolism is its relation to the energy of ultra-violet light. As yet we know very little about this subject, although it is evident that these rays must exert profound changes on metabolism, in view of the fact that they are able to exert a specific curative effect in rickets. Most of the investigations have given negative results; what has been learned has been restricted almost entirely to the metabolism of calcium and inorganic phosphorus. In 1922 Hess and Gutman reported that in infants suffering from rickets, sunlight induced an alteration in the inorganic phosphate of the blood—probably the first observation of a definite chemical change brought about in the body by ultra-violet rays. The fact that there is a seasonal curve of inorganic phosphate in the blood, an ebb during the winter followed by a flood during the spring and summer, is but a wider manifestation of this action of the sun. The ebb ensues largely, but not entirely, from the high incidence of rickets during the winter months and the flood from its "spontaneous" cure with the advent of the spring.

Orr, Holt and their co-workers have made the most complete study of the calcium and phosphorus metabolism in infantile rickets with special reference to ultra-violet irradiation. They found, as was to be expected, a definite increase in the retention of both calcium and phosphorus. Furthermore, these retentions were typical of rickets, in that there was an increase in the percentage of phosphorus in the urine, associated with a coincident decrease in the feces. The effect on the calcium partition was by no means so marked. The authors concluded that an increased absorption of these salts was brought about by ultra-violet irradiation and possibly also a decreased excretion of calcium through the intestine.

Animal experiments substantiate these conclusions. Orr, Magee and Henderson reported in 1924, in regard to pigs, that irradiation was associated with an increased excretion of calcium and phosphorus in the urine. Mayerson, Gunther and Laurens noted a similar effect on normal dogs and Hart, Steenbock and Elvehjem suggest a like relationship between fecal and urinary excretion in irradiated goats.

In connection with a consideration of the effect of light on the metabolism in rickets, it may be added that Hess, Weinstock and Sherman recently reported that the ultra-violet irradiation of a nursing woman brought about a marked increase in the antirachitic

potency of her milk, and that this effect was due to an augmentation in the antirachitic factor. This factor is probably activated ergosterol, which is elaborated in the skin and enters the general circulation. It can be found not only in the milk, but also in the liver.

Conclusions.—When the method of metabolic analysis was first applied to the investigation of rickets some twenty years ago, high hopes were entertained that in this way we should gain valuable information in regard to its pathogenesis. When we look back over this period and wade through the mass of literature and protocols which have been published during this span, it is with a feeling of disappointment and futility. In point of fact, however, much has been accomplished. In the first place it has been demonstrated that rickets is associated with an insufficient retention of calcium, the loss occurring more particularly by way of the intestinal tract. Of greater importance is the fact that these analyses of the body exchanges have shown that this loss of calcium occurs generally during the first months of life and, therefore, that there is a stage which precedes the clinical appearance of the disorder. It has thus taught us to appreciate the existence of latent and incipient rickets, conditions which we recognize in association with scurvy, beriberi, pellagra and other nutritional disorders. Of all the investigations, those of Schabad have been the most illuminating. He first turned our attention, too narrowly focussed on calcium, to the importance of phosphorus. From this point of view, his work must be regarded as the forerunner of the newer clinical studies which are based largely on determinations of the inorganic phosphorus in the blood and especially of the experimental investigations in which rickets has been brought about by diets deficient in phosphorus. The first proof of the specific value of cod-liver oil was furnished likewise by Schabad's metabolic work, although these studies were not accepted until some years later, after they had been fortified for the clinician by radiological observation and chemical tests of the blood.

In general, it may be stated that few metabolic studies have maintained a value, owing to the fact that the technique of this method is beset with so many inherent pitfalls. In the early studies, the collections of excreta were often inexact, the metabolic periods too short, the infants too old, and the diets so complex, through the addition of various organic constituents, that they cannot be interpreted and must be cast aside. In addition to these irregularities new factors have arisen which render interpretation still more difficult. For instance, the need of supplying an adequate quota of vitamins was not appreciated and, accordingly, we realize that one of the classical cases in the literature was complicated with subacute infantile scurvy. Furthermore, no precautions were exercised to prevent access of ultra-violet light. In addition it is

evident, as one reads the protocols, that many of the infants were suffering from complicating disorders which must have had an effect on the metabolism, and that absorption or excretion in the case of others must have been influenced by intercurrent infections preceding or corresponding with the tests. But apart from these difficulties which now are being realized and avoided, there are others which are inherent and which always will raise a question in regard to metabolic investigations. For example, it is clear to every clinician that physiologically all infants are not alike, that although they are normal, their metabolic processes evidently differ; for example, the fat and the thin infant, the quiet and the lively infant react differently or at different rates. There is quite another question, one fundamental to the method, namely, whether the very act of confining an infant to a metabolism bed does not in itself alter metabolism. Meig's experiments with cows are suggestive in this regard.

The most disturbing factor in appraising calcium metabolism is our inability to determine the amount which has been absorbed, due to the fact that calcium is not only absorbed from but excreted into the intestine; in other words, the calcium in the feces represents both unabsorbed calcium and that which has been absorbed and reëxcreted. At present there does not seem to be any way of extricating ourselves from this difficulty, but experiments on animals may furnish information in regard to the factors which control the excretion of calcium through the wall of the intestine. Another disturbing element is the variability of the kidney threshold for the excretion of calcium, the fact that although the level of the calcium in the blood may be the same, more may be excreted by the kidney under certain circumstances than under others. Finally, the avidity of the tissues varies greatly. It must be of moment whether the tissues contain a maximum or a moderate amount of calcium when we undertake our metabolic study.

The excretion of phosphorus is subject to similar vicissitudes. The recent studies of Bergeim and others make it seem quite possible that phosphorus, as well as calcium, may be reëxcreted into the gut. Furthermore, the phosphorus in the urine and feces may originate not only from the food and the bones but from the muscles and the glands, and we have no means of distinguishing between these sources.

It should be realized that we are still in the early period of the investigation of rickets by means of metabolic studies. Although it does not seem probable that its pathogenesis will be solved in this way, it is a method which always will be of great value for controlling the theories and hypotheses brought forward in connection with pathogenesis. At the present time there is an auspicious tendency to broaden the scope of metabolic studies, to consider not only the

rôle of inorganic but also of organic constituents in the blood, in the tissues and the excretions. It is probable that this trend will be developed in the near future. It seems quite possible that we may learn more concerning the pathogenesis of rickets through an indirect approach, for example, through studies of the pharmacological action of activated ergosterol or of ultra-violet irradiation, than has been accomplished heretofore by direct investigation of the body exchanges of infants or animals suffering from rickets.

CHAPTER VII.

THE PATHOLOGY OF RICKETS.

It has been pointed out in a previous chapter that our entire outlook in regard to the etiology of rickets has undergone a radical change during the past few years. This is not true of its pathology. The change in this respect came considerably earlier, as the result of the publication of Pommer's classic monograph, which brought about such a marked transition that we may fittingly speak of a pre-Pommer and post-Pommer period in the pathology of rickets. As a matter of fact, due to a peculiar chain of circumstances, the actual change in viewpoint did not occur until many years subsequent to the appearance of Pommer's publication. The history of this episode has an interest quite apart from rickets or its pathology. In 1885 Pommer, a young assistant in Graz, published his work on "Osteomalacia and Rickets, including a Consideration of the Absorption and Apposition of Bone," a study with which he had been occupied for some six years. His main thesis was that the characteristic histological lesion of rickets is an excess of osteoid tissue, which is produced in normal amount but which, for unknown reasons, fails to undergo calcification. Owing to the well entrenched and dominant opinion of Virchow and other authorities of that day, this novel conception was not considered on its merits but was summarily rejected. Not until twenty years later, in 1905, at the meeting of the German Pathological Society in Meran, was its validity and importance acknowledged. Pommer not only laid the foundation for future histological studies of rickets—those of Schmorl, M. B. Schmidt, Hansemann, Wieland and others, but was the first to suggest and support many of the concepts which are current at the present time. The idea that the deficiency in calcium involves the entire skeleton, that the etiology of rickets lies outside the province of the osseous system, that its pathogenesis cannot be solved merely by a study of the bones is today a commonplace. Much of the advance which he was able to accomplish was due to an improvement in technique which he himself devised and employed. Instead of decalcifying histological specimens completely by means of acid and examining them in an uncalcified state, he decalcified them only partially, using Müller's fluid for this purpose. This device allowed him to distinguish clearly between calcified and non-calcified tissue and to determine the width of the osteoid borders investing the cortex and trabeculæ.

Another pathologist who has greatly advanced our knowledge of

rickets is Schmorl, who for some twenty-five years has occupied himself with this and cognate subjects. He has furnished us also with valuable statistical data in relation to this disorder, data based on personal histological examinations carried out for a long period of years. Some of these tabulations have been made use of in a previous chapter to illustrate the etiology of rickets. One is reproduced here to illustrate the high incidence of rickets as demonstrated by the occurrence of characteristic histological lesions (Table 15). It will be noted that in Dresden among 386 children,

TABLE 15.—RICKETS AMONG 386 CHILDREN, AGED TWO MONTHS TO FOUR YEARS, NECROPSIED IN DRESDEN FROM 1901 TO 1908. (SCHMORL.)

Year.	Early.	Florid.	Healing.	Total.	No.	Healed.	No. of necropsies.
1901	4	16	3	23	4	6	33
1902	10	17	5	32	6	2	40
1903	6	12	5	23	5	5	33
1904	15	20	12	47	7	3	57
1905	11	25	10	46	4	8	58
1906	9	12	12	33	4	8	45
1907	5	15	16	36	4	17	57
1908	5	19	17	41	7	15	63
Total	65	136	80	281	41	64	386

from two months to four years of age, which were necropsied successively during the years 1901 to 1908, rickets was found in all but 41, in other words in almost 90 per cent. There can be no doubt that if the upper age limit had been reduced to two years, the incidence would have been far greater.

The recent work on experimental rickets which has been so fruitful in other aspects has not added significantly to our understanding of the pathology of this disorder, although it has fortified our knowledge. It has been confirmatory rather than constructive in character. It should be added, however, that the experimental method has enabled studies of a more quantitative nature to be carried out, due to the possibility of producing at will rachitic lesions of varying severity by means of carefully controlled dietaries. No new viewpoint has, however, developed from these investigations. Pathology has not been a factor in bringing about "the newer rickets," and has been unable to shed any light on the crucial question of its pathogenesis or explain the failure of the osteoid tissue to calcify. In view of this comparatively static condition during recent years, pathology will not be taken up in elaborate detail but will be dealt with in a manner which seems to fulfil the requirements of other aspects of rickets, such as pathogenesis and symptomatology.[1]

Until recently one of the moot questions was that of congenital

[1] Extensive expositions of the histological pathology of human rickets will be found in the publications of Pommer and of Schmorl, and of rat rickets in those of Erdheim.

rickets, whether the disorder occurs before or after birth. Indeed for many years this subject was uppermost in the discussions of the disorder. This aspect was vitalized about fifty years ago by the statement of Kassowitz, who published a large series of studies on rickets between the years 1880–1886, to the effect, that in his experience 80 per cent of infants showed signs of florid rickets at the time of their birth. He based his diagnosis on various clinical and pathological phenomena. On the other hand Pommer reported, at about the same time (1885), that in the course of necropsies on 100 new-born and premature infants he had not encountered a single instance of rickets. It seems unnecessary to review this episode in detail as it was thorougly threshed out some years ago. Most of the investigators, however, left the question somewhat open, for example Tschistowitsch in 1897, who reported an examination of the costo-chondral junctions of 100 new-born infants. He took the position that congenital rickets may occur but that the criteria on which Kassowitz based his diagnosis, hyperemia and an inflammatory increase of bloodvessels, could not be accepted as characteristic of rachitic lesions. Heubner, Stoeltzner, and many other pathologists also did not commit themselves unreservedly one way or the other. Schmorl, in a very large experience, failed to meet with any instance of congenital rickets; the youngest case which he reported occurred in the middle of the second month of life. The question was thoroughly treated both from a clinical and pathological viewpoint by Wieland in his monograph "On So-called Congenital and Early Rickets," published in 1910. From a clinical standpoint he showed that enlargement of the costo-chondral junctions at birth does not indicate rickets and is not associated with the characteristic histological lesions of this disorder. The same was found to hold true for the so-called craniotabes which not infrequently is present at birth and which will be discussed in detail in considering symptomatology. Wieland came to the conclusion that there is no pathological condition such as congenital rickets, at least in Kassowitz's sense of the term—no direct placental transmission. As brought out in the chapter considering pathogenesis, this is the position which is generally taken today. Possibly a rare case of congenital rickets may be found, but the disorder should be regarded as preëminently postnatal in origin. It is significant in this connection that in the provinces of China and India where osteomalacia is endemic and of frequent occurrence, an early incidence or unusual intensity of rickets has not been reported by European observers.

PATHOLOGICAL ANATOMY OF RICKETS.

As may be imagined, the gross pathological changes of rickets were recognized and noted by the earliest investigators. Careful

descriptions of the deformities of the bones may be found in the treatises of Whistler and of Glisson. The well-known illustration in Glisson's "De Rachitide" (frontispiece) shows the bent femur and the kyphotic spine, which in those days were regarded as characteristic of the disorder. Glisson refers to the "narrowness of the breast," "crookedness of the bone in the arm and the shank bone," "the reflection of the joints," and numerous other malformations. As these various anatomical changes form the basis of much of the symptomatology of rickets and will be considered in detail in the following chapter, they will not be described minutely in this connection. The characteristic alteration in the bones is their comparative softness, as would be expected in view of the fact that they contain much more water and less ash than normal. It is found accordingly that they are cut more readily than healthy bones, especially where the disorder is of marked degree. In the advanced cases, now rarely met with, the bones may have assumed an almost cartilaginous consistency.

In our account of the gross appearance of the skeleton we must necessarily follow the masterly account of Virchow, who described these lesions about the middle of the past century. The surface of the bones may have a slightly pinkish hue, the result of hyperemia which involves the periosteum and was formerly regarded as inflammatory. This membrane frequently is somewhat thickened and can be detached with difficulty from the underlying bone. According to Virchow, there may be a reddish, and at times somewhat white and cartilaginous appearing layer beneath the periosteum and closely associated with it.

Long Bones.—The main changes are in the long bones which are crooked and bent. The tendency in bending is for the normal curvatures to be exaggerated. For example, the convexity and concavity of the clavicle are intensified, the femur tends to be bowed anteriorly, the tibia to be bent inward in its lower part. These bowings are generally of slight intensity but may reach such a degree that they lead to infractions or even fractures, the commonest form of which is the well-known green-stick fracture, where the break occurs only on the convex surface of the bone. Such lesions are followed by callus formations on this aspect which tends to be larger than normal. These calluses are not only on the surface of the bone, but extend into the marrow cavity and on gross, as well as microscopic examination, may be found to have divided the marrow cavity into two separate parts. The fractures, however, are frequently complete, single or multiple, and may not have been suspected during life. The presence of numerous fractures should raise the question of whether we are dealing with a case of fragilitas ossium rather than with rickets. If the active rachitic process has ceased, the bones are usually firmer and harder than normal, leading

to the eburnation which is so characteristic a feature of healed rickets of moderate or marked degree. This thickening of the cortex may develop to such an extent as to increase the weight of the bones and make them resemble the well known "Marmorknochen" (marble bones). On sectioning a long bone the marrow is found to be abnormally red, a feature which was emphasized particularly by Kassowitz and was interpreted by him as an inflammatory tissue resulting from a toxin. The characteristic gross lesion, however, is the enlargement of the epiphyses, especially those at the costochondral junctions and at the wrists and ankles. These enlargements constitute the typical clinical sign of rickets and accordingly will be described in detail in considering the symptomatology. On sectioning the epiphyseal enlargement it is found that the swelling is due mainly to a thickening of the cartilage and to a less extent, of the contiguous spongy bone. The degree of enlargement varies markedly in proportion to the burden which has been placed on the bones; for example, if a rachitic infant has been allowed to creep a great deal, the epiphyses at the wrist will augment accordingly. The weight of the body tends to produce a characteristic alteration in the neck of the femur—a depression which gives it a more horizontal direction—leading to the well-known deformity termed coxa vara. The leg bones are most often bent, developing the form of genu valgum or varum. Closer examination shows that under these conditions not only are the bones themselves deformed, but that the interarticular cartilages, for example, at the knee are of unequal thickness at the outer and inner aspects, and that the ligaments are unduly lax, thus allowing an abnormal mobility of the joints.

As a result of the lack of calcification and growth of the long bones, a shortening of the entire skeleton may result, the stunting depending on the intensity of the disorder and its duration. In such cases the bones are of normal or even of excessive width, but suffer in length due to the involvement of the epiphyses. In extreme instances "rachitic dwarfism" comes about; these cases, however, are associated generally with some complicating disorder of nutrition.

Thorax.—The thorax is almost always affected in the course of the rachitic process. In severe cases it may be so greatly deformed as to impede respiration and lead ultimately to the death of the individual. In such instances there is generally a marked protrusion of the sternal area associated with marked narrowing of the lateral aspects. Deep vertical grooves of greater or less width are to be seen on either side of the sternum. In milder cases there is merely a flanging of the lower borders of the ribs and the well-known Harrison's groove or sulcus, which runs almost horizontally along the lower part of the chest corresponding to the attachment of the

diaphragm. The most distinctive feature of the ordinary case of rickets is the enlargement of the costo-chondral junctions, which leads to the production of the well-known "rosary," a sign having marked diagnostic significance. These enlargements or beads are at times so slight as to be distinguished with difficulty from the normal projections at these sites or again may stand out as large knobs along both flanks of the thoracic wall. They are almost invariably more prominent on the inner than on the outer aspect of the ribs, and may produce definite depressions on the surface of the underlying lungs. On sagittal section of these junctions it is noted that they are composed of a small white homogeneous sternal part, and of a much larger red area lateral to this. Instead of these articulations being round and knobby, they may be somewhat angular, expecially if the disorder has been under treatment and the lesion has undergone healing, but angulation is characteristic of infantile scurvy rather than of rickets. On microscopic examination it is found, generally, to have resulted from infraction at the costo-chondral junction. Although the sternum may bulge forward, giving rise to the well-known "chicken-breast," in other cases it is depressed with the contiguous cartilaginous ends of the ribs, leading to the formation of the so-called "funnel-shaped chest." This deformity is, however, not always due to rickets but may be of congenital origin.

The organs within the thoracic cavity generally show no changes. As stated, pressure of the enlarged costo-chondral junctions leads at times to collapse of the adjacent portion of the lungs, which in turn may induce the formation of compensatory emphysematous areas along the anterior borders. Pneumonia is a not infrequent complication of moderate or severe rickets, which causes a marked susceptibility to respiratory infection. The heart is rarely involved. Some thickening of the pericardium has been noted. The heart itself may be enlarged, especially the right ventricle, a change which has been considered analogous to the cardiac enlargement which so frequently is associated with infantile and adult beriberi. Very recently Meixner has described a new lesion in infants who have had rickets—enlargement of the left ventricle, associated with thickening of the endocardium and slight fibrosis of the muscle wall. He believes that some of the instances of cardiac enlargement which are found in adults are the result of rickets or of conditions associated with it.

Cranium.—Gross changes in the cranium are characteristic of rickets. The fontanel tends to be abnormally wide, as do the sutures, the edges of which may be very thin, or, more rarely, thickened. On closer examination of the cranial bones we find that the defects in the skull-cap are, broadly considered, of two kinds. The one type has a punched-out appearance and generally is found

in the parietal bones on either side of the sagittal suture; these defects vary in size and in number and usually are not associated with softening of the bones along the suture lines. This is a congenital pathological condition and is not true rickets but a bone defect. The differentiation between "congenital cranial defects" and true craniotabes is discussed in detail in the chapter on Symptomatology. The acquired form, in other words true craniotabes, can be distinguished usually even on gross examination. In this type the lesions likewise are multiple, but usually are confined to the posterior aspect of the skull-cap, to the part of the parietal bones superior to the lambdoid suture. They have not the punched-out appearance, and are associated with softening of the edges of the bones. It is on microscopic examination, however, that one can differentiate sharply between these two varieties of lesions.

On the other hand, instead of the surface of the skull showing defects and being soft and depressible, it may be exceptionally hard and thick in circumscribed areas, particularly about the centers of ossification in the frontal bones. Such foci of hypertrophy may be noted also posteriorly in the neighborhood of the ossification centers of the parietal bones. These various areas of thickening of the skull lead to the development of the large frontal and parietal bosses and the square head which give such a characteristic appearance to the rachitic individual and which may persist throughout life.

On removing the skull-cap, generally nothing abnormal is noted on its inner surface; Virchow described a thin layer of congested tissue on this surface due to absorption of bone about the Haversian canals. Some pathologists are of the opinion that a mild degree of hydrocephalus almost always is associated with rickets, and that there is an increase in the size and weight of the brain. There can be no doubt that severe rickets tends to the development of hydrocephalus. In his study on "Dementia Rachitica" (1926), Huldschinsky claims that in severe cases there is a relative and probably an absolute enlargement of the brain, which he suggests is due to hydrocephalus. In order to measure the growth of the brain he worked out a cranial index and found that there is regularly a disproportion between the cranial vault and the cranial base.

Spinal Column and Vertebræ.—Usually the spinal column and vertebræ are not deformed. In the severe case, however, the column may be curved giving rise to scoliosis, to kyphosis, or to irregular combinations of both, with associated deformities of the thoracic wall. When such deformities are present in acute cases, the vertebræ themselves are found to be abnormally soft, the intervertebral discs of varying width and the ligaments somewhat flabby. When present, the kyphosis is located generally between the ninth thoracic and the third lumbar vertebræ.

Pelvis.—The pelvis also is involved. The deformity of the bones may be so great as to cripple the individual. In its typical form it consists of the characteristic "rachitic pelvis" with its lateral narrowing, its bulging at the symphysis, and projection forward of the sacrum—the trefoil contour. These lesions bring about the narrowing of the entrance to the pelvic cavity which leads to such grave difficulties and complications in the course of labor. Illustrations of pelves of this description will be found in connection with the clinical consideration of this deformity (Figs. 25, 26). The softening of the pelvic bones allows the heads of the femora to press the acetabulæ inward into the pelvic cavity. These various malformations are generally of such slight degree that they can be ascertained only by means of measurement. In osteomalacia, however, they constitute one of the most characteristic and important signs of the disease. It is of interest to note that Christeller depicts the pelvis of a rachitic monkey which shows the same trefoil outline (Kartenherzform) which is typical of human rickets and osteomalacia.

The abdominal organs are the seat of no specific changes. The enlargement of the spleen and lymphoid nodes, which is found associated with rickets, should be regarded as due to complicating factors.

THE MICROSCOPIC PATHOLOGY OF RICKETS.

The Epiphyseal Junctions.—The normal epiphyseal junction, for example, of the rib and its cartilage, is composed of different layers of cells which have a remarkably constant and orderly arrangement, and which undergo characteristic alterations in the course of rickets. These changes naturally vary from case to case, but the distinctions are of degree rather than of kind. In order to elucidate this effect, it would seem of advantage to describe briefly the architecture of a normal junction and of one which has been transformed by the chemical and mechanical action of rickets.

The zones which may be distinguished in the *normal* as well as in the abnormal juncture are those of the resting cartilage, the proliferating cartilage, the zone of preparatory calcification, of endochondral ossification and the cortex (Fig. 15). The proliferating cartilage arises sharply from the layer of resting cartilage. Its characteristic feature is the orderliness in the arrangement of its cells, which are aligned in vertical columns, running parallel to the axis of the bone. Its cells lie embedded in an uncalcified matrix, and are of increasing size as we approach the line of preparatory calcification. The latter zone, which is firm and strong and most important for the maintenance of the normal pattern and rigidity of the junction, is composed of a well calcified matrix, in which are comparatively large cells, having a poorly staining cytoplasm and nucleus. This zone generally is four to six cells in depth and presents a com-

paratively straight border-line which runs horizontally, separating the cartilage sharply from the adjacent bone. The bone itself, which has been formed by ossification of the zone of preparatory calcification, is composed of a varying number of trabeculæ of two kinds—numerous, slender bars, the so-called primary spongiosa and the few heavier trabeculæ, the secondary spongiosa, situated within the marrow cavity. The strength and width of these various trabeculæ depend upon the age and the nutrition of the individual. All of them have an osteoid border or mantle, which may however

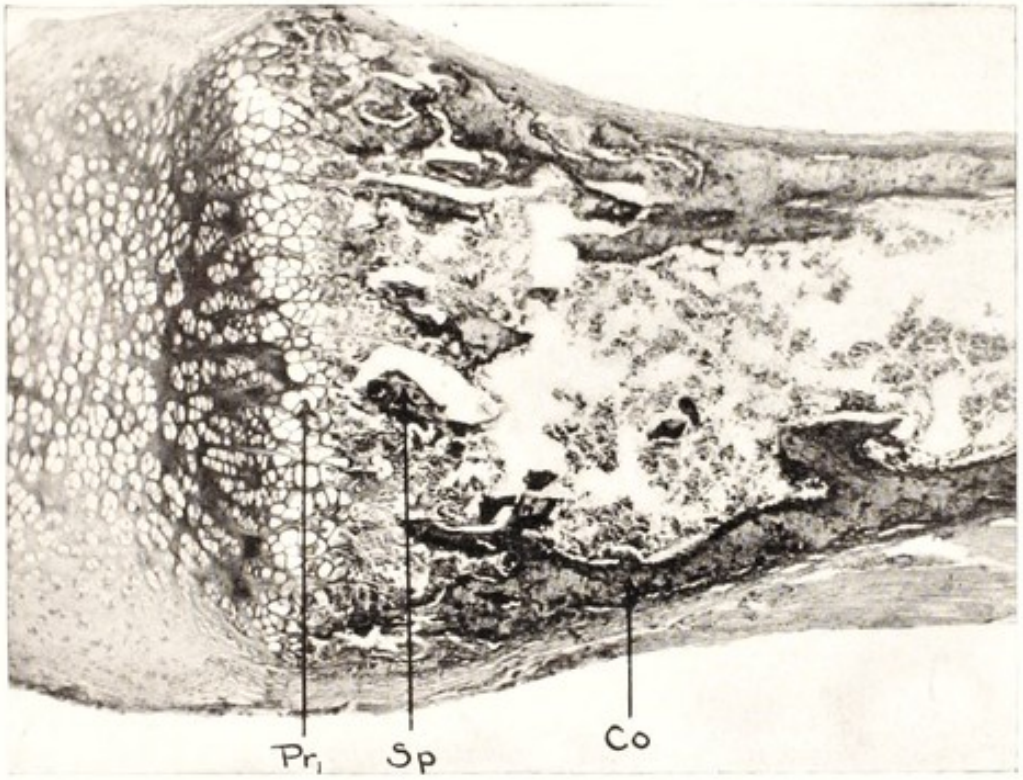


FIG. 15.—*Normal costochondral junction.* (Rickets-producing diet. White rat which was exposed daily to the mercury vapor quartz lamp for one and a half minutes at a 3-foot distance). Rib: The zone of preparatory calcification (Pr_1) averages four cells in depth; matrix calcified. Complete calcification of spongiosa (*Sp*) and cortex (*Co*). No visible osteoid. No rickets. Decalcified in Müller's fluid for five days. Hematoxylin-eosin. (Hess, Unger and Pappenheimer, Jour. Exper. Med., 1922, **36**, 427.)

under normal conditions be so thin as to be hardly visible. The more rapidly the animal is growing the wider is this border; in adults growth may be so feeble that osteoid tissue is almost absent. Surrounding these trabeculæ is the marrow rich in cells, which vary in kind according to its functional activity. The cortex varies greatly in thickness with the strength of the individual. It is prolonged beyond the cartilaginous layer as far as the base of the proliferative zone, as a thin fibrous extension underlying the perichondrium.

We are indebted mainly to Pommer and to Schmorl for our understanding of the microscopic pathology of human rickets, and to the painstaking studies of Erdheim for an appreciation of comparable lesions which develop in the rat. In *rickets* the costo-chondral and other epiphyseal junctions are markedly altered (Figs. 16 and 17).

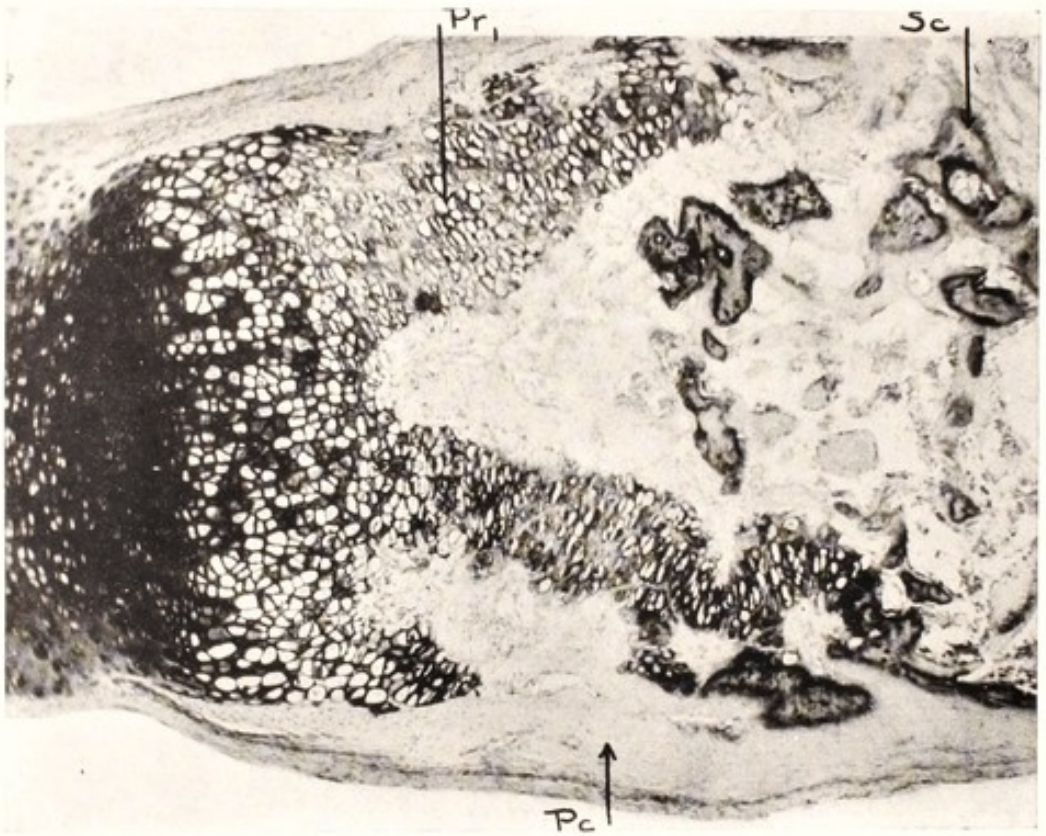


FIG. 16.—*Rachitic costochondral junction.* (Rickets-producing diet. Black rat which was exposed to the mercury vapor quartz lamp for one and a half minutes at a 3-foot distance). Rib: The zone of preparatory calcification (Pr_1) is almost wholly free from calcium, and is greatly increased in depth and prolonged into the metaphysis. There is great excess of perichondral (*Pc*) and subchrondral (*Sc*) osteoid. Marked rickets. Decalcified in Müller's fluid for five days. Hematoxylin-eosin. (Hess, Unger and Pappenheimer, Jour. Exper. Med., 1922, **36**, 427.)

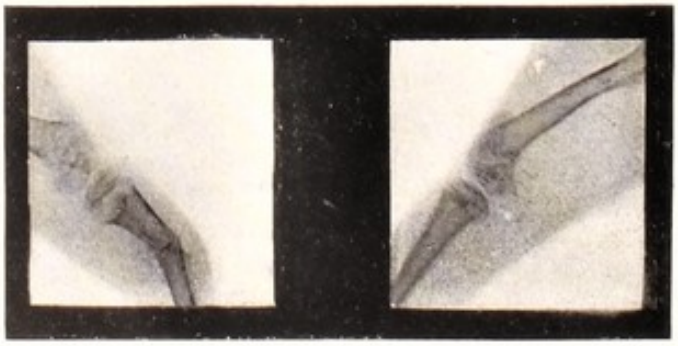


FIG. 17.—Radiogram of black rat showing marked rickets with fracture of the tibia (left). Radiogram of the white rat which showed a normal epiphyseal line (right). (Hess, Unger and Pappenheimer, Jour. Exper. Med., 1922, **36**, 427.)

Indeed, if the disorder is moderately advanced the changes are evident at a glance. However, microscopic examination of the tissues is necessary in order definitely to establish the diagnosis, as other lesions may lead to swelling or deformity of the joints resembling rickets macroscopically. The main disturbances are in the zone of preparatory calcification and preëminently in the osteoid tissue of the trabeculæ and the cortex. The proliferating cartilage is more or less exuberant and is difficult to demarcate sharply from the zone of preparatory calcification. As stated, it is in this location that the normal picture is found to have undergone such a striking change. Instead of orderly rows of cells, sharply limited at the spongiosa, we find a marked overgrowth of the cellular layer, which may be ten or more times wider than normal. This overgrowth sends out numerous prolongations of varying depth into the metaphysis, giving to the cartilage an irregular and markedly indented rather than a straight border. The degree of hypertrophy depends on the stage of the rachitic process as well as on the rate of growth of the animal. In cases associated with marked gain in weight, the increased width in the zone of proliferating cartilage is especially great, whereas in those associated with malnutrition and stationary weight, the augmentation is comparatively slight. But it is quite common to find that this layer assumes astonishing proportions even in animals fed a markedly deficient diet, for example, the Sherman-Pappenheimer ration, which lacks inorganic phosphorus, vitamins A, B and C, as well as adequate protein.

An equally striking phenomenon is that the zone of preparatory calcification is almost completely free of calcium, failing to take the specific stains, such as nitrate of silver. The small areas of calcium which are observable lie generally along the outer walls of the epiphyseal junction and were laid down previous to the onset of the rachitic process. The columnar arrangement, so characteristic of the cells of this zone, is completely absent or is evident only at the base. The cells themselves are of various shapes and sizes.

The spongiosa is also greatly altered. The trabeculæ have lost their orderly arrangement and their regularity of shape and size. Some are short, others long, some thin, others broad, and they may be irregular in contour or fused. The main alteration, however, is that they are composed of a greater or less amount of calcium-free osteoid tissue. This pathological condition may be limited to an abnormally wide border of osteoid; on the other hand the trabeculæ may be composed entirely of osteoid, or the osteoid may contain merely a core of bone or groups of cartilage cells. This non-calcified tissue is to be found in excess not only in the neighborhood of the bony trabeculæ but also along the perichondrium and the cortex. In the former location it constitutes a mass which encompasses the cartilage, increasing the width of the junction, thus tending to pro-

duce the characteristic enlargement of the epiphyses, for example, beading of the ribs. The osteoid is likewise markedly increased on the cortex, especially at the epiphysis but on the shaft as well. Along the outer surface it gives rise to the condition which formerly was termed "rachitic periostitis." On the inner aspect it may be so extensive as to encroach upon the lumen of the marrow cavity.

The marrow itself is markedly congested and contains a large number of blood sinuses, a feature unduly emphasized by Kassowitz. Here and there fibrillar zones of connective tissue may be noted, especially in proximity to infractions or fractures; the entire marrow may be atrophied and contain a lack of cellular elements associated with mucoid areas. The osteoblasts investing the walls of the trabeculæ are not decreased in number, but frequently appear flat, a sign of functional inactivity.

Craniotabes.—When we come to a consideration of the symptoms of rickets we shall find that there has been and still is considerable confusion in regard to the significance of softening of the skull bones. Not that there is any doubt as to the diagnostic value of true craniotabes, but rather as to the interpretation of the softening under various conditions. In regard to this question we must for the present be guided by the findings of the pathologist, by the microscopic examination of these porotic areas. The gross appearance of the two types of craniotabes, the false and the truly rachitic, has been described, and their characteristic locations emphasized—the former situated generally along the sagittal suture, and the latter superior to the lambdoid suture. Wieland, in his monograph on this subject, states that he found the sagittal defects in approximately 20 per cent of the cases. In these areas the osteoid border did not exceed the physiological limits, having a minimum width of 2 to 4 μ, a maximum of 12 to 13 μ, and an average of about 7 to 10 μ. It is true that this is a wider zone than is found investing the trabeculæ of the ribs at the costo-chondral junctions, but a greater width is to be expected in view of the exceptional growth of the cranial bones at this period of life.

Microscopic examination of the areas of true craniotabes shows a different picture. Here we find along the borders of the trabeculæ an excessive amount of osteoid such as we associate with the lesions of rickets. In other words, the two forms of cranial defect can be differentiated into a non-rachitic and a rachitic type by means of the usual histological criteria. This differentiation does not, however, inform us as to whether the purely osteoporotic defects are not closely allied to rickets and whether rachitic craniotabes, as described by Elsaesser, develops more readily on the basis of a preëxisting osteoporotic lesion. Such a predisposition might be expected in view of the diminished content of calcium and phosphorus in the

porotic bone, although a lack of these salts is by no means the most important factor in the development of rickets.

Histological data in regard to the cranial bones is remarkably scanty, considering the fact that material of this kind is readily available and that the question has been the subject of discussion for so many years. The recent monograph of Hottinger, which includes a microscopic study of the skull bones of a series of premature infants is therefore welcome and timely. Hottinger substantiates the distinction between true and false rickets of the cranial bones, and, in addition, brings out some points which will be referred to in connection with symptomatology but have interest also from the standpoint of pathology. In the first place he shows by means of convincing illustrations that mild lesions at the costo-chondral junction are not incompatible with marked rachitic lesions in the parietal bones. Furthermore, these typical lesions, characterized by a marked excess of osteoid, may go hand in hand with questionable radiological signs at the epiphyses of the wrist and a normal concentration of inorganic phosphorus in the blood—in the most striking instance, 5.1 mg. per 100 cc. Such conflicting phenomena must be interpreted as indicating that, in the final analysis, we must rely on histological examination of the bones in determining the nature of cranial defects in the new-born.

From a pathogenetic standpoint, it should be remembered that the truly rachitic defects are not present at birth, but develop during the first months of life, whereas the osteoporotic lesions are prenatal developmental defects. It may be stated that further confusion has been added to this subject by confounding the cranial lesions of congenital syphilis with true craniotabes. Histological examination of these lesions shows quite a different picture—the osteoid tissue is decreased rather than increased in amount, the only similarity between the two conditions being the irregularity in the formation and in the calcification of the proliferative cartilage zone.

From time to time a specific *rachitic myopathy* has been described. These lesions do not seem to be distinctive of rickets, and occur only in the severe cases. A review of this subject will be found in the work of De Toni (1923).

LESIONS OF LOW-CALCIUM RICKETS.

The usual rachitic changes in the bones are associated with a low percentage of inorganic phosphorus in the blood, the calcium undergoing but slight change. This fall of phosphorus comes about although the diet of the infant consists almost always of an adequate amount of milk which entails a large intake of both phosphorus and calcium. In animals, for example, in rats and in puppies, it has been found that rickets can be brought about by a dietary which

contains either a small amount of phosphorus in relation to calcium, or a small percentage of calcium in relation to phosphorus. When the ratio of calcium to phosphorus is low it leads to a *low-calcium rickets*. Whether these two kinds of rickets occur primarily in infants is open to question. Shipley and Park believe that these two forms should be distinguished not only from the clinical but from the pathological point of view. Most investigators take the stand that there is but one form of rickets, namely the one which is associated with a low percentage of inorganic phosphorus in the blood, and that when the calcium content of the blood is low—a state associated with the clinical signs of tetany—the condition should be regarded as a complication of rickets rather than as a distinct type of this disorder. This question can be decided only by ascertaining whether cases of rickets occur which throughout their course or for a prolonged period are associated with low calcium, rather than with low inorganic phosphorus of the blood. It is probable that there are such cases, but they must be comparatively rare. It should be mentioned in this connection that in some instances of osteomalacia where blood analyses have been made, the serum calcium has been found to be low. But in none of these have the bones been sectioned and the histological lesions determined.

Although this is a moot question in relation to infants, there can be no doubt that a low-calcium as well as a low-phosphorus type of rickets can be brought about at will in rats by appropriate alterations in the diet, and furthermore that these two types are associated with characteristic pathological lesions. The changes in the costo-chondral junctions of rats which have been fed rations relatively low in calcium are by no means as marked as in those fed the low-phosphorus diet. The width of the zone of the proliferative cartilage at the costo-chondral junction frequently is not much greater than normal. This is true likewise of the other epiphyses, for example, those at the knee-joint, a phenomenon which renders it difficult to diagnose this type of rickets by means of the Roentgen rays. Not only are the endochondral changes relatively slight or absent, but the calcium deposition in the matrix of the cartilage is decidedly more abundant. These lesions have been studied and described with particular attention by Shipley, Park and their co-workers who have summarized their observations as follows: "Microscopic examination showed that the cartilage was entirely or nearly free from calcium and was invaded in an irregular manner by the vascular elements of the shaft. In consequence, the cartilage extended toward the shaft in irregular prolongations. The cells of the cartilage in proximity to the shaft showed evidences of degeneration and metaplasia. The intermediate zone was composed of cartilage in a more or less degenerated state, osteoid trabeculæ, bloodvessels surrounded by marrow elements, and a few deposits

of calcium for the most part situated near the periphery and connective tissue. The trabeculæ of the shaft were bordered by rather broad zones of osteoid. A loosely arranged fibrous tissue invested many of the trabeculæ, and in those places in which it filled in the spaces between the trabeculæ it gave rise to histological pictures which closely resembled those furnished by the fibrous marrow in the rickets of human beings. The pathological conditions did not, however, correspond at all points to that usually found in the human subjects of the disease. The metaphysis was composed in larger part of osteoid trabeculæ. Though these osteoid trabeculæ were free from calcium deposition, they nevertheless retained a certain semblance of orderly arrangement. The osteoid zones about the trabeculæ were not always so broad as in the rats on the diets of the first group (phosphorus deficient), though they were quite as broad as the osteoid borders in the bones of rachitic children."

It would be interesting to ascertain whether a similar histological picture is found in the epiphyses of infants who have had tetany, in a latent or active form, for a prolonged period. In the cases of infantile tetany which I have observed the radiological picture of the epiphyses has been no different from that in rickets.

At first it was thought, as the result of Mellanby's investigations on puppies, that typical rachitic lesions developed as the result of a deprivation not only of the antirachitic factor but of the so-called fat-soluble vitamin (vitamin A). Such, however, is not the case. Although there are no histological examinations of human tissues on which to base this conclusion, experimental studies in animals and clinical observations of infants offer convincing evidence that, from a pathological point of view, a definite and sharp distinction can be drawn between these two nutritional factors. The histological study of Hess, McCann and Pappenheimer showed that rats fed a diet which was adequate except in respect to vitamin A did not develop the lesions typical of rickets but those of osteoporosis—a narrow zone of preparatory calcification, absent or poorly developed osteoid borders along the trabeculæ, and flattened, inactive osteoblasts. That in all likelihood the same holds true for infants deprived of this dietary factor would seem to follow from the clinical report of Hess and Unger, who found an absence of radiographic evidence of rickets in infants deprived of this vitamin, and of those of Bloch of Copenhagen, who noted a similar lack of rachitic lesions among the infants who developed xerophthalmia during the World War as the result of being restricted to milk which had been robbed of its butter fat.

It may be mentioned, in passing, that the rickets brought about in animals by giving strontium, as described by Lehnerdt, Stoeltzner and by Shipley, Park and their co-workers (see page 81), is in all respects similar to that of human rickets. The only distinction

seems to be a marked tendency to the overproduction of osteoid tissue, which may almost completely fill the marrow cavity. This "strontium rickets" does not respond to cod-liver oil or to irradiated ergosterol.

THE HEALING OF THE RACHITIC LESION.

The healing of the rachitic lesion has been studied intensively by Schmorl. In some instances it is difficult, even for the experienced pathologist, to determine whether the histological picture indicates healing. For example, Ziegler classified a case as beginning rickets, which Schmorl showed to be healing, and Virchow fell into a similar error. This interesting aspect of the pathology has been clarified by the studies of experimental rickets in the past few years, notably those of Pappenheimer and of Shipley and Park. The artificial production of rickets in animals provided an unprecedented opportunity for investigating this problem from a quantitative point of view, for observing the character and degree of the histological changes which took place when minimal amounts of various curative agents were added or when dietaries of various composition were fed. It also enabled a comparison to be made of the action of the specific curative factors, for example, of cod-liver oil and its active fraction, or of ultra-violet irradiation. Although the process has been found to be the same in animals as in infants, and no difference could be determined in the mode of action of various specific agents, our knowledge has been rendered much more precise as the result of these well-controlled observations.

As in the development of the rachitic lesion, so in its reparation the processes may be divided broadly into those which take place in the bone and those in the cartilage. In the former, the corrective process is very simple—the osteoid tissue becomes more or less rapidly calcified, any excess being absorbed. In the course of this repair the calcium is laid down in granular form, a point of interest in connection with the chemical reactions underlying calcification. The granules are especially evident along the border of the cartilage, where they may appear as an irregular fringe. In marked cases a certain degree of thickening of the osseous tissue may remain, especially where the pressure or strain is great. Schmorl states that in some instances he has noted excessive absorption of the newly-formed bone, which brought about infractions and hemorrhage. This observation is of interest as it is a microscopic picture which readily may be mistaken for the "Geruestmark" of infantile scurvy.

The developments in the cartilaginous zone are far more complex, and are still further complicated by the fact, as may be observed by clinical as well as radiographic examination, that the course of

rickets is characterized by a remarkable tendency to remissions and exacerbations. These varying phases may render interpretation exceedingly difficult. In this regard the study of experimental rickets comes to our aid, as at will we can bring about uncomplicated healing or relapse. Just as the first evidence of rickets is a disturbance in the zone of preparatory calcification, so healing is first evidenced by a reparative process in this zone, an observation

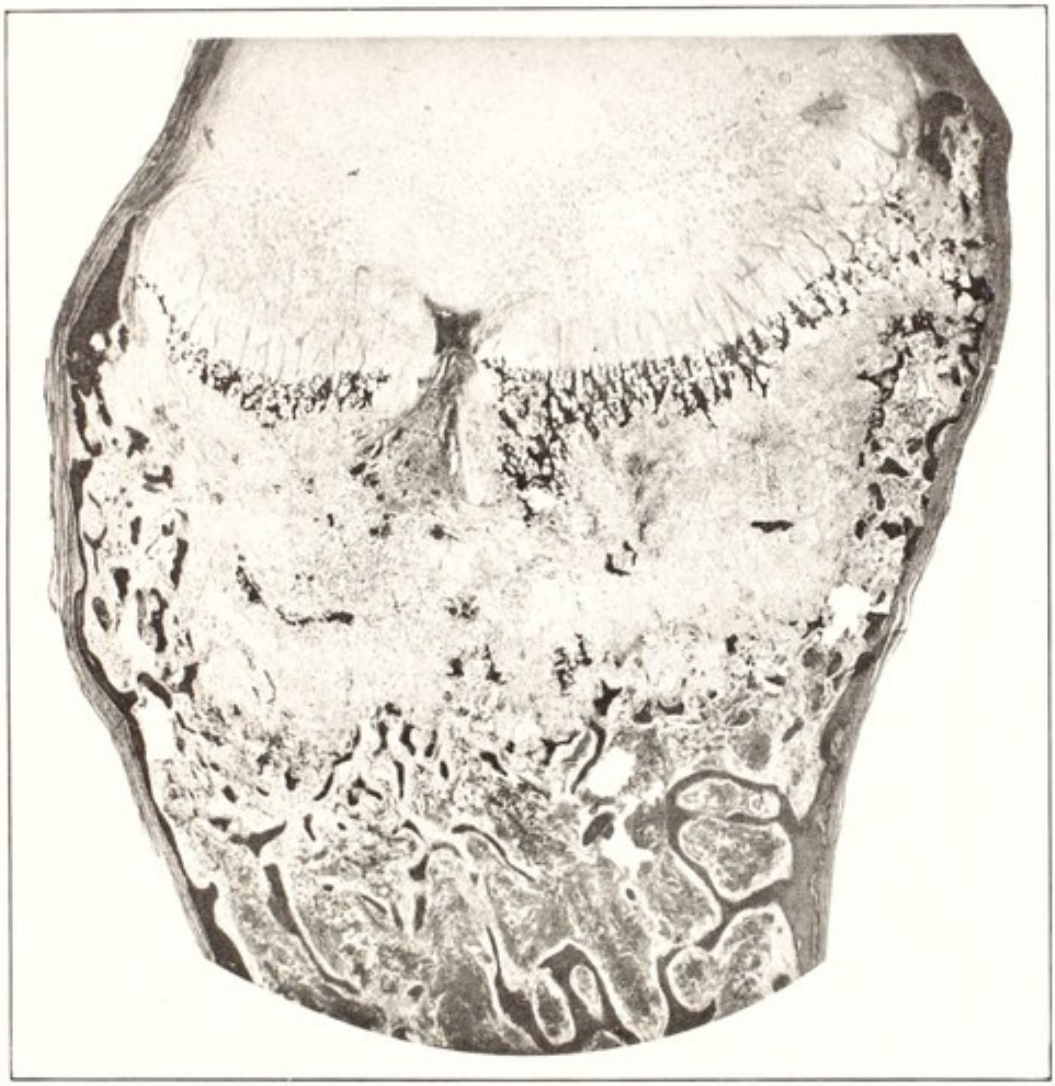


FIG. 18.—*Healing rickets.* A transverse band of calcification has been laid down in the broad cartilaginous zone. (Schmorl, Ergeb. d. inn. Med. u. Kinderh., 1909, Julius Springer, Berlin.)

which was made many years ago by Mueller and by Pommer. Perhaps the most interesting phenomenon in connection with healing is the fact that calcification of the cartilage takes place not at the normal location—the boundary of the cartilage and bone, but much nearer the epiphysis. It traverses the rachitic zone as a continuous or more or less interrupted septum, and when well developed may be seen with the naked eye as a yellowish-white line near the zone

of resting cartilage (Fig. 18). This phenomenon is the basis of the so-called "line test" which is used so extensively in experimental rickets as a criterion of healing. The line is located in a definite area, namely where calcification would have taken place had rickets not developed. In cases where healing has intervened in the early stage—which occurs especially in the spring—remains of the original zone of calcification may be seen, and in another part of the field and at a different level the new line of calcification may be apparent. The width of the zone of uncalcified cartilage between these lines of calcification gives approximate information as to the duration of the rachitic disorder (Fig. 19).

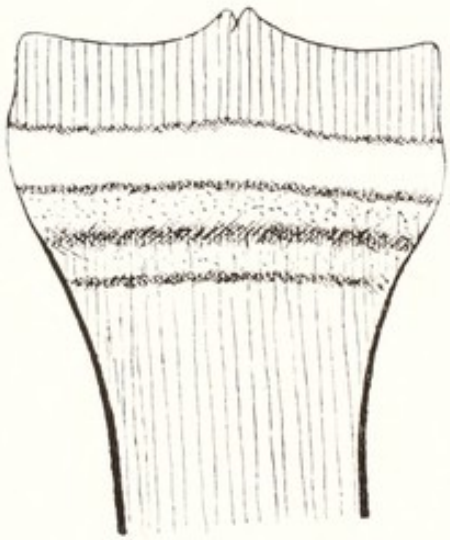


FIG. 19.—Diagram of intermittent healing and relapses in rickets. The two lower transverse areas represent relapses; the transverse lines represent remissions. (Looser, Deutsch. Ztschr. f. Chir., F. C. Vogel, Leipzig, 1920, **152**, 307.)

Following the formation of a new line of preparatory calcification, which begins in the lateral aspects of the cartilage, bloodvessels enter the zone of proliferating cartilage in increasing numbers and more or less rapidly dissolve the cartilage cells, leading eventually to the formation of normal lamellar bone. This occurs irregularly, so that for a considerable period after healing has begun, masses of undissolved cartilage may be evident which serve as a framework for the new trabeculae. "It is important to note," as Pappenheimer states, "that this destruction spares the cells at the base of the cartilage where the columnar alignment is still preserved. Usually rows of four or five cells remain uninvaded by the bloodvessels and these basal cells eventually form the new zone of preparatory calcification, when healing is completed." At this period, the increased congestion of the marrow which has been described in connection with the development of rickets, becomes much more marked and large sinuses of blood are seen within the medullary cavity.

In a large number of cases, 40 per cent in the experience of

Schmorl, healing does not progress steadily but is interrupted by a relapse. In considering metabolism we have noted how this ebb and flow in the course of rickets has played havoc with studies of the calcium and phosphorus balances. Such relapses are associated with a partial or complete absorption of the newly-formed zone of preparatory calcification. In this manner a succession of horizontal tiers of calcification may develop at different levels, due, according to Schmorl, to the action of the vessels which traverse the cartilaginous zone horizontally (Gefaessétage). The tier situated nearest the epiphysis is the one which has been formed most recently, whereas those lying nearer the marrow cavity are the result of previous remissions; the latter are apt to be thinner and less continuous due to absorptive processes. Schmorl never has seen more than three lines of calcification.

It is probable that calcium may be laid down in the cartilage zone quite apart from remission. This is a question which it is difficult to decide from a study of human tissue, where the occurrence of remission cannot be definitely excluded. In animals fed a thoroughly controlled diet and protected from ultra-violet light more accurate deductions may be made. In rats which have been fed, for an uninterrupted period, an amplified rickets-producing dietary—the Sherman-Pappenheimer ration, in which 5 per cent of dried milk has replaced an equivalent percentage of flour—definite calcification of the cartilage may frequently be seen. Occasionally it is evident on this ration even without the substitution of dried milk. That such is the case is not surprising in view of the fact that negative calcium balances are the exception rather than the rule in rickets; generally there is a slight retention of both calcium and phosphorus.

The evidences of healing are summarized by Pappenheimer, as the result of his investigations of the effect of cod-liver oil on rats, as follows: "(1) Deposition of calcium in the distal half of the widened zone of preparatory calcification; (2) invasion of the calcified portion from the lateral and subchondral sides by large bloodvessels, with destruction of the cartilage cells; (3) changes in the osteoid tissue which may be taken to indicate beginning lysis or halisteresis; (4) great dilatation and congestion of the blood sinuses in the metaphyseal region; (5) deposition of granular calcium in the perichondral and pericortical osteoid." He states that he has "observed beginning calcification within twenty-four hours after the administration of a single dose of pure cod-liver oil, and after five to seven days calcium is present often throughout the greater portion of the cartilage."

These characteristic evidences of healing can be brought about regularly in infants or in animals by means of ultra-violet irradiation or by giving cod-liver oil or activated ergosterol by mouth or subcutaneously. As will be discussed in detail in connection with

treatment, it has been thought, mainly as the result of the writings of Kassowitz some forty years ago, that *elementary phosphorus* can stimulate similar reparative processes. That this belief is fallacious and based on a misconception was shown recently in an investigation by Hess and Weinstock. In view of the currency of this opinion, especially abroad, it may be of advantage to summarize this experimental study:

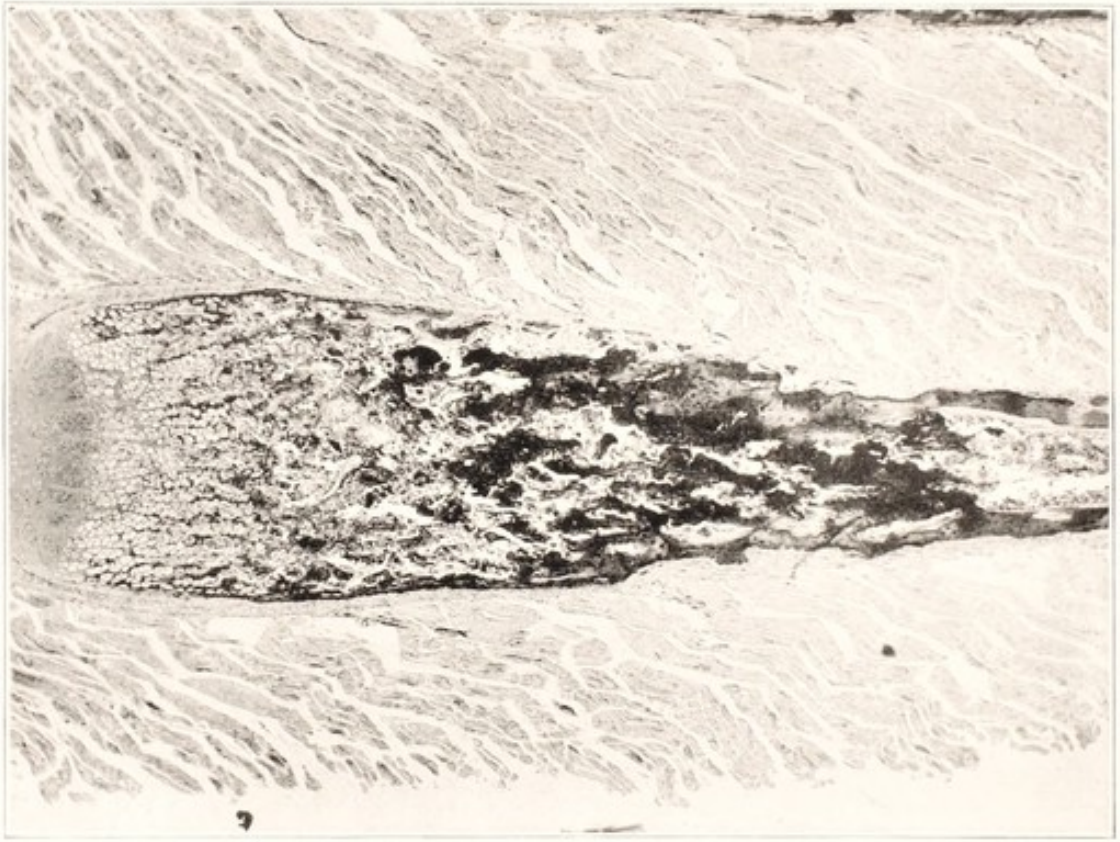


FIG. 20.—Photomicrograph of epiphysis of rat which received rickets-producing diet (containing 20 per cent of dried milk) and, in addition, elementary phosphorus. Development of rickets and of "*phosphorus band.*" (Hess and Weinstock, Jour. Am. Dis. Child., 1926.)

"The feeding of small amounts of elementary phosphorus to rats leads to the production of 'a phosphorus band' at the epiphyses of the long bones. This consists of a transverse layer of dense compact osseous tissue, lying transversely, immediately adjacent to the proliferating cartilage. It is clearly visible on gross examination when the head of the bone is sectioned longitudinally, and stands out prominently in the roentgenographic picture. On microscopic examination, the band is found to consist of heavy trabeculæ of bone, and to be limited to the subepiphyseal region of the shaft. As little as 0.007 mg. of phosphorus a day sufficed to bring about this change in the epiphyses (Figs. 20 and 21).

"Elementary phosphorus, whether given in small or in large doses,

was unable to prevent the occurrence of rickets to any degree whatsoever. Even when the diet was but slightly rachitogenic, the addition of phosphorus did not protect against rickets. Furthermore, combining phosphorus with an inadequate amount of cod-liver oil failed to render the oil adequate. These failures in protective action were noted on diets low in phosphorus as well as on a diet low in calcium.

"A marked increase in calcification of the long bones (subepiphyseal band) took place concurrently with the development of typical rachitic lesions. That such is the case indicates that rickets must be regarded not as the result of a failure of calcification, but as a disorder characterized by specific changes in the preparatory cartilage and in the growing bone. Elementary phosphorus fails because it is unable to bring about calcification within this cartilage or to prevent the undue formation of osteoid tissue."

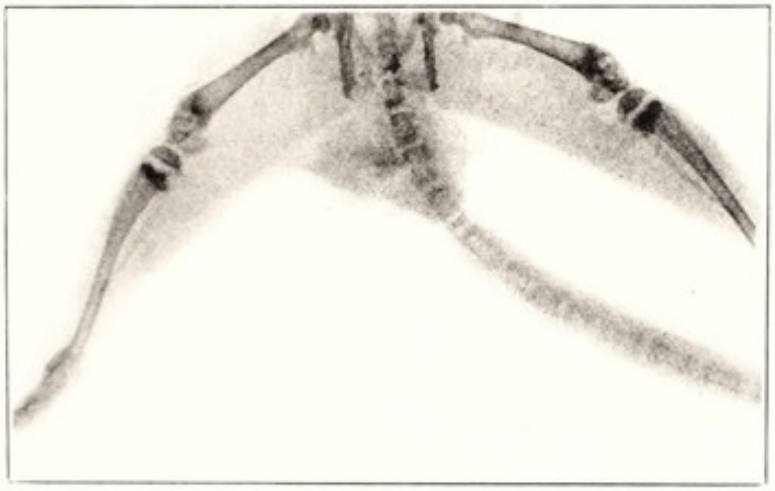


FIG. 21.—Radiogram of rat which received the standard rickets-producing diet plus elementary phosphorus. Co-existence at knee-joints of rickets and of subepiphyseal "phosphorus band." (Hess and Weinstock, Jour. Am. Dis. Child., 1926.)

It should be added that there is still another factor which induces repair in rachitic bones similar to that brought about by the specific agents. I refer to the action of starvation. This effect has not been proved for infants, but it would seem that, at the present time, it may be taken for granted that in general the curative agents for rickets act alike in animals and in man. A few years ago McCollum and his collaborators showed that "starvation causes healing of the rickets in a rat just as do cod-liver oil and sunlight, and the mechanism of the deposition of calcium salts in the proliferative cartilage may be the same," "Not one of the starved animals failed to show reformation of the preparatory zone of calcification, and other evidences of the healing of the rachitic process." The result is thought to be accomplished by means of a mobilization of phosphorus from other tissues of the body. No doubt this is the curative factor

which at times is responsible, especially in connection with a complicating infection, for the evidences of abortive healing apparent in the zone of preparatory calcification in infants.

INVOLVEMENT OF THE TEETH IN RICKETS.

The question of the involvement of the teeth in rickets will be discussed in connection with symptomatology. The subject is one which is rendered difficult by the wide-spread incidence of caries among children both in urban and rural communities. Some believe that rickets is responsible for most of the dental decay in the deciduous and permanent teeth. There has been considerable experimental investigation on this subject, but most of it does not attack the problem directly but shows merely that defects in the teeth can be brought about by various deficiencies in the dietary. Erdheim demonstrated that removal of the parathyroid glands in rats led to gross pathological changes in their teeth. In general it seems that dental caries is apt to be associated with clinical conditions in which the calcium content of the blood is low, for example tetany. It should be added, however, that in the cases of osteomalacia reported from China it is definitely stated that the teeth were not carious. The most intensive work on this subject during the past few years has been carried out by May Mellanby, whose conclusions on this subject, published in 1926, are as follows: "Some evidence has been given to show that the spread of caries in children fed on diets having approximately the same energy value and containing approximately the same amounts of proteins, carbohydrates, fats, calcium and phosphorus, is less when those diets include more calcifying vitamin obtained from milk, eggs and cod-liver oil and less of the anticalcifying substance found in cereals and especially in oatmeal."

PATHOLOGY OF THE ENDOCRINE GLANDS IN RICKETS.

Almost all the endocrine glands have been held responsible for the development of rickets, tetany and osteomalacia. Pathological changes, however, have been found only in the parathyroid glands. The suprarenals, thymus, pituitary, pineal and pancreas have not evinced definite pathological alteration. Gross and microscopic changes of *the parathyroid glands* have been found in experimental rickets, as well as in human rickets, osteomalacia and tetany. A definite and close association has been proved between these glands and calcium metabolism, a subject which will be considered in detail in the chapter devoted to Tetany. The first report on this subject was made by Erdheim in connection with his study of rickets in rats. He found a marked increase in size of the parathyroids of rachitic

animals, this enlargement being the result both of general hyperplasia of the glands and hypertrophy of the individual cells. He regarded this hypertrophy rather as the result than as the cause of the rickets. This study on animals was soon followed by a similar investigation of the parathyroid glands in children. Erdheim summarizes this study in the following words: "In agreement with Schmorl I cannot, at any rate as yet, decide from the microscopic appearance of the parathyroids of children whether they have been removed from a rachitic or non-rachitic child. Nevertheless, I have frequently been impressed by the important fact that the parathyroids from rachitic children are relatively large and full on microscopic examination." Some years later Ritter carried out a study of the parathyroid glands in 10 rachitic children, aged from five months to five and a half years, and came to the conclusion that in prolonged and severe rickets a marked enlargement of the parathyroids comes about which seems to be associated with the early stage of healing. Pappenheimer and Minor examined the glands from 22 rachitic and 19 non-rachitic infants. One of the conclusions which these authors drew from their study was the following: "That there is a very definite increase in the size of the parathyroid glands in cases of human rickets, and that this increase in size is due to multiplication of cells, not to an increase in the size of individual cells. This agrees with Ritter's findings, and does not agree with Erdheim's findings of an increase in size of individual cells in the parathyroids of rachitic rats." It is of interest to note that Nonidez and Goodale found that "the combined effect of lack of direct sunlight and a ration poor in antirachitic vitamine on the parathyroids of growing chicks is expressed in enlargement of these glands."

In none of these studies were analyses of the blood carried out and therefore we cannot be certain whether the cases of rickets were not associated with low calcium and evidences of tetany. In general, it may be stated that the association between pathological changes of the parathyroid glands and osteomalacia and tetany has been far closer than it has been with rickets. In his classic monograph on Rickets and the Parathyroid Glands to which we have referred, Erdheim cites instances of tumor of the parathyroid associated with the development of marked knock-knee, as well as 6 instances of puerperal osteomalacia of which 5 showed microscopic enlargement of the parathyroids. He cites similar observations and points out that where changes in the parathyroids have been noted in rickets the cases have been of the late or delayed type of this disorder. Recently Mandl has collected from the literature 44 cases in which enlargement of the parathyroids has been associated with rickets, osteitis deformans, osteomalacia, senile osteoporosis, and generalized osteitis fibrosa. It would seem that

the subject may be summarized by the statement that the association between hypertrophy of the parathyroids and osteomalacia and tetany is definite and unquestionable, but that its connection with uncomplicated rickets of the low-phosphorus type remains to be substantiated, although it is probable that an interrelationship exists.

THE PATHOLOGY OF OSTEOMALACIA.

Virchow contended that the histological appearances of rickets and osteomalacia showed them to be essentially different. As he expressed it in 1853: "In osteomalacia there is absorption, what has been firm becomes soft . . . in rickets nothing essential is absorbed, soft tissue merely does not become firm." This dualistic point of view has been generally abandoned. In 1885, in his classic work on Osteomalacia and Rickets, Pommer established two fundamental principles—one to the effect that bone is not a fixed tissue, but that throughout life it is subject to absorption and apposition to the same extent as many of the soft tissues of the body, the other, that in both disorders the lesions are due, not to an increased absorption of bone but to a decrease in calcification, in other words to a disturbance in ratio between physiological apposition and absorption. This exposition has been accepted for rickets, but not so fully for osteomalacia. There have been and still are distinguished pathologists who believe that osteomalacia, as well as the most severe form of infantile rickets, sometimes termed infantile osteomalacia, are associated not only with a lack of calcification but with a decalcification of bone which has been laid down. Ribbert, Marchand and M. B. Schmidt have been of this opinion. The question is by no means easy to decide and has led to exceptionally acrimonious discussions. The point of view of halisteresis has been championed by von Recklinghausen, who although he believed in the essential unity of rickets and osteomalacia, maintained that both disorders are associated with dissolution of bone. As Schmorl has remarked, it is very difficult to interpret the histological pictures, as they are rendered most complicated by the fact that the course of both rickets and osteomalacia is not continuous but frequently interrupted by remissions and relapses. These successive changes often follow one another so closely that they bring about most complex patterns of calcification, producing a structure which presents almost impossible difficulties for analysis. In the opinion of Schmorl, as well as of Looser, both rickets and osteomalacia are due to a failure of calcification and not to decalcification or halisteresis. Pommer states in this connection that he was able to convince himself of halisteresis in osteomalacia in only a few areas, and that in these places it seemed to be slight and probably temporary. Subsequently, some twenty-five years later, at the meeting of

the German Pathological Society in 1910, he said that he had noted evidences of decalcification in only one instance, a case of long-standing osteomalacia, and in this case only at a site of marked deformity. He concluded that in exceptionally severe cases of osteomalacia and during its most active period, decalcification may take place.

This subject has been rendered still more complicated by the investigations of von Recklinghausen who described what he termed "Gitterfiguren" (lattice or trellis work), which he interpreted as evidences of decalcification. Schmorl, as well as Schmidt, showed that such figures could be demonstrated in bone which was surrounded by osteoblasts and which was therefore in a state of active apposition. Axhausen also reported the presence of Gitterfiguren in newly-formed bone, as well as their appearance in areas which contain little or no lime salts. Although the Gitterfiguren may well be artefacts, the question of the occurrence of halisteresis cannot be regarded as settled. Quite apart from the histological findings, it is difficult to understand how such marked softening of the bones as has been noted in some cases can come about without the withdrawal of lime salts. This is true likewise in regard to the negative calcium balances which frequently have been reported by reliable observers in cases of osteomalacia. The fact that osteomalacia occurs almost solely in the female sex inclines one to the belief that there is a factor in its pathogenesis which is absent in rickets.

Reference has been made to *infantile osteomalacia*, a condition described some fifty years ago by Rehn and subsequently by von Recklinghausen. The gross anatomical and the clinical picture of this disorder is very different from that of infantile rickets. In a paper published in 1883, Rehn described a series of 5 cases occurring in infants aged one to two years, which were distinguished by the marked softening of the long bones. The epiphyses were not markedly enlarged and the lower extremities straight. The outstanding feature was the exceptional softness and pliability of the bones, especially of those of the arms. This lack of rigidity was associated with marked tenderness of the extremities. In all instances the infants were markedly anemic and thin; one had been nursed for fifteen months. Cod-liver oil was of the greatest value in one case. The outstanding feature, in my opinion, is that all of the infants were of the female sex. This fact calls to mind so sharply the sex incidence of adult osteomalacia that it would be unwise to consider it merely fortuitous. Although there are no histological data which enable a further analysis of these cases, and even though on histological examination they might be found to differ in no respect from infantile rickets, it is quite possible that some etiological factor plays a part in this condition which is not operative in the typical case of infantile rickets.

As is well known, Hanau in 1892 described a "physiological osteomalacia" which occurs during pregnancy and involves especially the pelvic bones, the vertebrae and the ribs. These are not true rachitic lesions. M. B. Schmidt examined bones of this kind and found that "there was no disturbance of balance between lacunar absorption and apposition."

Late or juvenile rickets need not be considered separately, as it is not a pathological entity, but is classified separately because it develops at a period of life far removed from infancy, when growth has almost ceased. As will be brought out in subsequent chapters, there is an unbroken and insensible transition between late rickets and osteomalacia. From a histological point of view, late rickets has not been shown to differ essentially from early rickets. The outstanding distinction is the comparatively slight endochondral disturbance, a phenomenon to be expected and readily understood in view of the lessened growth impetus at the epiphyses during this period of life. It should be remembered that late rickets is preëminently a disease of the male. It would be of great interest to know whether it is associated more particularly with a lowered calcium or phosphorus content of the blood.

The pathology of the bones must still be regarded as the foundation of the concept of rickets. All clinical conditions associated with characteristic bone changes, more especially an excess of osteoid, are included in this category; all others rigidly excluded. This standpoint has been a healthy one. It has resulted in the differentiation and separation of congenital syphilis, chondrodystrophy, fragilitas ossium and other pathological states, which resemble rickets but are essentially different. It is quite possible that the experimental method or the introduction of new histological technique may enable us to differentiate and segregate further pathological entities.

At the present time the question is as to the lesions which should be admitted into the precincts of rickets. Should the pathological picture which has been so ably delineated and defined by Pommer and his successors be insisted upon as the *sine qua non* of rickets? This question has become all the more urgent since it has been shown that the specific curative agents, cod-liver oil, activated ergosterol and ultra-violet radiations, exert a prophylactic and healing effect on disorders of the bones which are at present regarded as being outside the precincts. The result of specific treatment, a criterion employed so frequently to determine the essence and unity of pathological disorders—for example, the use of the antiscorbutic vitamin in the diagnosis of scurvy—is not accepted as conclusive evidence in connection with rickets. For the time being this point of view is sound; otherwise, for example, osteoporosis, a disturbance which is

definitely improved by the various antirachitic agents, would have to be regarded as a form of rickets. To regard osteoporosis as a form of rickets would be a mistake, in view of the fact that porosis can be produced artificially by a mere deficiency of calcium—a relationship long since proved untenable in regard to rickets. On the other hand, osteoporosis, as well as other disordered states of bone, may well bear some kinship to rickets. A similar question has arisen in considering the classification of various diseases of the skeleton which have been described recently in animals, for example the "leg weakness" of chickens and the "cage paralysis" of monkeys. Are such pathological conditions to be included or entirely excluded from the category of rickets or brought into harmony with it? Of late there has been a tendency either to beg the question or to make confusion worse confounded by the creation of a new nomenclature for pathological conditions of bone, by coining a terminology which comprises an appalling number of groups and subgroups.

Furthermore, although there can be no doubt that the lesions of rickets result from a lack of calcification of newly-formed tissue, rather than from a withdrawal of calcium from preformed bone, the question as to the occurrence of halisteresis cannot be considered as absolutely disproved. This is true for osteomalacia and possibly also for some cases of rickets. It is by no means certain that we are able to determine by means of the microscope whether or not calcium has been withdrawn from tissue. Perhaps the employment of potent parathyroid extracts, such as have become available recently, might be helpful in solving this vexed problem. The calcium which is rapidly poured into the blood stream following injection of this hormone is withdrawn from the bony skeleton.

It is clear that the relation of rickets to cognate bone disorders will have to be reconsidered. Such a revision probably will result in the criteria of rickets becoming broader and more flexible. But a study of this kind will have to await a clearer understanding of the etiology and pathogenesis of the various bone diseases, a time when we shall be able to make a classification on the basis of etiology rather than on morphology.

CHAPTER VIII.

THE SYMPTOMATOLOGY OF RICKETS.

In rickets, as in all nutritional disorders, the clinical picture undergoes radical transformation as the disturbance advances. There is a gradual and insensible progression from the early stage when it requires an experienced and careful clinician to establish the diagnosis to the later stage when the signs are so apparent and characteristic that a glance suffices to reveal their true nature. There is indeed a still earlier phase—a latent period as yet inaccessible to diagnostic methods, when rickets is a state of disordered nutrition rather than a nutritional disorder. This form of disorder is similar to the type which is recognized in connection with infantile and adult scurvy, with beriberi, pellagra and xerophthalmia. In considering descriptions of rickets it must be borne in mind that the disease is not static and therefore that a stereotyped account cannot correspond to clinical conditions.

It might be supposed that the symptomatology of a disorder which was clearly delineated over two hundred and seventy-five years ago, would by this time be definitely established and crystallized. As a matter of fact there are still many moot clinical questions, some of them of even prime importance, for example, the significance of early craniotabes, the rachitic origin of carious teeth, the diagnostic value of delayed teething, etc., concerning which there is marked divergence of opinion. The symptomatology of rickets has recently undergone a revision as the result of the introduction of two new laboratory methods, the roentgenological examination of the epiphyses, and the quantitative estimation of inorganic phosphorus in the blood. Although this revision has not fundamentally altered previous conceptions, it has provided valuable checks on methods which are strictly clinical and subjective. But of greater importance is the fact that it has enabled us to diagnose rickets earlier, partly through the direct use of these newer methods and partly, as always happens, through their aid in reappraising signs which had been judged according to the clinical experience of generations. The distinctive characteristic of both of these tests, compared to those previously available, is that they are essentially objective rather than subjective and furnish criteria which can be visualized. In addition the results of the chemical analysis of the blood can be formulated quantitatively in milligram amounts. Although stereo-

typed descriptions cannot portray clinical conditions which in their very nature are variable and in a state of flux, it seems of advantage to preface a consideration of individual signs and symptoms by a picture of a mild and of a severe case of rickets.

THE SIGNS OF EARLY RICKETS.

The early signs must be specifically searched for and will rarely be detected by routine observation, or even in the course of a careful general physical examination. Furthermore, notwithstanding the most detailed and elaborate descriptions, every physician will have to learn by experience how to elicit the various signs—where and how to palpate the skull and the thorax, and especially how to interpret the symptom-complex which is incompletely developed. The earliest symptoms are restlessness, irritability and head sweating, of which the last is most significant. But even head sweating is a sign which is suggestive rather than distinctive and cannot stand by itself, but must await the development of corroborative evidence. The sweating generally is confined to the head, and may lead to loss of hair over the occipital region, especially when it is accompanied by head rolling.[1] The typical baby suffering from early rickets is at about the middle of the first year of life, is fairly well nourished and, on casual examination, apparently healthy and normal. It is only detailed clinical examination which discloses various deviations from the norm. Closer investigation may reveal that the head is somewhat square, and the fontanel too widely open, with osseous borders which are thin and yield too readily to pressure. Areas of cranial softness may be found posteriorly in the parietal bones adjacent to the lambdoid suture. Teething may be delayed, as well as the ability to sit or to stand. Moderate enlargement of the costo-chondral junctions will be found if sought for. The musculature is poorly developed, the muscles being flabby rather than atrophic or wasted. A radiograph of the epiphysis at the wrist taken at this time may fail to show the changes in the ulna which are typical of rickets and which are described in detail elsewhere. A test of the blood at this period generally reveals a lowered concentration of inorganic phosphate. Naturally all of these signs or symptoms will not be present in every case. In an infant which appears to be thriving, of average weight and of healthy appearance, it is evident that such slight deviations may readily be overlooked even by the experienced clinician and pass unnoticed unless specifically sought for.

[1] In the report of the British Commission which studied rickets in Vienna from 1919 to 1922, we find this interesting comment: "Sweating of the head, which is so frequent in England in cases of early rickets, was not commonly seen in Vienna even in severe rickets."

SIGNS AND SYMPTOMS OF WELL-DEVELOPED RICKETS.

The well-developed or advanced case presents an appearance which is recognizable at a glance and requires but little experience to diagnose. It is the common text-book picture. The head has become square and perhaps slightly enlarged. The thorax is deformed and shows two lateral rows of visibly enlarged costo-chondral junctions, and perhaps a shallow horizontal groove traversing its lower part, or even deeper perpendicular furrows compressing and deforming it on either side. The abdomen is large and protuberant, and constitutes the most striking feature of the infant, whose limbs at this stage are generally more or less thin and atrophic. The legs are bowed, and the posture may give evidence of laxity of the ligaments. Roentgenological examination shows characteristic involvement of the distal epiphyses of the ulna and the radius, and the inorganic phosphorus of the blood is reduced to a marked degree.

In the United States the disease rarely progresses beyond this stage except in negroes. The succeeding stage is characterized by an exaggeration of all bony deformities. The chest becomes so misshapen that the pressure of the ribs impedes respiration and the spinal column becomes bent to such an extent that the infant acquires a grotesque appearance. A condition of extreme atrophy develops and we have the picture of a wan, pale infant, with large square head, wasted and deformed body, and immense abdomen. It may be able to sit, but if so, the back is markedly bowed and bent.

There is a still more exaggerated form, at all times rare and now no longer met with, which the text-books and atlases of fifty or seventy-five years ago delighted in portraying. In these infants, almost always female, the bones are twisted so that they have lost all semblance of their normal contours, resembling the advanced osteomalacia of adults; indeed this condition has been termed the "osteomalacic form" of rickets. Such extreme cases are practically never seen in this country or in Europe. It is not known whether they occur in countries such as India, China and Bosnia, where osteomalacia is still prevalent. They remind one of the curiously distorted skeletons, in the zoölogical museums, of monkeys which have lived and died in captivity.

CHANGES IN CRANIAL BONES.

Although rickets involves perhaps all the tissues and organs of the body it must be regarded, from a clinical standpoint, as a disorder of the bones and cartilages. Changes in the *cranial bones* (craniotabes), strangely overlooked by Glisson—anatomist as well as clinician—have been a central point of interest for many years. Its pathology has been considered in a previous chapter. As was

pointed out, congenital lesions, those which may be noted in the new-born, must be sharply differentiated from those which develop in the course of the first few months of life. There is no longer any difference of opinion in regard to the nature of these congenital lesions. Histological examination has demonstrated that they should be regarded not as the result of rickets, but as developmental defects in the formation of the cranium. They should not be termed craniotabes, but rather *congenital cranial defects*, in order to distinguish them from the postnatal cranial lesions which are true poroses. Wieland has suggested the designation "soft skull" or "ossification defect." Generally they are situated in the parietal bones near the sagittal suture, and may be one or several, but always are sharply circumscribed and have a punched-out appearance. This is the contour that we should expect them to have in view of their etiology —a defect in construction, rather than a gradual wasting or thinning of preformed bone. Similar lesions at times may be felt laterally in the temporal bones, or in the parietal bones at a distance farther from the mid-line. Wieland, who clarified this subject in 1910 in his monograph on Congenital Rickets, noted these defects clinically in about 20 per cent of the new-born. They are found less often in premature infants; in Rosenstern's series of cases in 7 per cent, and in 11 per cent among the 188 cases studied by Hottinger.

Wieland has described three distinct courses in the modification of the congenital cranial defects: a spontaneous healing in the first few weeks of life, an initial healing followed by later softening, and a third type characterized by progressive softening, in which the defect forms the nucleus of an increasingly large and soft area. In regard to the first type there can be no suspicion of rickets, in regard to the latter types, the moot question is as to whether the subsequent softening is due to rickets. It may be added that Hottinger has established these same three groupings in connection with the congenital cranial defects in premature infants.[1]

In contradistinction to these congenital cranial defects is the *true craniotabes*, which consists of an abnormal thinning of the bones. This is the lesion described in 1843 by Elsaesser of Stuttgart in a paper entitled "Der weiche Hinterkopf, etc." This classic article treats of the condition which is properly designated craniotabes, a softening of one or more areas of the vault of the skull, most often of the lower part of the parietal bones. It is in regard to these lesions that a marked difference of opinion has always existed and to a certain extent still exists. The question is whether all of these

[1] The significance of osteoporosis and its relation to rickets is unknown. Up to the present time animal experiments have tended to confuse rather than to clarify the question. The fact that true craniotabes shows a definite tendency to develop at the site of the congenital cranial defect must be regarded as evidence in favor of osteoporosis predisposing to rickets.

lesions should be regarded as rachitic or whether some are simple osteoporosis. But before discussing this highly controversial question, it seems necessary to add a few words in regard to the method of eliciting this important sign and to some of its clinical features.

Craniotabes may, according to the classification of Wieland, be divided into two types—the common or progressive form, where the softening begins at the lambdoid suture and advances slowly upward, at the same time that the sutures and the fontanel become wide and their edges unduly compressible. In this way the entire occiput gradually may become soft, accompanied by the development of the well-known signs of rickets in the long bones. The other type, the retrogressive form, is less common and more readily overlooked or misinterpreted. Under these conditions the craniotabes above the lambdoid suture becomes steadily less and may entirely disappear in the course of a fortnight or a month. As there are no other symptoms of rickets at this time, the disorder is readily overlooked. In such cases, rickets may be manifested in later infancy by minor signs, such as a wide fontanel, prominent bosses of the skull or delayed dentition.

The softening or thinning is detected by exerting pressure on the cranium with the tips of the fingers, a procedure which may find the bone indentable like parchment or like a celluloid or rubber ball, or may disclose merely one or more discrete areas hardly as large as the tip of the finger. The lesions may be symmetrical, but almost always are more pronounced on one side than on the other. The examination for craniotabes requires skill and care; and unless every portion of the vault is palpated an area of softening is readily missed. Even the most experienced are guilty occasionally of an oversight of this kind. The head of the infant should be held between the palms of the hands in such a way that the index and middle fingers can palpate the entire surface of the occipital and parietal bones. The most common mistake is a failure to note small lesions in the parietal bones just posterior to the upper level of the mastoid processes along the lambdoid suture. Care must be taken, especially in the very young infant, not to confound a yielding or rocking of the entire bone, with actual softening. A very slight give or compressibility should not be regarded as craniotabes. Extreme pressure should not be exerted, for the periosteum is very sensitive, and babies who smile and appear happy throughout a physical examination will cry when the skull-cap is forcibly palpated.

Following in the footsteps of Elsaesser, some have regarded postnatal softening of the cranial vault as pathognomonic of rickets, whereas others, as stated, distinguish between a rachitic and nonrachitic form of craniotabes. Parrot and Fournier, the famous

French syphilographers, considered craniotabes a lesion of syphilis. Marfan, author of an excellent monograph on rickets, even today is of the opinion that many of these lesions are due to syphilis. Kassowitz looked upon craniotabes as the symbol of rickets, and maintained that he could defend this thesis with convincing histological evidence. On the other hand, many believe that craniotabes, employing this term in its broader sense, may be the result of a simple osteoporosis. It is evident that in such a situation, a mere statistical statement of the incidence of craniotabes is open to more than one interpretation from the standpoint of rickets, even when the congenital cases have been omitted from consideration. Bearing in mind this qualifying circumstance, it may be of interest to mention that Jacobi found 40 per cent of infants to have craniotabes and that Cohn, a careful student of this subject, observed it in about 35 per cent in the course of a routine examination of over 1000 infants. These figures correspond closely to my personal experience; among 289 infants in the clinic, 121 had definite softening of the cranium, in other words somewhat over 40 per cent. These infants were all under six months of age, 200 were under four months and presented 93 instances of craniotabes, and 89 over four months and included only 28 cases. This gives a good idea of the age incidence. All are agreed that premature infants develop craniotabes far more often than those born at full-term. In infants under two months of age, Rosenstern found the incidence among the former to be twice that among the latter.

There are other factors which play a rôle in incidence and must be considered. Season has a marked influence, as it has in connection with all other signs of rickets. This factor was emphasized in the report of the British investigators in Vienna, who showed how much more often craniotabes was found in the winter and the spring than during the summer months. They add the interesting comment that "craniotabes appears to be much more common in Vienna than in London or Glasgow;" indeed they noted it in Vienna in 75 per cent of the untreated infants under six months of age. When we remember that Glasgow represents the acme in the incidence of rickets, it would seem that racial factors may determine the extent to which rickets involves the vault of the skull. We know that a localization of lesions to certain parts of the skeleton has been established in connection with so-called "family rickets."

In regard to the nature of true or postnatal craniotabes, there is closer agreement than was the case some years ago, but the question as to its rachitic origin is still not settled. Wieland and Hottinger, who have given this subject so much consideration, believe that all craniotabes should be regarded as evidence of rickets. On the other hand, Barenberg and Bloomberg, Wilson and Seldowitz, Hojer, Jundell and others are of the opinion that some of the

lesions may be simple osteoporosis. Rosenstern believes that the craniotabes which at times develops in premature infants, especially the areas in the upper part of the parietal bones, are non-rachitic manifestations.

This question is very much more difficult than at first appears. In fact, it cannot be definitely solved at the present time. The best method of approach would seem to be to appraise craniotabes in the light of the well-established criteria of rickets. What about the other signs of rickets associated with craniotabes? What is its relationship to the concentration of inorganic phosphorus of the blood, to the roentgenological changes in the epiphyses and more especially to the histological lesions in the cranium? First let us consider the associated clinical phenomena. An approach from this point of view affords but little information. It is true that at the period when craniotabes is present, other signs of rickets, such as beading of the ribs, enlargement of the epiphyses, etc., generally are absent. But those who believe that all craniotabes is rachitic in nature answer quite properly that this merely indicates that rickets manifests itself first in the bones of the skull; the fact that the cranium grows most rapidly during the first months of life would lead us to expect this order of sequence. Moreover, these infants show signs of rickets elsewhere a few months later. On the other hand, the fact that infants with craniotabes show other evidences of rickets later can be given little weight, when we bear in mind that fully 75 per cent of all infants develop rickets. Recently, however, Hottinger has emphasized a point of clinical importance. He states that in every case of craniotabes he has also found softening along the suture lines, which either preceded or was associated with the craniotabes, in other words that the craniotabes was not an isolated phenomenon. This observation must be made the basis of further clinical investigation, to determine whether this association is invariable.

A few years ago it would have been thought that the Roentgen rays could help us out of our dilemma; but it is now recognized that the roentgenological diagnosis of rickets is possible only when the metabolic disturbance has been under way for a considerable period. Great weight cannot, therefore, be attached, in this connection, to the data in Table 16 which show that among 68 infants having craniotabes, under the age of four months, only 1 presented evidence of rickets by the Roentgen rays. Furthermore, as will be brought out in discussing the diagnosis of rickets, the roentgenological examination of the epiphyses is subject to interpretation and cannot be considered a purely objective sign.

The same is true, although to a less extent, in regard to the estimation of the inorganic phosphorus concentration of the blood. As will be brought out in the succeeding chapter, this is an early, as well

TABLE 16.—RELATION OF CRANIOTABES TO OTHER SIGNS OF RICKETS IN INFANTS UNDER FOUR MONTHS.[1]

	Craniotabes, first examination			Coincident signs of rickets			
Case.	Date.	Age, weeks.	Degree.	Beading.	Roentgenogram.	Phosphorus (inorganic).	Comment.
1	Sept. 16	2	Slight	Negative	Negative	...	
2	Mar. 15	4	Slight	Negative	Negative	3.8	
3	April 23	8	Slight	Negative	Negative	4.3	
4	Feb. 28	6	Slight	Slight	Negative	3.9	
5	Mar. 12	8	Slight	Slight	Negative	3.7*	
6	April 30	4	Slight	Slight	Negative	4.1	
7	Mar. 3	6	Slight	Negative	Negative	4.0	
8	Oct. 22	5	Slight	Negative	Negative	...	
9	May 14	8	Moderate	Negative	Negative	4.5	
10	May 30	2	Marked	Negative	Negative	...	
11	Oct. 21	8	Slight	Negative	Negative	...	Twin
12	Jan. 15	4	Slight	Negative	Negative	4.5	
13	April 1	6	Slight	Negative	Negative	...	
14	May 18	6	Marked	Negative	Negative	...	
15	June 29	7	Slight	Negative	Negative	...	Premature
16	Sept. 2	8	Marked	Negative	Negative	...	Premature
17	Jan. 30	2	Slight	Negative	Negative	...	
18	Feb. 25	5	Marked	Negative	Negative	...	
19	Aug. 16	8	Marked	Negative	Negative	4.3	
20	Nov. 30	4	Slight	Negative	Negative	...	
21	Dec. 2	4	Slight	Negative	Negative	4.0	
22	July 27	4	Marked	Negative	Negative	...	
23	Aug. 7	4	Slight	Negative	Negative	...	
24	Dec. 19	2	Slight	Negative	Negative	...	Twin
25	Sept. 12	6	Moderate	Negative	Negative	...	
26	Oct. 20	4	Marked	Negative	Negative	...	
27	Dec. 15	2	Marked	Negative	Negative	...	Twin
28	Dec. 15	2	Marked	Negative	Negative	...	Twin
29	May 16	10	Slight	Negative	Negative	4.1	
30	Oct. 3	4	Marked	Negative	Negative	...	
31	Nov. 17	2	Marked	Negative	Negative	...	Twin
32	Nov. 17	2	Marked	Negative	Negative	...	Twin
33	Aug. 1	8	Moderate	Negative	Negative	5.4	Premature
34	Nov. 17	8	Slight	Negative	Negative	...	Premature
35	Sept. 30	4	Slight	Negative	Negative	...	
36	June 15	2	Slight	Negative	Negative	4.5	
37	Feb. 16	8	Slight	Slight	Negative	...	
38	Mar. 2	4	Slight	Negative	Negative	...	Twin
39	Mar. 2	4	Slight	Negative	Negative	...	Twin
40	Mar. 2	4	Slight	Negative	Negative	...	
41	May 6	10	Slight	Negative	Negative	4.7	
42	May 6	6	Moderate	Negative	Negative	4.5	
43	Mar. 23	4	Slight	Negative	Negative	4.4	
44	April 29	4	Slight	Negative	Negative	4.6	
45	Jan. 21	4	Marked	Negative	Negative	...	
46	Nov. 17	6	Slight	Slight	Negative	...	
47	Mar. 14	8	Slight	Negative	Negative	...	
48	June 13	3	Slight	Negative	Negative	5.1	
49	May 15	8	Slight	Negative	Negative	4.0	
50	Dec. 11	6	Slight	Slight	Negative	...	
51	April 25	12	Slight	Slight	Negative	3.9	
52	June 13	8	Slight	Negative	Negative	5.1	
53	Mar. 13	13	Slight	Negative	Negative	...	
54	Aug. 3	2	Marked	Negative	Negative	...	
55	Sept. 11	4	Slight	Negative	Negative	...	
56	Sept. 12	8	Slight	Negative	Negative	...	
57	Mar. 5	2	Marked	Negative	Negative	...	
58	June 20	6	Marked	Negative	Negative	...	
59	June 25	14	Slight	Negative	Negative	...	
60	May 9	12	Moderate	Negative	Negative	4.1	
61	April 7	12	Slight	Slight	Negative	4.3	
62	April 12	12	Moderate	Negative	Negative	4.1	
63	Oct. 1	14	Marked	Slight	.....	...	Twin, premature
64	Oct. 1	14	Slight	Slight	.....	...	Twin, premature
65	Jan. 30	14	Slight	Slight	Slight†	...	
66	Aug. 31	14	Marked	Negative	Negative	...	Premature
67	Feb. 27	12	Marked	Negative	Negative	...	
68	Mar. 23	14	Slight	Negative	Negative	4.7	

[1] Am. Jour. Dis. Child., 1924, **28**, 716.

* Youngest case to show low inorganic phosphorus. (Normal concentration by the Bell-Doisy method is 4 to 5 mg.)

† Youngest case to show rickets by roentgenogram.

as a valuable sign of rickets. But, possibly, the local cranial lesions develop at a still earlier period. For example, some years ago in appraising "the significance of clinical, radiographic and chemical examinations in the diagnosis of rickets" (Hess and Unger), it was shown that beading of the ribs often develops before diminution of phosphate in the blood. Data in regard to the chemical constitution of the blood in craniotabes were included in the study from my clinic by Barenberg and Bloomberg (Table 16). This investigation showed that among 68 infants, under the age of four months, who had craniotabes, only 1 had a concentration of inorganic phosphate less than 3.75 mg. (These tests were carried out by the Briggs modification of the Bell-Doisy method, according to which the normal concentration ranges from 4 to 5 mg.) On the other hand, among infants over four months of age, who had craniotabes, the inorganic phosphorus was generally, but not always, less than 3.75 mg. per 100 cc. of plasma. Wilson and Kramer, Rosenstern and Bruns report similar results in an analysis of a small series of cases. These results coincide, therefore, with the clinical experience, which indicates no chemical changes in the blood in rickets at the time craniotabes develops. This is not, however, conclusive evidence against the rachitic nature of the cranial softening.

It is remarkable that more studies have not been carried out to ascertain the histological changes in the skull bones. Little has been attempted in this field since the publication of the monograph of Wieland in 1910. Very recently Hottinger published a painstaking histological study of the cranial bones of a number of premature infants. From this study he concluded that all postnatal craniotabes is of rachitic nature and that it is associated with the typical lesions of rickets, more particularly an increase of osteoid tissue.

This report includes a histological examination of 6 cases of true craniotabes in premature infants. Signs of cranial softening were noted clinically in 3 of these by the time the infants were two months of age. One case is particularly convincing—that of an infant ten weeks of age, which showed the characteristic histological changes in the parietal bones, as well as at the costo-chondral junctions, although the concentration of inorganic phosphorus was 5.1 mg. per 100 cc. of blood.

This investigation indicates that a greater number of these cranial lesions are rachitic than had been believed. However, the fact that the infants were premature, and more particularly that the number of observations were few, excludes their being accepted as conclusive.

The matter of prematurity requires special consideration in connection with all the clinical manifestations of rickets, but especially with the development of craniotabes. The ordinary signs upon

which we depend for diagnosis occur much less frequently in the premature than in the full-term infant. Typical cup-shaped depressions in the epiphyses of the ulnæ generally fail to develop even when the diagnosis of rickets is definite. In this respect, the premature infant reacts much like the atrophic infant; it is a representative of the "passive" rather than of the "active" type of disorder, if we adopt the classification of Wimberger. Likewise the changes in the concentration of the inorganic phosphorus and of the calcium in the serum cannot be relied upon to establish the diagnosis in the premature infant. It has been shown by Scheer and Salomon and by Hottinger, that rachitic premature infants tend to have a high concentration of phosphorus and a low concentration of calcium in the blood. These observations I can confirm from personal experience. The following cases in point may be cited; they are included in Table 32 in the chapter on Treatment.

B. Y., a triplet, was admitted to the institution when aged two months, weighing $5\frac{3}{4}$ pounds (2.6 kg.). In spite of receiving cod-liver oil, craniotabes developed (+++) and marked beading (++). At four and a half months of age the weight was $8\frac{3}{4}$ pounds (4 kg.). *Roentgenographs showed slight but definite rickets, associated with osteoporosis, when the serum calcium was 10.1 and the inorganic phosphorus 6.3 mg. per 100 cc.* The beading, and especially the craniotabes, were benefited within twenty-four days by irradiated ergosterol, the roentgenographs showed healing and the inorganic phosphorus rose to 9.6 and the calcium to 11.4 mg.

F. H., a premature infant, was admitted when aged five days, weighing 3 pounds 11 ounces (1.7 kg.), and $17\frac{1}{2}$ inches (44.5 cm.) in length. The fontanel was large and the sutures wide. At two months of age she weighed 6 pounds 3 ounces (2.8 kg.), had marked bilateral craniotabes (++), moderate beading (+), and the epiphyses showed very mild rickets with osteoporosis. At three months of age the baby weighed 8 pounds 10 ounces (3.9 kg.) and was $22\frac{1}{5}$ inches (56.5 cm.) in length. The craniotabes, as well as the beading had increased and the legs were slightly bowed. Small doses of irradiated ergosterol were given. *The Roentgen rays showed progressive rickets, in spite of the fact that the calcium of the blood was 13.6 and the inorganic phosphorus 4.2 mg. per 100 cc.* Two weeks later, however, healing was evident in the roentgenographs; at that time the concentration of calcium was 12.3 and that of inorganic phosphorus 6 mg.

The first case is an instance of the development of marked craniotabes with a serum calcium of 10.1 and an inorganic phosphorus concentration of 6.3 mg. per 100 cc. of blood. The second case is still more striking. Here we find that a premature infant has marked craniotabes and evidence of progressive rickets according to the Roentgen rays, but shows a concentration of 13.6 mg. of

calcium and of 4.2 mg. of inorganic phosphorus in the blood. Such figures are never found associated with rickets in full-term infants. They indicate that the regulatory mechanism of calcium and phosphorus is not the same in the premature as in the full-term infant.[1]

In view of the present status of our knowledge in regard to craniotabes, it would seem advisable to welcome it as an early and valuable indicator of rickets but not to conclude that every instance of craniotabes which develops in postnatal life is of rachitic origin, for it still seems probable that osteoporotic lesions may develop in the vault of the skull, particularly in cases where the head is large. From the clinical, in contradistinction to the pathological, point of view, the congenital defects are also a source of confusion. If we are fortunate enough to have the opportunity to examine the infant soon after birth we are in a position to recognize the prenatal origin of the lesions. But if we see the infant for the first time at the age of six or eight weeks, the distinction between false and true craniotabes is by no means easy. For this reason the sign possesses increasing value the greater the age of the infant, and often is equivocal in infants under two months of age. This is especially the case when the site of the lesion is not characteristic and other signs of rickets are wanting.

Areas of thickening rather than of thinning may develop in the skull. The most common sites naturally are the centers of ossification where growth is most rapid. The parietal eminences become hypertrophied and prominent, giving to the head a brachycephalic conformation. The frontal bones also may be involved in this process, leading to the imposing "Olympian front" which is so characteristic of rickets, and may be carried into adult life as one of the vestiges and indications of this disorder. When the parietal as well as the frontal eminences are enlarged the head becomes square, the "caput quadratum" of Parrot. In extreme instances grooves develop along the course of the sagittal and the frontal sutures which divide the vertex into four segments and lead to the formation of the "natiform" skull and to an appearance which has been compared to that of a hot cross-bun. Extreme types of frontal bossing frequently develop as the result of congenital syphilis, and are difficult to distinguish, by mere inspection, from the rachitic bosses. In general it is true that the syphilitic enlargements are more pronounced, affect both frontal bones, and have a greater tendency to be symmetrical. Although the characteristic rachitic head appears large, the capacity of the skull is not increased unless hydrocephalus

[1] The entire lack of all clinical signs of rickets in some cases raises the question as to whether some infants, more particularly premature infants, cannot suffer from the metabolic disturbances of rickets and nevertheless give no evidences whatsoever of a derangement of intermediary metabolism, in other words whether there may not be a form of rickets which remains absolutely latent for a prolonged period.

develops. The appearance of increased size is due to the thickening and overgrowth of the cranial walls. Recently Huldschinsky has worked out a cranial index in order to measure the growth of the brain and found that there is a disproportion between the cranial vault and the cranial base, and that in some cases there is an absolute enlargement of the brain.

DEFORMITIES OF THE FACIAL BONES.

Some are of the opinion that rickets brings about frequent and marked deformities of the facial bones, of both the *inferior and the superior maxilla.* Marfan has been strongly of this opinion for many years. He considers a lower jaw in which the arch is flattened between the canine teeth as typical of rickets; at times the chin protrudes (menton de galoche). This deformity does not come about until the second year of life and may prevent the normal development of the teeth. The deformity of the superior maxilla, the high, angular and somewhat narrow palatal arch, Marfan considers one of the most reliable and permanent stigmata of rickets. This exaggeration of the longitudinal axis of the superior maxilla was mentioned by Fleischmann in 1877. Personally I have found it very difficult to interpret this deformity on account of the marked variation in shape of the palatal arch in infants. Even young infants only a few months of age and entirely free from rickets may have a high, angular arch or an overlapping ("overbite") of the superior maxilla.

Marfan believes that the upward projection of the superior maxilla leads to an obstruction of the nasal fossæ, which is erroneously attributed to the presence of adenoids. This is a question of importance and requires more careful study and corroboration. It is possible that rickets, which in general leads to hypertrophy of cartilage, may be the cause of some malformation of the cartilaginous septum of the nose.[1]

DEFORMITIES OF THE THORAX.

The thorax is almost always involved in rickets. The typical change is the enlargement of the costo-chondral junctions which is known as "*beading*" *of the ribs* and in its entirety constitutes the "*rachitic rosary.*" In its marked and well-developed form, the rosary is evidenced by two, more or less symmetrical, rows of small knobs or circumscribed elevations running almost longitudinally

[1] This subject could be satisfactorily studied in an area such as the West Indies where rickets practically does not occur. It would be interesting to obtain reliable data regarding the incidence of deformities of the nose and of the jaws in natives of these islands.

along the sides of the chest wall. It is distinctive of rickets, and is in danger of being confused only with the far less frequent "scorbutic rosary;" the differentiation between the two will be discussed in considering diagnosis. In two instances I have noted marked "beading" in cases of diabetes, and Andrews observed it in the Philippines in infants which had died from beriberi. The difficulty in regard to this sign lies in defining what degree of beading should be designated as rachitic, in determining the enlargement which is compatible with a normal junction of rib and cartilage. Its appraisal, as in the case of most clinical phenomena, can be learned only at the bedside. A slight elevation should not be considered of significance, especially the beading which is so frequently palpable in the new-born or in infants during the first two or three months of life. It is a sign which cannot be checked by means of Roentgen rays, as the rosary is not apparent by radiograph until it is well advanced. Recently Dalyell and Mackay made microscopic examinations of costo-chondral junctions to determine the histology of the enlargements. They found that when beading of the ribs had been noted, characteristic rachitic lesions were almost invariably found histologically at the junctions; that the error lay in quite the other direction—typical histological changes frequently being found where the beading had been considered too slight to warrant a diagnosis of rickets.

From a clinical point of view the most frequent error is one of omission and not of misinterpretation, of failure to examine carefully for this sign. Another error is due to faulty technique, to palpating for the rosary along a plane median to the costo-chondral junctions. The enlargement involves generally the middle tier of ribs, the fifth, sixth, seventh and eighth, and may be difficult to elicit if the ribs are overlaid with fat or muscle. In an experience of some thousands of routine physical examinations carried out in the course of a study of rickets, beading of the ribs has been found to be the most constant early clinical sign.[1] Far greater reliance has been placed on it than on craniotabes, bowing of the legs, head-sweating or the roentgenographic picture. The accompanying roentgenograph, taken at necropsy, shows that the epiphyses at the wrist may present a normal appearance in spite of the fact that marked beading of the ribs has developed (Fig. 22). "Beading" is of especial value as an early sign during the first year of life. By the second year it may become obliterated or obscured by the recession of the costo-chondral junctions which accompanies the formation of the transverse depression known as "Harrison's groove." The rosary may persist

[1] Schmorl, in the course of his extensive histological experience, found the chronological sequence of rickets to be as follows: costo-chondral junctions, lower epiphysis of femur, upper of humerus and upper of tibia and fibula, lower of radius and ulna, upper of femur, metatarsus and phalanges of feet.

throughout childhood and, in extreme cases, even into adult life, and constitute one of the telltale vestiges of rickets. A sharp distinction should be drawn between the value of beading of the ribs for early diagnosis and its value as a criterion of healing or of cure. No reliance can be placed on this sign in judging the efficacy of a curative agent, nor is the presence of a rosary an indication that an infant is suffering from active rickets.

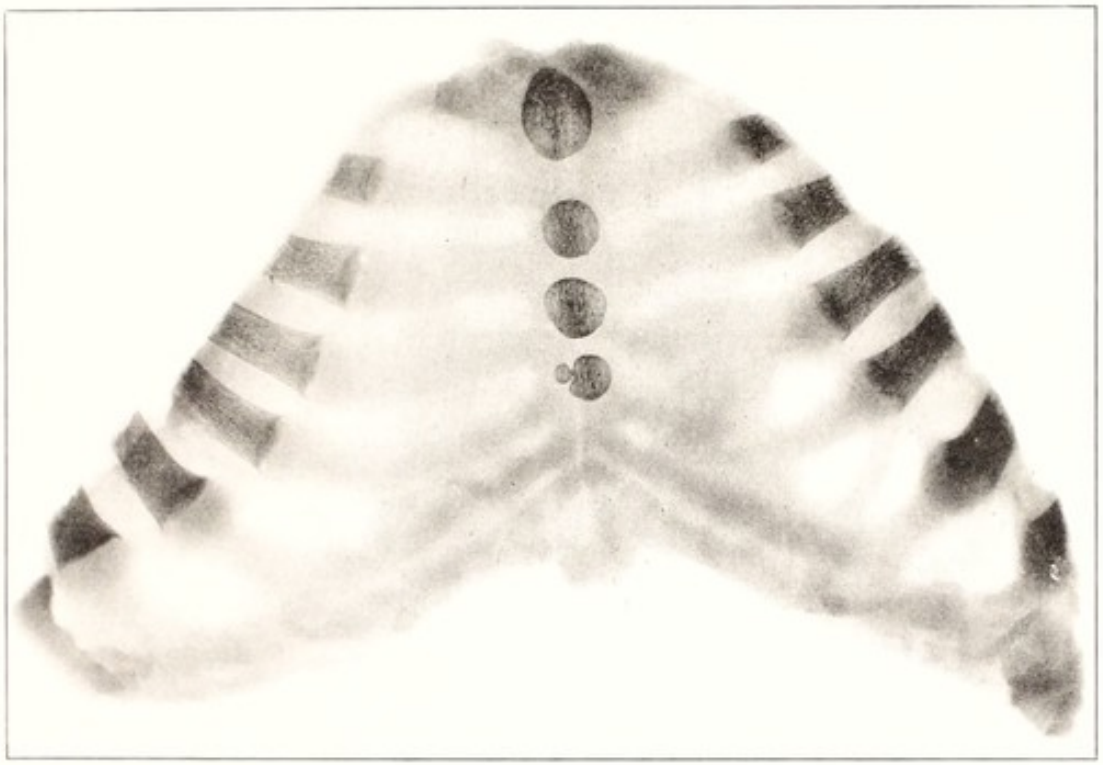


FIG. 22.—Radiograms taken postmortem of costochondral junctions and of epiphyses of wrist. Marked beading of ribs coincident with normal epiphyses of the radius and ulna. (Hess, Abt's Pediatrics, 1923, W. B. Saunders Co., Publishers.)

Mention has been made of a transverse depression termed *Harrison's groove* or sulcus. Of the two characteristic sulci formed on the

anterior chest wall as the result of rickets, this deformity occurs the more frequently. It constitutes a furrow or concavity which runs horizontally across the lower plane of the thoracic wall at the level of the attachment of the diaphragm, and extends anteriorly from the base of the ensiform cartilage to the posterior folds of the axillæ (Fig. 23). Generally it is less marked on the right than on the left

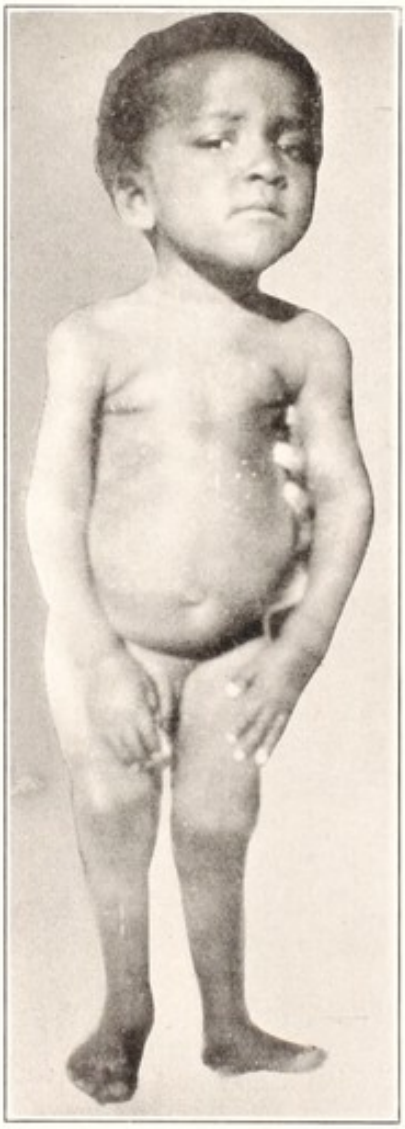


FIG. 23.—Colored child, aged four years, with marked rickets. Stunting; square head; Harrison's groove; enlargement of wrists; knock-knee. (See Fig. 26, p. 228, showing pelvis of this child.) (Courtesy of Drs. M. Gleich and S. Goodman.)

side, due to the underlying support of the liver. This deformity may be noted even in mild cases and generally disappears in later childhood, but its occurrence may be revealed for many years by an outward flanging of the lower border of the false ribs. In severer cases longitudinal grooves may develop, either anterior or posterior to the plane of the "rosary." They are not vertical or parallel, but diverge outward as they descend. As a result of these depressions

the chest may become greatly deformed, so that the sternum with its adjacent cartilages projects forward, giving the thorax the appearance which Glisson likened to the "keel of a ship," or "breast of a hen" and others to the contour of a violin. It is commonly termed "pigeon breast." Although the "pigeon breast" may be the result of rickets, it can develop quite independently of this disorder, due to the strain and tension of a prolonged respiratory disease such as whooping cough. The same is true in regard to the "funnel-shaped" chest in which the sternum and sternal ends of the cartilages are sunken. Both of these deformities may be moderately developed at birth or appear in infants a few months of age.

Another abnormality which is considered pathognomonic of rickets is *pliability or softness of the ribs*, a condition characterized by marked yielding of the thoracic wall when pressure is exerted upon it. Kassowitz laid great stress on this sign. A recent study (1924) of this condition convinced me that this softening may come about as the result of malnutrition, in infants who have never manifested any evidence of rickets, as judged by clinical, chemical or roentgenological tests. Nor does this abnormal compressibility yield to specific antirachitic therapy—to cod-liver oil, ultra-violet irradiation or activated ergosterol. Infants who have had marked craniotabes, which has resulted in flattening of the occiput, will often be found to have "non-rachitic softening of the ribs."

In severe cases the chest may become so deformed that pressure is exerted upon the lungs and thoracic bloodvessels, leading to disturbances in respiration and in circulation. Such deformities are rarely seen in this country, but may be found among negro babies, as recently described by Park and his associates. The chest may be misshapen in various directions as the result of the tugging of the diaphragm and of the muscles of the thoracic wall. Polypnea may result, bronchitis is frequent, and death may ensue if pneumonia develops; in such cases the development of whooping cough almost always results fatally. The pulse-rate has a tendency to be rapid. Some years ago the English heart-specialist, Balfour, called attention to "the simulation of aneurism by malposition of the aorta due to rickets," a condition which must be thought of where the chest is deformed and a pulsation is noted in the second or third intercostal space.

The *shoulder girdle* likewise may be involved. In fact, the only bone in which lesions have not been recorded is the sternum. The clavicle is misshapen even in cases of moderate degree, the deformity consisting of an exaggeration of the normal curves—a rule which holds good in regard to all bony deformities in rickets. The inner two-thirds becomes excessively convex and the outer third abnormally concave. There is a characteristic projection of its acromial end which may persist far into childhood. Fractures, generally

incomplete and of the "green-stick" variety, are not infrequent and lead to the formation of calluses near the attachment of the sterno-cleido-mastoid muscle. The changes in the scapula are of anatomical rather than of clinical interest and consist of a thickening of the border and a bending which renders the anterior surface concave rather than flat.

DEFORMITIES OF THE SPINE.

The spine frequently is deformed. As mentioned in the chapter on History, some are of the opinion that the name "rickets" is derived from the Greek word for spine. Even in mild cases, such as are becoming relatively more common, the vertebral column may be found to bow unduly when the infant sits. This is due mainly to the laxity of the supporting ligaments. In severe cases, a *kyphosis* of greater or less degree develops which is generally attributed to the pressure exerted on the vertebræ by the weight of the body. The kyphosis is situated in the thoracic region and has been confused with that of Pott's disease. It differs from this kyphosis in several respects; it is curved rather than angular, reducible (in the prone position) when the infant's thighs are raised and gentle pressure is exerted on the kyphos, and is unaccompanied by spasm. However, where the deformity has existed for a long period the differential diagnosis may not be so simple. Exceptionally, this condition is attended by pain and tenderness. I have met with a few instances of this kind. For example: A few years ago an infant in my clinic, aged fifteen months, developed localized tenderness over the upper thoracic vertebræ. It had moderate rickets, associated with lordosis. There were no signs of tuberculosis or other infection. The tenderness was definite and lasted for about five days. The infant remained in the institution for many months and showed no signs of a complicating disorder.

It should be added that many clinicians of twenty-five or fifty years ago believed in bone tenderness as a sign of rickets. The following quotation from Barlow (1890) who was quite alive to the pitfalls of infantile scurvy, is interesting in this connection: "It seems to be in the main a bone tenderness, and to reach its maximum in the epiphyseal-junction region, but it is often very ill-defined." And again, "Along with the tenderness of the limbs ought to be mentioned the irritability which sometimes accompanies the acute phase of the formation of the cranial bosses, and which is possibly due to the overgrowth of vascular osteoid material and the accompanying stretching of the pericranium."

Scoliosis may likewise develop but makes its appearance later in life and will be referred to in considering late or juvenile rickets. It occurs more frequently in girls than in boys, and has not the same

tendency to correct itself when the erect posture is assumed; it is the lesion which gives rise to the high shoulder and high hip. Exaggerated lordosis associated with the typical pot-belly and flat-foot combine to create what has been termed the "rachitic posture."

DEFORMITIES OF THE EXTREMITIES.

The typical rachitic lesion of the upper extremities is the *enlargement of the epiphyses* of the lower ends of the radius and the ulna. This swelling gives to the wrist the appearance of being double-jointed and was considered so characteristic by laymen that in Germany it led to rickets being popularly dubbed the "double-joint disease." Enlargement of the epiphyses, whether of the bones of the wrist or of the ankle, is by no means easy to determine unless the swelling is pronounced. Not only is there a marked variation in the size of the epiphyses in normal individuals but also in various races. For example, the Arabs have small wrist bones, whereas those of the negro are exceptionally large; it may be added that rickets tends to more frequent and to greater enlargement of the epiphyses in the negro than in the white infant. Furthermore large heavy infants are subject to enlargement of the epiphyses more often than are atrophic babies. Ylppö drew attention to the fact that premature infants usually do not develop enlarged epiphyses or other deformities in the course of rickets; the tendency is rather to an atrophy of bony tissue, associated with roentgenological "fraying" of the epiphyses. In my opinion the occurrence of epiphyseal enlargement has been unduly stressed as an early sign of rickets. It should be regarded rather as one of the later signs, as it is preceded usually by craniotabes, beading of the ribs, diminution of inorganic phosphorus in the blood and roentgenological signs. Previous to the routine use of cod-liver oil in my clinic almost all the babies sooner or later developed rickets in a mild degree, but enlargement of the epiphyses was found in but a small percentage. In spite of the fact that roentgenograms of the wrist frequently showed the typical changes, definite enlargement was not noted by palpation. Perhaps the fact that these infants rarely crawled, an activity which throws additional weight on the epiphyses, may account for the infrequency of this deformity. There can be no doubt that enlargement of the epiphyses depends to a certain extent on simple mechanical factors.[1] When hypertrophy of the

[1] In this connection the recent experiments of Mueller are of interest (page 127). By resecting the lower end of the radius in dogs he was able to transfer the burden of weight from the epiphysis of the radius to that of the ulna. This led to an hypertrophy of the epiphyseal cartilage of the ulna with microscopic changes resembling rickets. The enlargements of the costo-chondral junctions are probably also due in part to mechanical factors. At this site the exciting factor is the constant respiratory movement.

ends of the radius and the ulna occurs to a marked degree, the deformity may persist into adult life and serve as an indication of previous rickets.

The shafts of the bones of the forearm may be bent, the curve being an exaggeration of the normal contour with an increase of the convexity at the wrist. Such deformity is noted on clinical examination only in the severer cases, but is quite commonly seen in roentgenological films, where it may constitute the sole evidence of healed rickets. The Roentgen rays may likewise disclose one or more fractures of the ulna or of the radius in association with rickets. This was noted in two instances in which the most careful clinical examination gave no indication of fractures, which were of the incomplete or "green-stick" variety. One of these babies was well nourished and breast-fed, the other poorly nourished and bottle-fed; both had clinical as well as roentgenological signs of rickets.

The fingers at times are altered in shape, a change which may be noted incidentally in radiographs, or be evident on direct inspection. The phalanges are spindle-shaped, giving rise to a deformity which Koplik termed "the rachitic hand." Siegert believed that the change in outline was due to an elongation of the joints rather than of the bones, however in rickets both ligaments and epiphyses are involved.

The *lower extremities* are frequently affected by rickets, the typical deformities being either bow-legs (genu varum) or knock-knee (genu valgum). In the lay mind rickets is largely associated with bowing of the legs, in fact the Italian and the negro mothers bring their babies to the clinics and health centers to obtain cod-liver oil to protect them from becoming "bandy-legged" (Fig. 24). *Bowing of the legs* is often present in the new-born and in infants a few months of age. But the deformity at this early period is not the result of rickets but of the cramped posture of the fetus in the uterus. The bowing due to rickets is a later sign, and although not uncommonly met with during the first year of life, more often does not develop until the second year. It has long been the accepted opinion that the bowing or bending results from the bones being insufficiently firm to support the weight of the body. This point of view is supported by the undoubted fact that heavy babies who begin to stand or to walk early in life are especially prone to this deformity. But extreme bowing occurs also in poorly-nourished infants who have never stood on their feet. Instances of this kind are encountered among the extreme cases of rickets seen in colored infants in which rickets is combined with osteoporosis. In general a clinical distinction must be made between the rickets in the poorly-nourished and in the well-nourished infant and especially in regard to bowing of the legs.

In robust, heavy babies, bowing may occur unaccompanied by

other signs of rickets. In a report from my clinic by Barenberg and Bloomberg it was pointed out that 14 infants developed definite bowing of the legs while in the institution, although at no time had they shown beading of the ribs, roentgenological lesions of the epiphyses, diminution of blood phosphorus or other established signs of rickets (Table 17). The course of these babies was followed from four to twelve months, during which period routine monthly roentgenological and clinical examinations were carried out. It is evident therefore that from an etiological standpoint a *non-rachitic genu*

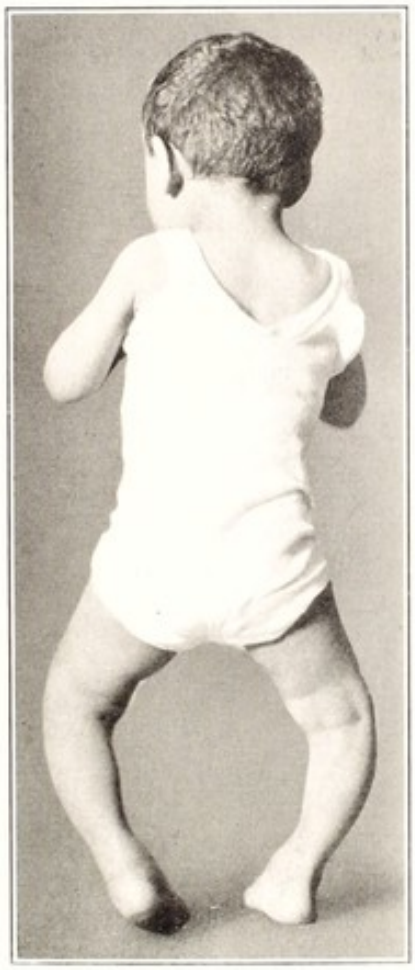


FIG. 24.—Marked bow-legs in an Italian child.

varum must be recognized. The bowing to which I have reference is the common form which involves the lower third or quarter of the shaft of the tibia. Whitman describes a type "in which the deformity is greatest at the knee, and which is accompanied, as a rule, by marked laxity of the ligaments."

Knock-knee (*genu valgum*) may develop instead of bow-legs. The statistics of the Hospital for Ruptured and Crippled, in New York, for a period of fifteen years, as given by Whitman, record 8760 cases of deformities of the legs; among this number about two-thirds were

instances of bow-legs and one-third of knock-knee, the bow-legs occurring in males in 60 per cent of the cases and knock-knee being about evenly divided between the sexes. Knock-knee is more frequently associated with bodily weakness, and mild grades may result from laxity of the ligaments with little change in the internal structure of the joint. In marked cases there is deformity of the femur and of the upper end of the tibia with a disturbance in relationship between these bones.

TABLE 17.—BOWING OF LEGS WITHOUT OTHER SIGNS OF RICKETS.[1]

	Previous course in regard to rickets.*				First appearance of bowing.		Coincident signs of rickets.			Subsequent course in regard to rickets.†						
Case	Age, months	Beading	Roentgenogram	Phosphorus (inorganic)	Age, months	Weight, lbs.	Beading	Roentgenogram	Phosphorus (inorganic)	Age, months	Beading	Roentgenogram	Phosphorus (inorganic)	Stood age, months	Number of examinations	Duration, months
1	11	Slight	Neg.	4.1	12	20	Neg.	Neg.	4.0	13	Neg.	Neg.	...	9	5	5
2	10	Neg.	Neg.	3.8	12	19	Neg.	Neg.	...	14	Neg.	Neg.	...	—	8	12
3	6	Neg.	Neg.	4.5	8	14	Neg.	Neg.	...	12	Neg.	Neg.	...	—	6	12
4	7	Neg.	Neg.	...	9	16	Neg.	Neg.	...	14	Neg.	Neg.	4.0	—	10	13
5	9	Neg.	Neg.	...	10	18	Neg.	Neg.	...	13	Neg.	Neg.	...	9	4	4
6	14	Neg.	Neg.	...	15	21	Neg.	Neg.	...	18	Neg.	Neg.	...	14	8	8
7	6	Slight	Neg.	4.1	10	19	Slight	Neg.	...	12	Neg.	Neg.	...	—	4	12
8	10	Slight	Neg.	4.0	14	21	Neg.	Neg.	...	20	Neg.	Neg.	...	10	4	13
9	2	Slight	Neg.	...	3	9	Slight	Neg.	4.5	14	Slight	Neg.	...	14	5	12
10	2	Neg.	Neg.	4.7	7	17	Slight	Neg.	...	12	Slight	Neg.	...	12	3	10
11	6	Neg.	Neg.	4.6	10	18	Neg.	Neg.	...	12	Neg.	Neg.	...	—	5	11
12	6	Neg.	Neg.	5.1	8	17	Slight	Neg.	...	14	Slight	Neg.	...	11	6	12
13	2	Neg.	Neg.	...	5	14	Slight	Neg.	4.5	8	Neg.	Neg.	...	—	4	6
14	11	Slight	Neg.	4.5	15	19	Slight	Neg.	...	—	—	—	...	11	4	13

[1] Am. Jour. Dis. Child., 1924, **28**, 716.

* Refers to last examination showing signs of rickets. If rickets was absent, the examination just previous to the appearance of bowing was included. (Bell-Doisy method of analysis used.)

† Refers to first appearance of rickets. If rickets was absent, the last examinations were included.

These are the most common deformities of the legs. However, as Whitman states "in the marked distortion of the lower extremity, induced by rickets, the bones may be twisted and bent in various directions, although the outward expression of the deformity may be genu valgum." For instance, there may be anterior bowing or convexity of the leg, which results from an habitual posture in which gravity causes the weight of the foot to drag on the lower end of the tibia; or the knee may be overextended on standing, the so-called "back-knee" or genu recurvatum, which leads to weakness and insecurity.

Although these deformities have been considered as occurring in the first two years of life, when growth is most rapid and the upright position is first assumed, a small percentage of them occurs at a later period. When nutrition is poor and the physical strain great, bow-legs and more especially knock-knee, may come about during the second intense growth period—puberty. This was noted in the "Central Empires" during and more especially in the years immedi-

ately following the World War. In Vienna, Berlin, Warsaw, etc., hundreds of such cases developed among young adults and were treated at the orthopedic clinics. In normal times, however, these adolescent cases are comparatively insignificant in number.

The mild and moderate cases of bow-legs and of knock-knee right themselves spontaneously before the child has reached school age. It is often amazing to note that legs which at two or three years were markedly bowed and the cause of great concern, have become perfectly straight by the time the child has reached the age of five or six years. Deformity of the legs is very common among the little runabouts in the negro districts of New York City, and yet if one observes the older negro school children of these districts as they romp from the schoolhouse at recess, one is surprised at the straightness of their legs and the infrequency of deformities. Nature has effected a cure.

The radiographic alterations of the epiphyses are similar to those which are noted in the upper extremities, and will be considered in detail in the section especially devoted to this topic. The lower end of the femur and upper and lower ends of the tibia are most frequently involved. The fibula is notably spared. This bone may, however, be the site of fracture—a lesion which is observed often in the roentgenological films of rats in which rickets has been induced. The epiphyses of all these bones are enlarged, but slight degrees of swelling are even more difficult to determine by palpation than in the upper extremities.

Another deformity which may result from rickets is *coxa vara* or depression of the neck of the femur. This is a rare occurrence, at any rate in a degree which leads to clinical symptoms. It is generally noted about the time of adolescence, attention being attracted to the child by its peculiar, waddling gait. When due to rickets the lesion, as would be expected, is bilateral. It leads to shortening of the limbs, adduction, knock-knee and flat-foot. The diagnosis can be substantiated by the Roentgen rays (Fig. 26). Formerly these cases were confused with hip disease.

Flat-foot has been attributed by many to rickets. On this question there is a marked difference of opinion, some experienced orthopedists regarding rickets as the chief etiological factor of this deformity, whereas others, for example Whitman, leave it out of consideration. The flat-foot frequently does not develop until adolescent or adult life, rendering it difficult to trace its origin. Whatever may be the rôle of rickets in bringing about a depression of the arch of the foot, it seems certain that this condition can be occasioned by general weakness associated with poor musculature and lax ligaments. It would seem also that in some families there is an inherited tendency to flat-foot.

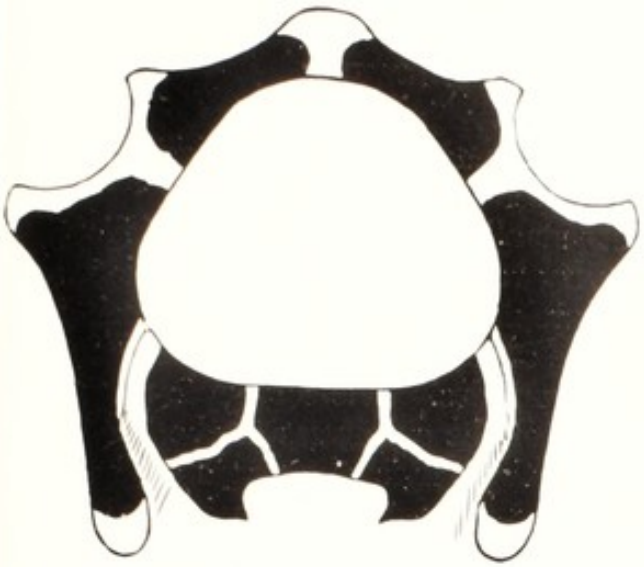
DEFORMITIES OF THE PELVIS.

One of the most important lesions of rickets is deformity of the pelvis. This condition may result in obstruction during labor, leading to injury or death of the fetus and may necessitate operative interference. Although all obstetricians acknowledge that rickets is an important cause of pelvic deformity, they are by no means unanimous as to the types of deformity which should be ascribed to it.

The pelvis may be involved or remain entirely unaffected in the course of rickets, depending on the severity of the disorder as well as when it begins and when it ceases. Many years ago Elsaesser made the observation that "rickets travels through the skeleton, proceeding from the head through the pelvis to the lower extremities." He described how it may skip the upper and involve the lower extremities according to the age when it develops, and in this way accounted for the fact that certain skeletal regions are spared.

There are various sources to which we can have recourse for information as to the rôle of rickets in the causation of deformities of the pelvis. Among these, by far the most convincing is the pathological material obtained at necropsy from rachitic infants and young children. We can furthermore acquire valuable information from a study of the geographical and racial distribution of these deformities, for example by ascertaining whether there is a parallelism between the occurrence of pelvic deformity and the incidence of rickets in certain races or within circumscribed areas. Thirdly, the measurements of the pelvis obtained by obstetricians during life furnish data of value, although they are subject to individual interpretation. Finally we can bring to our aid data, collected in the clinic or postmortem room, concerning deformities of the pelvis in infants.

Kehrer was the first to study the evolution of the rachitic pelvis. In an article written about fifty years ago he describes and portrays the pelves of 4 rachitic children. The classical work on this subject, however, is that of Breus and Kolisko (1904), a two-volume work on Pathological Types of Pelves. These authors found that rickets affects the pelvis in various ways. In the first place, it leads to marked decrease in the growth of the bony structure so that the pelvis is small, although its thickness is not diminished. The pelvis of a rachitic child two or three years of age may be no larger than that of a normal infant less than one year old. This retardation in growth may be noted at one year of age, but the contrast between the age of the child and the size of the pelvis becomes increasingly great after the third year. Instead of, or associated with, a retardation in the growth of the bony pelvis, there may be a disproportion of its various parts. This lack of proportion results from abnormal and unequal growth and is due more particularly to the



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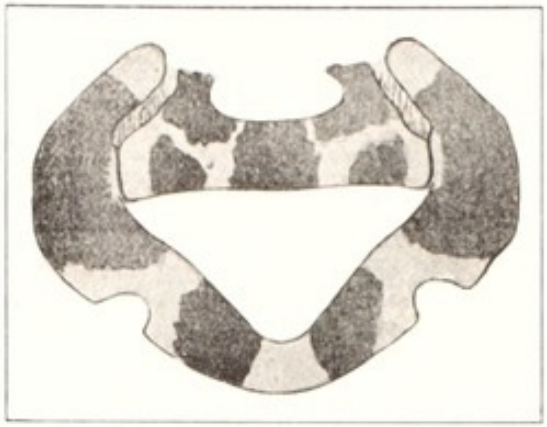

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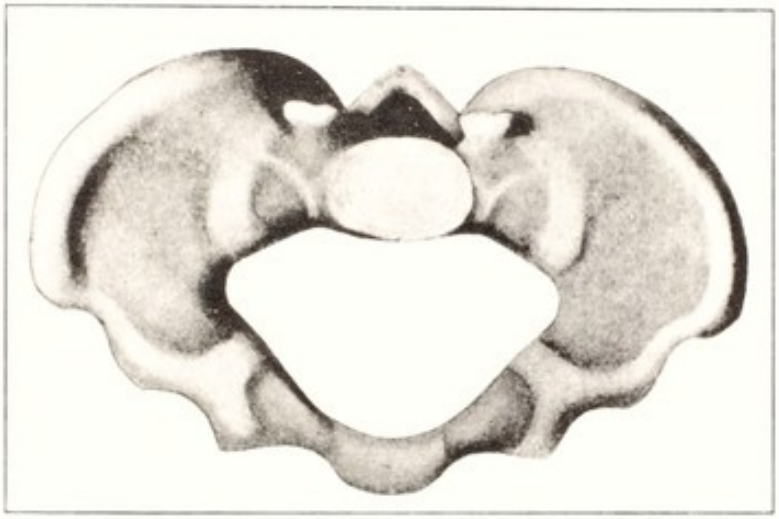

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(*d*)

FIG. 25.—(*a*) Schematic drawing of normal pelvis of infant about two years of age. (*b*) (*c*) Schematic drawing and photograph of *rachitic pelvis* of infant two years of age. (*d*) Sagittal view of rachitic pelvis of four-year-old child. (Breus and Kolisko, F. Deuticke, Leipzig, 1904.)

fact that the pars iliaca does not develop normally, which leads to a decrease in the antero-posterior diameter of the pelvic cavity. In addition to the rachitic pelvis being small or disproportioned, it is frequently deformed due to the faulty texture of the bones which are abnormally soft and yield readily to mechanical influences, such as the weight of the body, the pressure of the head of the femur and the pull of the various ligaments and muscles. The cartilages may be enlarged in a way similar to those of the epiphyses of the long bones. The cartilaginous portions of the pelvis, the crests of the ilia, the symphysis of the pubis and the acetabular region, are especially involved. The Y-cartilage at the latter site is often exceptionally swollen and may project into the pelvic cavity. The typical deformity, however, is the "rachitic flat pelvis" in which the entrance is narrowed partly by the shortness of the iliac bones, but especially by the projection of the sacrum, which instead of being concave in its upper part is flat or even convex. (Its lower part may be drawn forward so as to obstruct the pelvic outlet.) The posterior promontory may project to such an extent that the conjugate is 3 cm. smaller than that of the normal child. These various deformities are portrayed in the accompanying illustrations of normal and of rachitic pelves of young children (Fig. 25).

Von Recklinghausen found similar deformities of the pelvic bones in rachitic infants during the second year of life. He emphasized especially the "Kartenherzform"—the pelvis having the shape of the conventional outline of the heart. Although in these studies the pathologists laid stress on the imperfect development of the pelvic bones due to rickets, they fully realized that posture also played a rôle. The fact that the rachitic infant often is unable to stand or to walk and remains therefore in the seated posture for prolonged periods is stated to induce a secondary deformity of the softened bones.[1] This occurs quite as often in the male as in the female infant.

It is possible that in some cases malformations may be manifestations of late or juvenile rickets developing about the time of puberty, for pelvic deformity, as is well known, occurs commonly at this time of life in connection with osteomalacia. There are no data on which to base a discussion of this important question. The extreme malformations of the pelvis which occur in the course of osteomalacia will be referred to in the chapter devoted to this subject.

As stated, the importance of rickets in the etiology of pelvic deformity may be studied from the viewpoint of the geographical or

[1] In view of this etiological factor it would seem advisable to have markedly rachitic infants maintain a recumbent position, lying preferably on the abdomen. In this way it might be possible to avoid the deformities of the sacrum and the projection of the posterior promontory into the pelvic cavity.

racial distribution of this disorder. Is there any parallelism between the incidence of rickets in certain sections and the incidence of deformities of the pelvis? Looking at the subject from this viewpoint we find that in Glasgow, where rickets is especially frequent and severe, Cæsarean section is performed almost as frequently as in the great metropolis of London, and that in Manchester, where rickets is also unusually prevalent, the number of such operations is higher than in Liverpool, although the population of these two cities is approximately the same.[1]

Williams has had an exceptional opportunity to study the racial aspect of this question at the Johns Hopkins Hospital, Baltimore, where many negro, as well as white women, are delivered. Among 4000 obstetrical cases, including approximately 2500 white and 1500 negro women, deformity of the pelvis was noted only in 330 instances among the former as compared to 617 among the latter; in other words, in about 13 per cent of the white and 40 per cent, three times the number, of the negro women. Williams states that "rhachitic pelves were noted in 0.64 per cent of the white and 11.03 per cent of the black women. In not a few cases," he writes, "the disease undergoes spontaneous cure, so that no trace of its existence can be discovered in later life; while in many instances permanent skeletal deformities result which are frequently localized in the pelvis. Again, it is also not unusual to meet with women who to all appearances are quite normally formed, but whose pelves upon examination present rhachitic deformities."[2] In view of the fact that the most marked difference between these races in regard to diseases of the skeleton is the preponderating frequency of rickets among the negro, the high incidence of pelvic deformity in this race may be attributed to rachitic lesions.

Until recently there was no clinical study of pelvic deformity in infants. It is surprising that in the course of the many years of investigation of rickets this aspect has not been carefully studied. Recently Hoffa has examined the pelves of a series of rachitic infants by means of rectal palpation. As the result of this investigation he came to approximately the same conclusions as the pathologists Breus and Kolisko. He found a striking feature to be the small size of the pelvis, especially in its true conjugate diameter. The promontory was marked, indeed there was sometimes a "second promontory formed by the fifth lumbar vertebra." The entrance to the

[1] In 1911 Routh published the data of a series of 1282 cases of Cæsarean section in Great Britain, including a complete record of all cases operated upon in Great Britain and Ireland by obstetricians living June 1, 1910. In 1058 of these cases the indication for operation was pelvic deformity. Among these operations 383 were performed in London and 304 in Glasgow, 155 in Manchester and 96 in Liverpool.

[2] In this connection it is of interest to note that, according to a report (1922) of the hospitals of the United Fruit Company, in the West Indies, where rickets is exceptional even among the negroes, Cæsarean section rarely has to be resorted to.

pelvis was triangular or heart-shaped, the acetabular region pushed inward in the severe cases showing the form designated as the "pseudomalacic pelvis." In some cases a cartilaginous "rosary" was felt on the posterior surface of the junction of the symphysis. The psoas muscle was markedly hypertonic which, it is suggested, probably accounts for the flexion of the thigh commonly noted in rickets. These changes were observed especially in the second year of life, the youngest infants affected being from seven to eight months of age. Children over four years of age seemed to have recovered and the pelvis to have become almost normal. At six years of age it was no longer possible to palpate the pelvic wall, but in some children of this age the pelvis remained small and deformed.

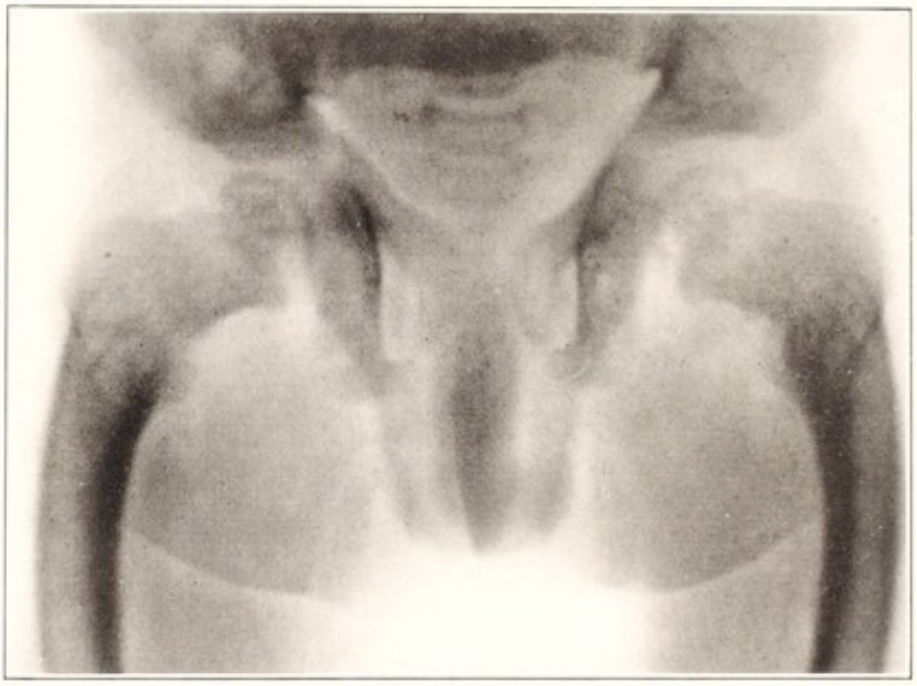

FIG. 26.—Marked rachitic pelvis of colored child, aged four years. Moderate coxa vara and bowing of femora. (See Fig. 23, p. 216 for photograph of child.)

This method of diagnosing rickets and of noting gross lesions of the bony pelvis seemed promising. However in practice I have found that it is fraught with doubts and difficulties. In the first place the normal dimensions of the pelvis and of the symphyseal epiphyses of infants are difficult to gauge by means of palpation. It was found that although in some instances the sacral promontory is felt to be exceptionally prominent and the symphyseal junction bulging, these signs did not run parallel with the well-established clinical signs of rickets. Possibly further studies, supported by pathological investigation, will serve to orient and correlate this sign. The method has value, however, as a means of ascertaining whether the pelvis is involved in severe instances of rickets. The case illustrated in Fig. 26, could be definitely diagnosed by palpation.

One of the greatest benefactions to which we may reasonably look forward in connection with the eradication of rickets through an extensive use of cod-liver oil, activated ergosterol and direct and indirect ultra-violet therapy, is the prevention of such deformities of the pelvis as lead to serious consequences to mother and child. The various "accidents" in connection with child-birth which result from pelvic deformity are a proper charge against rickets and should be incorporated in the morbidity and mortality statistics of this disorder. They constitute the foremost burden of rickets on the community, and endow it with a special significance for the welfare of the female.

INVOLVEMENT OF THE TEETH IN RICKETS.

The question of the involvement of the teeth in rickets has occupied the attention of physicians ever since the days of Glisson, but is still the subject of heated discussion. Glisson wrote: "the

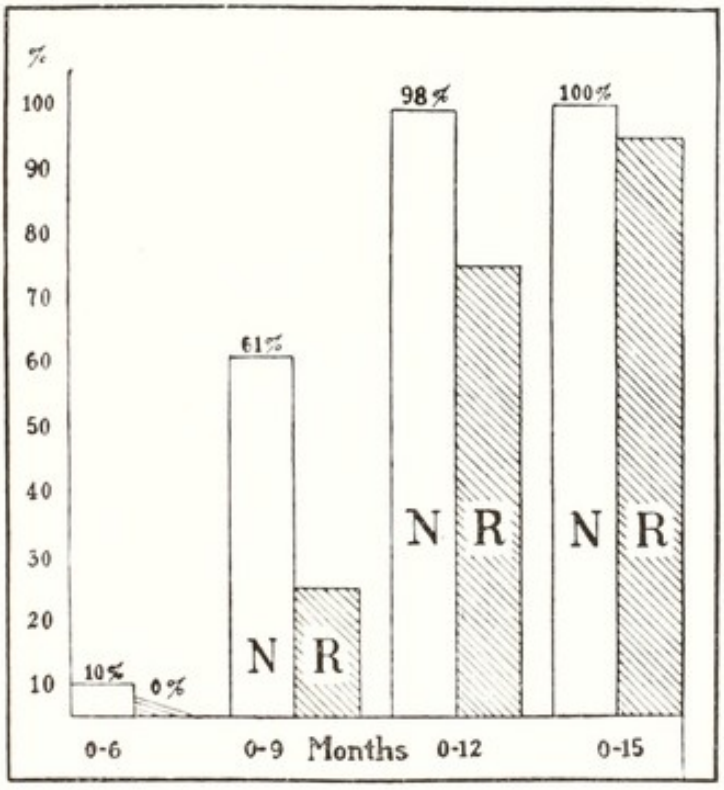

FIG. 27.—Comparison of time of eruption of first tooth in normal and in rachitic infants. Delayed eruption during first year due to rickets. (Blum and Mellion, Jour. Am. Med. Assn., 1926.)

faults of breeding of teeth also are sometimes justly ascribed to this disease going before," and that "many times the teeth themselves fall out by pieces." There are these *two distinct aspects—the one relating to the evolution of the teeth, and the other to their structure;*

but whereas the former has led to only mild discussion, the latter is still a center of controversy. It has long since been observed that rickets occasions a delay in dentition, the eruption of the first tooth being postponed sometimes until toward the end of the first year. The elder Kassowitz even went so far as to employ the rate of dentition as a gauge of the efficacy of antirachitic therapeutic measures. Heubner, Marfan, Still and Holt all make mention of retarded dentition, Still believing that this symptom is "one of considerable value in diagnosis." Recently Blum and Mellion, of my clinic, carried out an investigation of the relation of rickets to teething, as exact data on the subject were found to be scanty and it had not been studied since the era of the newer rickets. An exceptional opportunity was afforded for an accurate investigation of this kind as the infants could be supervised for a period of months or years and their hygienic surroundings and diet were exceptionally good. These investigators summarized their results as follows: "A study of mild rickets by means of clinical, roentgenological and chemical methods showed that dentition is delayed even in this group of cases." The accompanying table and diagram (Fig. 27) form the basis of this conclusion, and among other points show that whereas about one-half the number of normal babies developed a tooth between the sixth and the ninth month, only about one-fourth of the infants with mild rickets had a tooth at this age. In spite of these figures the secondary conclusion was drawn that "as a diagnostic sign of rickets, delayed dentition possesses little significance, however, owing to the variability in the time of eruption of the deciduous teeth."[1]

TABLE 18.—TIME OF APPEARANCE OF FIRST TOOTH (QUARTERLY PERIODS) IN INFANTS WITH AND WITHOUT RICKETS.

Age in months.	Number of cases.	
	Without rickets.	With rickets.
0 to 6	7	0
6 to 9	35	23
9 to 12	25	42
12 to 15	1	18
15 to 21	0	4
Total	68	87

[1] Many years ago Teichmann stressed the influence of familiar and hereditary tendencies in relation to the time of dentition, and in going through my records it has seemed to me that this factor was evident. Exceptionally early or late dentition may be noted in two or even three generations. It is certain that teething does not run at all parallel with general nutrition. Very often well-nourished, overweight babies are slow in teething, whereas those which are atrophic and underweight develop a tooth before the sixth month. Some years ago I examined a group of infants suffering from scurvy and extreme malnutrition and was surprised to find that teething had progressed at the normal rate.

The more important question is that of the rôle of rickets in the development of *dental caries*. Until recently the opinion prevailed that caries is brought about by a solution of the inorganic salts of the teeth resulting from acid fermentation in the mouth, and that this fermentation is accompanied by a solution or digestion of the organic substances by proteolytic bacterial ferments. This conception was based on the well-known experiments which Miller carried out some twenty years ago. Recently, however, the bacterial theory has been displaced by the concept of inadequate nutrition. Dick has carried out the most extensive clinical investigations in this field and it will be well to illustrate this point of view by citing his conclusions. He found that it was practically impossible to make accurate observations of the temporary teeth of children of school age as caries was so universal and extensive as to completely mask the hypoplasia. In a study of the permanent teeth, however, of 586 children who had suffered from rickets, 42 per cent were found to have teeth which were normal, and 58 per cent teeth which were defective or decayed. Among the latter, 20 per cent showed hypoplasia frequently combined with decay, and 38 per cent showed simple decay.

In order to understand the point of view of those who believe that caries is the result of rickets, one must bear in mind the prenatal and postnatal periods of calcification of the temporary and the permanent teeth. This is sometimes presented in the form of diagrams, but it is probable that the process is by no means regular. The usual statement is that "at birth one-half the crowns of the incisors, the tips of the canines and the cusps of the molars are calcified in the temporary set, and by about six months after birth the calcification of the crowns is completed."

After a careful search for a hypoplastic condition of the biting edge of the milk incisors, Dick failed to detect a case, either in school children or in the babies who attended infant welfare centers. This, as he states, is strong evidence that rickets is not a congenital condition.

In the permanent teeth, the enamel which is attacked is believed to be identical with that laid down during the first two years of life, in other words that of the lateral incisors, the tips of the canines and the crowns of the first molars. Of the cases with carious teeth Dick found that the lower first molar was decayed in 80 per cent and the upper first molar in 30 per cent. The fact that the lower first molars decay out of proportion to the others "is to be attributed rather to the main part of the enamel of the crown having been laid down in the first two years of life when rickety conditions are operative."

The most extensive experimental investigation of this subject is that of May Mellanby, carried out on the puppies which her husband

used in his well-known nutritional studies of rickets. The diet of these dogs consisted mainly of bread and separated milk, and it was so devised as to be deficient in the fat-soluble vitamins. The author summarizes her results as follows:

"A diet containing in abundance those articles with which the fat-soluble A accessory food factor is associated—*e. g.*, cod-liver oil, butter, etc.—allows the development in puppies of sound teeth.

"A diet otherwise adequate but deficient in the substance with which fat-soluble A is associated brings about the following defects in puppies' teeth: (*a*) Delayed loss of deciduous teeth. (*b*) Delayed eruption of the permanent dentition. (*c*) Irregularity in position and overlapping, especially of the incisors. (*d*) Partial absence of, or very defective enamel. (*e*) Low calcium content."

Recently May Mellanby and Pattison have carried out a clinical study of some of the dietary factors which influence the spread of caries in children and conclude that "those dietetic substances which have been found in animal experiments to produce perfect and imperfect teeth are also those which raise and lower respectively, the resistance of erupted teeth to caries." Milk, eggs, and cod-liver oil had a favorable action and cereals (especially oatmeal) unfavorable action on the structure of the teeth.

A similar but much less extensive investigation was carried out in rats by Grieves. He takes a different point of view and writes: "It must not be concluded that diets which produce experimental rickets also induce caries-like lesions," and that on a low-calcium and low-fat-soluble diet "rachitic and caries-like lesions are rarely coexistent." He stresses the importance of a proper "calcium-phosphorus-organic factor balance in the dietary."

These investigations furnish an adequate idea of the present status of experimental research on caries of the teeth in relation to rickets. Although they are of decided value and show that hypoplasia can regularly be brought about by defective diets, they do not answer satisfactorily the question as to the main cause of the widespread dental caries. It is the general experience, of physicians as well as laymen, that carious teeth are to be found in children of the well-to-do and the wealthy, children who have had a liberal diet and who have never suffered from rickets. I have encountered many such instances, both in institutional and in private practice. Some of these had been given cod-liver oil throughout infancy. Indeed Hellman, who has studied this question with great care, writes that the "dentures of the wealthy children show a normal percentage of 17.64 per cent, the poor as high as 59.51 per cent normal occlusion!"

In a recent study of "the physical status of the urban negro child," carried out by Sterling of the U. S. Public Health Service, the teeth

of 5000 children between six and fourteen years of age were examined in the schools of Atlanta, Georgia. It was found that "the percentage of children free from dental caries in this negro group compares very favorably, according to various reports, with that among white children of the same economic status, and of even many of better social environment."[1]

In this connection, it should be mentioned that delayed dentition is associated especially with the form of rickets which is accompanied by slight degrees of hydrocephalus, as illustrated by the following case: S. G., admitted to the institution when aged about four months, weighed 4.25 kg. It showed beading and craniotabes in spite of the fact that it had been breast-fed. Its length was 58.8 cm., head circumference 39.2 cm. and chest 36.8 cm. At six months of age its head was almost 4 cm. larger than the chest, at eight months almost 6 cm., at ten months 5.5 cm., at thirteen months 3.5 cm., and at eighteen months only 1.5 cm. It received cod-liver oil when somewhat over seven months of age, and soon thereafter showed signs of healing by the Roentgen rays, as well as disappearance of craniotabes and of beading. The first tooth did not appear until fourteen months, at which time the baby began to sit; at eighteen months it had nine teeth.

There are numerous clinical observations which cast doubt on the validity of ascribing dental caries to preëxisting rickets. For example, dental caries is very prevalent in Kingston, Jamaica, both among the white and the colored population. A few years ago while visiting this island, I consulted several dentists in regard to the question and was told that caries was about as common in this city as in the cities of northern United States. One of the dentists, whom I consulted, had practiced for many years in Vermont. The people of this island are almost free from rickets as we should expect, considering the abundance of sunshine which they enjoy. I was able to find but slight signs of rickets among the babies in the hospital and in the welfare clinics of Jamaica. The diet of the people consists largely of fruit and vegetables, an indefinite amount of carbohydrates, and occasionally chicken, eggs and milk. As

[1] In passing, a phenomenon may be referred to which has been particularly striking among institutional children who are under four to five years of age. I refer to the marked tendency to caries, and the decided delay in eruption of the teeth, of mentally backward children as well as of those suffering from organic brain lesions. This is a matter which is little stressed and yet is so striking that it must have been observed by many. It would seem to point to the importance of the central nervous system in the development of the teeth. Ultra-violet light and cod-liver oil therapy have no effect on this condition. For example: A mentally-backward infant was admitted to the institution when nine months of age. It was poorly nourished and had slight "rosary" and "soft ribs." It was at once treated with cod-liver oil and exposure to the rays of the mercury-vapor lamp. Nevertheless, the first tooth did not make its appearance until the baby was fifteen months of age, at which time it sat up for the first time.

mentioned above, the women of this region rarely present evidences of pelvic deformity.[1]

Before leaving this subject it should be mentioned that a causal relationship has been established experimentally between *the parathyroids and dental defects*. Erdheim extirpated the parathyroid glands in rats and induced lesions in the teeth similar to those which developed in rachitic rats—hypoplasia rather than caries. I shall have occasion to refer again to this investigation in connection with the pathogenesis of tetany and of osteomalacia. This observation may well be linked to that of Fleischmann who believed that tetany is associated with a susceptibility of the teeth to caries. It should be noted, however, that tetany often is not associated with dental decay and, of course, that marked caries is met with unassociated with any evidence of tetany.

Although there is no doubt that faulty nutrition plays a rôle in dental caries, we do not know as yet how great a rôle it plays and, more particularly, what are the defects of the diet which lead to premature erosion of the teeth. One of the difficulties lies in the fact that there is no characteristic pathological lesion of the teeth which is distinctive of rickets. In the long bones the diagnosis of rickets is established by the presence of osteoid tissue, of overgrowth of cartilage, etc., but in the teeth the criteria are simply hypoplasia and caries, which are not specific lesions but result from various factors, congenital, dietetic, hygienic. Another source of confusion lies in the fact that the observations on animals refer almost entirely to hypoplasia of the teeth, whereas the clinical phenomenon is mainly caries. These two pathological conditions may prove to be distinct from an etiological standpoint. It has been found impossible to induce caries regularly in the dog or in the rat, and I understand that these animals rarely, if ever, develop carious teeth under normal conditions.

THE EFFECT OF RICKETS ON THE CIRCULATORY SYSTEM.

The only effect on the circulatory system which has been described is hypertrophy of *the heart*, but it is possible that rickets may lead to disturbances in the innervation of the heart or bloodvessels. Many writers have called attention to the enlargement of the heart

[1] Stefansson showed that there has been a marked deterioration in the teeth of the Eskimos and of the natives of Northern Alaska, following the invasion of the white man. The fact is undoubted but its interpretation difficult. It seems certain that this phenomenon should be ascribed to a change in the diet of the people, and even that it is due mainly to a great increase in the consumption of carbohydrates. But it is evident that, even if such is the case, it does not mean that the dental caries is a manifestation of rickets. It merely indicates the uncertain status of this question and of dietetic problems in general, and emphasizes the fact that we are only at the threshold of an understanding of the nutritional values of the foods and combinations of foods which enter into our dietaries.

which is occasioned by the various deformities of the dorsal spine. This complication is associated only with severe cases of rickets and is, therefore, not encountered as frequently as heretofore. It has been referred to in this chapter in connection with deformities of the thoracic wall, where attention was drawn to the danger of confusing the condition with aortic aneurism. But quite apart from this type of hypertrophy, which is of secondary nature, some have raised the question as to whether there is not a true rachitic cardiac hypertrophy. Baginsky described hypertrophy following involvement of the lung and quite independent of any bone deformity. Finkelstein has stressed the involvement of the heart in rickets. He states that hypertrophy of the heart, especially of the right heart, is found at necropsy in some cases. In all such instances there was marked rickets of the thoracic wall and indurated pneumonia. The enlargement, according to Finkelstein, can be noted often during life by the increase in cardiac dulness, cardiac asthma, cyanosis, edema; enlargement of the liver and spleen also may occur. These cases may have been due to chronic pneumonia or induration of the lung which is an occasional accompaniment of rickets. From a pathogenetic point of view the question of a primary hypertrophy of the heart, especially of the right heart, assumes added interest and significance, in view of the fact that this condition has been found both clinically and at necropsy in infantile scurvy and beriberi. If a similar enlargement does occur as the result of rickets, it is certainly far less common and less marked than in infantile scurvy. I do not remember noting it in the course of an examination of a large series of radiographs of the chests of rachitic infants.

SYMPTOMS OF THE RESPIRATORY TRACT IN RICKETS.

Although the respiratory tract is not involved directly by rickets, it is frequently the site of secondary processes. The most common of these are the indurative pneumonias underlying the Harrison's grooves in the lower thoracic wall, the pneumonias of the base of the lungs due to pressure of the distended intestines, or the paravertebral pneumonia noted in the interscapular region. It has been the general experience that infants suffering from rickets are more predisposed, and evince less resistance, to respiratory infections than do normal infants. This may be the result of a deficiency of protective substances, as has been claimed, or to a local susceptibility of the mucous membrane lining the respiratory tract. Whatever its pathogenesis, pneumonia constitutes the chief danger for the rachitic infant and is the main cause of death. It is interesting that in New York City the Italian infants are especially prone to rickets and also that the mortality from pneumonia is particularly

high among them; the mortality from gastro-intestinal diseases is exceptionally low. The pneumonia is generally of the lobular, rather than the lobar, type. Milder forms of respiratory infections, such as coryza and bronchitis, occur also with exceptional frequency.

Although there can be no doubt that rickets leads to an increased susceptibility to disorders of the respiratory tract, it must be remembered that these observations date back to a period when rickets was of a far severer type than it is today. Now that, with the aid of more careful technic, we find evidences of rickets among more than three-quarters of the infants in the larger cities, it seemed necessary to reconsider its relationship to respiratory diseases and to investigate whether, in its prevailing form, it is attended with a similar predisposition. An excellent opportunity to carry out a study of this kind was afforded in my clinic by comparing the incidence of pneumonia among the infants cared for some years ago who developed mild rickets, and those who more recently have been protected by cod-liver oil and ultra-violet irradiation. A comparison of the incidence of pneumonia in these two groups has been published by Barenberg and Abramson as part of a study of the relation of the nutrition of infants to respiratory diseases. To our surprise, it was found that the incidence of pneumonia among 114 rachitic infants between the ages of six and eighteen months was even less than that among the 122 non-rachitic infants. Without laying too great stress on the relative percentages, it would seem that only moderate or severe rickets leads to respiratory infections and that the milder and more common type carries with it no such susceptibility.

GASTRO-INTESTINAL SYMPTOMS IN RICKETS.

Whistler, the predecessor of Glisson, drew attention to the involvement of the viscera as well as of the bones by dubbing rickets "paedosplanchnosteocaces," which in turn Samuel Gee dubbed "one of his mighty inkhornisms." The gastro-intestinal tract may play an important rôle in the pathogenesis of rickets, but it does not contribute greatly to its symptomatology. Constipation or diarrhea, or an alternation of these symptoms has been described by many authors as preceding or accompanying rickets. For many years Marfan has supported this point of view, even claiming that "digestive troubles generally coëxist with rickets." My personal experience has been that infants develop rickets who have never manifested gastro-intestinal disorder, and that the derangement must be rather of a metabolic nature and take place without occasioning vomiting, diarrhea or constipation. The fact that digestive disturbances occur in the summer, at a time when rickets rarely develops, is valuable clinical evidence in favor of this point of view. It may be stated, in general, that the stools of rachitic babies

are more apt to be constipated than loose, and that the reaction tends to be alkaline rather than acid. An attack of diarrhœa, in infants as well as in animals, far from inducing or intensifying the rachitic process, leads to a decrease in its severity. The outstanding intestinal symptom associated with rickets is the large abdomen, the "pot-belly" which constitutes such a prominent feature in cases of even moderate severity. It has not been ascertained to what extent this abnormal distention is due to digestive disturbance, to weakness of the musculature of the walls of the intestine and of the abdomen, or to deranged intestinal innervation.

ENLARGEMENT OF THE SPLEEN IN RICKETS.

The attention of clinicians has been directed especially to the spleen, because enlargement of this organ seemed fraught with significance from a pathogenetic point of view. Consistent hypertrophy of the spleen in the course of a disorder has always been interpreted as testimony of its toxic or bacterial origin, and has been adduced to support this theory of the nature of rickets. Marfan has construed its occurrence in this sense. On the other hand, it is realized by all that the spleen does not necessarily enlarge in all toxic states. The question of enlargement of the spleen, of the occurrence of what may be termed a rachitic spleen, has been a moot point for many years. The basis for the difference of opinion lies in the fact that whereas some consider all palpable spleens in rachitic infants to be due to rickets, others believe the enlargement to result from infection, or at any rate, to be secondary. There is considerable literature on this topic, much of it devoted solely to a consideration of the spleen and some including the question of enlargement of the lymphatic glands. It is surprising how little satisfactory evidence can be gathered from a study of these various reports. Many of the writers do not give their results in statistical form, a criticism which applies more particularly to the accounts in the standard treatises, where merely general conclusions are given. For example, the well-known Russian children's specialist, Filatow, simply states that the spleen is often enlarged. But the main difficulty is that one cannot be certain that the cases are truly rickets, or rather that they are uncomplicated rickets. Marfan states that the spleen is enlarged in about 20 per cent of the cases. Froehlich, whose study relates more particularly to lymph nodes, records enlargement of the spleen in 29 instances, or 15 per cent of his cases. These infants were mainly of the poorly-nourished type and had rickets of moderate or marked degree. Rehn, in Gerhardt's Handbuch, records the examination of 48 rachitic infants under two years of age and states that 34, or 70 per cent, had enlargement of the spleen. Sasuchin found splenic enlargement in

15 per cent of his 66 cases. These selections from the literature indicate the diversity of opinion. In the course of the study of rickets carried out for many years in my clinic, an enlarged spleen was always looked for, and its presence or absence noted. It should be added that these infants, all showing a negative Wassermann reaction, were examined month by month for a period of six to eighteen months. Occasionally, the spleen was palpated upon one occasion and overlooked in the succeeding examination, but in general the notations were remarkably consistent. The spleen was found to be palpable in 20 per cent of infants who gave no evidence of rickets by clinical examination, radiograph or blood phosphate test, and in about 25 per cent of the infants who were rachitic. This rickets, it should be understood, was of mild or, at most, moderate degree. Palpable spleens were not met with less frequently during the summer months when active rickets had practically disappeared. Furthermore, an enlarged spleen showed no tendency to diminish following treatment with cod-liver oil. Indeed, in several instances of rickets associated with enlarged spleen and anemia, cod-liver oil failed to exert its usual therapeutic effect. In simple anemia, rickets may improve, accompanied by an increase in the inorganic phosphorus of the blood, and the anemia nevertheless progress. In my opinion an enlarged spleen should not be regarded as a sign of rickets. It is frequently palpable in well-nourished, heavy infants who have been overfed either at the breast or with cow's milk. The spleen in the poorly-nourished infant is rarely large. Some time ago I observed for a year or more an atrophic infant, aged seven months and weighing but 8 pounds, which suffered not only from marked rickets but from chronic furunculosis as well. The spleen was at no time palpable. Finkelstein touches on this subject when he states that in thin infants where the spleen is palpable we should suspect a complication with some other disease, especially a blood disease.

Pathologists have not been able to come to our assistance in solving the question of the significance of an enlarged spleen. This was to be expected from the very nature of the case, for none of these children die of rickets but of some complicating disease, generally pneumonia or gastro-intestinal disturbances. Unfortunately, Schmorl in his excellent study of the pathological lesions of rickets, did not give any consideration to the spleen, either from the macroscopic or the microscopic point of view. One of the most careful pathological studies of the spleen is that of Starck, who noted its size and condition in 113 necropsies of young children who died from various diseases. The spleen was found enlarged in 53 instances of the rachitic cases, that is to say 60 per cent, and in 77 instances, or almost 50 per cent of the non-rachitic cases. In other words, there was very little difference in incidence between the infants which had

rickets and those which were non-rachitic. The mesenteric glands were less frequently enlarged and bore no relation to the enlargement of the spleen, and the same was true of the bronchial glands. The liver was found to be enlarged less often in rickets than the spleen. In 2 of the 113 cases he reports an induration of the pancreas.

An interesting observation made in the course of this investigation was that the younger the child, the more often the liver was found to be enlarged, whereas the enlargement of the spleen reached its greatest frequency after the age of six months. This is similar to the experience of the illustrious pathologist and clinician, Richard Bright, who in reporting an instance of enlarged spleen in a child about two years of age remarked: "I adduce this as an instance of the great size to which the spleen attains during infancy."

ENLARGEMENT OF LYMPH NODES, TONSILS, AND ADENOIDS IN RICKETS.

Some include enlargement of the lymph nodes and tonsils, as well as the formation of adenoids, as signs of rickets. Marfan has upheld this view for a number of years, contending that a general hypertrophy of lymphatic tissue results from the absorption of toxins in connection with the development of rickets. He believes that there is probably also an enlargement of the deep lymphatic nodes in the mediastinum and in the mesentery. This theory has been discussed in the chapter on Pathogenesis, so that it is unnecessary to consider it once more. From a clinical standpoint, the question is whether enlargement of these glands should be regarded as a sign or indication of rickets. At the outset it must be stated that enlargement of the superficial lymph nodes, especially of those in the neck and the groins, is of such common occurrence that little sigficance can be attached to it. As is well known, during infancy there is a characteristic tendency for all the lymphatic tissue in the body to undergo hypertrophy—the lymph nodes, tonsils, pharyngeal "adenoids," etc.; the lymphocytosis of the blood is but another expression of this age peculiarity. It seems to me that Froehlich, who tabulated 185 cases of rickets from this point of view, is correct in concluding that there is no definite connection between rickets and glandular enlargement. The association is rather between rickets and infection.

The conception that *enlarged tonsils* and the development of *adenoids* are closely associated with rickets has been brought forward at intervals ever since rickets was first described. About a hundred years ago the illustrious French surgeon and anatomist, Dupuytren, after describing an almost typical rachitic chest stated that "one remarkable point about these deformities is that they are almost

invariably accompanied by considerable enlargement of the tonsils, an association which it is difficult to account for." That enlarged tonsils and adenoids are not true rachitic lesions is evidenced by the fact that they do not respond in the slightest degree to any of the specific antirachitic agents, cod-liver oil, irradiated ergosterol or ultra-violet light. It is not so easy, however, to determine whether they have a more remote connection with rickets—whether this disorder does not favor their development either indirectly or as the result of secondary infection. Clinically there is no parallelism between the intensity of rickets and the degree of hypertrophy of faucial lymphatic tissue. In the temperate zone, enlarged tonsils, and adenoids, as well as rickets, occur in such a large proportion of infants that it is difficult to analyze their interrelationship. In the tropics or subtropics, however, where rickets is practically nonexistent the question is rendered less involved. An inquiry in some of these areas which are comparatively free from rickets has elicited the information that adenoids are by no means infrequent. In Kingston, Jamaica, for example, all the physicians of whom I have inquired report that adenoids are of common occurrence. During the past few years I have noted both adenoids and enlarged tonsils in infants who had received cod-liver oil since the first month of life and who showed no signs of rickets; and lately, in some infants who had been systematically treated with ultra-violet rays. If rickets tends in any way to the development of adenoids, it does so in a minor degree and is certainly not one of the main causes of this pathological condition. The presence or absence of adenoids in a child cannot be regarded as evidence for or against rickets.

ENLARGEMENT OF THE THYMUS GLAND IN RICKETS.

What has been stated in regard to tonsils and adenoids applies with equal force to enlargement of the thymus gland which some believe to hypertrophy in the course of rickets. There has been no evident relationship between thymic hypertrophy and the presence of rickets in the cases which have come to my attention. In two marked instances, which were substantiated postmortem, the degree of rickets was of mild intensity. Whatever the pathogenetic relationship may prove to be, there is no apparent clinical association.

INVOLVEMENT OF THE NERVOUS SYSTEM IN RICKETS.

The nervous system is not spared in rickets. The most striking manifestation of its involvement is the development of tetany with its various signs of hyperirritability of the cerebral centers and peripheral nerves. In this clinical condition, which will be considered

in a separate chapter, the increased irritability is secondary to a deficiency of calcium in the tissues. Almost the entire nervous system shows a lack of stability, with the occurrence of convulsions, laryngospasm, and general mechanical and electrical hyperexcitability of the peripheral nerves. But quite apart from tetany, with its typical diminution of blood calcium, nervous phenomena may develop. Among these one of the most characteristic is the head-sweating, especially marked during sleep, which has long been recognized as an early sign of rickets. Another symptom is the restlessness which also is noted early. Convulsions may occur without any of the signs of tetany, especially during the second half of the first year of life, and frequently are associated with tetany in latent form. Epstein thought that a moderate degree of catalepsy frequently accompanied rickets, and Marfan mentions catatonia.

The question of whether rickets is accompanied by pain, whether the sensory nerves are involved in this condition, is one which has been raised many times but never satisfactorily answered. The early descriptions of tenderness of the extremities date back to the period when infantile scurvy was confused with rickets, but even today many clinicians are of the opinion that rickets, as well as scurvy, is associated with hyperesthesia. I have frequently attempted to investigate this point, but have found it extremely difficult and perplexing. Pain and tenderness are certainly not present to an appreciable degree in the ordinary case of rickets. In this connection it may be recalled that Pommer, who has contributed so much to our knowledge of the pathology of rickets, was of the opinion that rickets is primarily due to an involvement of the nervous system. I have encountered three instances where definite tenderness of the bones seemed to be present. Two were in negro babies with advanced rickets. The third was the case of a baby in my clinic who had moderate rickets associated with tenderness of some of the thoracic vertebrae; this tenderness persisted for some days and then permanently disappeared.

A phenomenon which is inexplicable is the fact that in osteomalacia—the rickets of adolescence and adult life—tenderness of the bones is of common occurrence, indeed one of the typical symptoms. Perhaps the incongruity is partly explained by the very frequent association of low blood calcium with osteomalacia.

Spastic paresis has been described by Vierordt as occasionally following pressure of the vertebrae on the spinal cord, and intercostal neuralgia by Bernhardt.

There is quite another aspect of the relation of rickets to the nervous system. I refer to its effect on *the mentality* of the child. Many are of the opinion that rickets results in mental retardation, and have attempted to support this position with comparative intelligence tests of children of school age. It is evident that tests carried

out several years after rickets has occurred are fraught with many pitfalls. A review of the literature bearing on this question leads to the opinion that there are so many complicating factors that it would be unwise to draw any conclusion from the data. This is likewise true of intelligence tests carried out on rachitic infants—a field which is so new and in which the norms are still so poorly defined that it is impossible to make reliable comparisons. A further series of reports, for example that of Looft, deals with the mentality of premature rachitic infants. These investigations as a rule do not distinguish sharply between the effect of the rickets and of the prematurity which, as we know, frequently leads to a delay in mental development. My experience has been that mild degrees of rickets, such as are commonly met with in private practice and in institutions, do not result in mental retardation. Such children do not begin to talk later than the children in the same environment who did not develop rickets. In severe cases of rickets, such as are found among the negro babies, there is sometimes definite retardation in intelligence. These infants are frequently poorly nourished, and suffer from disorders of nutrition in addition to rickets, so that it is difficult to determine to what extent the mental inferiority is due to rickets and to what extent to general malnutrition. As is well known, infants who suffer from severe degrees of marasmus or atrophy often give evidence of mental backwardness. The difficulty attending this entire subject may be appreciated when one adds that some claim that the rachitic child is exceptionally precocious.

Recently Huldschinsky published an interesting monograph on this subject. In the first place he worked out a cranial index in order to measure the growth of the brain, and found that there was regularly a disproportion between the size of the cranial vault and the cranial base, the former being excessively large. He found severe rickets to be associated with an absolute enlargement of the brain, which may result from hydrocephalus. These organic changes lead to a "dementia rachitica," which manifests itself in infancy as neurasthenia, passes gradually over to a state of catatonia, and persists throughout a long period as negativism and defective mentality. He believes, however, that rickets does not lead to a permanent defect of intelligence.

INVOLVEMENT OF THE SKIN, MUSCLES AND LIGAMENTS IN RICKETS.

The skin is but little affected in rickets. In the cases accompanied by malnutrition, the skin is apt to be dry as one would expect; however, in the other group, which comprises well-nourished infants, the skin may be smooth and elastic. Where the disorder

is of long standing, the skin is generally pale and areas of pigmentation may be noted.

Except in very mild cases, the *muscles* and ligaments are involved in the course of the rachitic process. The muscles are exceptionally soft and flabby and various microscopic changes of the fibers have been described. The muscles of the thighs appear to be most affected but almost any group may be involved. The normal turgor is lacking, a condition which is especially evident in thin, poorly-nourished infants. This is a symptom which was greatly emphasized some years ago by Hagenbach-Burckhardt and, more recently, has been stressed by Findlay and his co-workers. There is no parallelism between the static function and the firmness of the muscles. My records show many instances in which infants with flabby thigh muscles began to stand at normal age, and, moreover, others where the muscles improved in spite of the fact that rickets was developing, as shown by the radiographic picture and the decrease in the inorganic phosphorus of the blood. Infants may begin to sit or stand during the development of active rickets. Weakness of the abdominal muscles leads to the typical "pot-belly," to a bulging of the flanks, and to marked diastasis of the recti. However, diastasis is rarely lacking even in average non-rachitic infants, but is of more marked degree in cases of rickets. Not infrequently it is associated with umbilical or parumbilical hernia, or with a small hernia at the ensiform region.

Muscular weakness, as well as the laxity of the ligaments accompanying it, leads to the development of the various curvatures of the spine, to knock-knee, flat-foot and other deformities. Almost three centuries ago Glisson observed that in rickets the joints are capable of marked hyperextension and that the infants assume unusual and grotesque postures. Frequently, they may be seen doubled up like a jack-knife or with their feet extended over their heads, reminding one of the well-known attitudes of the mongolian idiots. The muscular weakness may reach such an extreme degree that it resembles paralysis. I have encountered two such cases in negro infants. But even in instances of such intensity, tenderness of the muscles, tendons or ligaments, as described by Kassowitz, could not be elicited. It is of interest to note in connection with the well-established hereditary and familiar character of diseases of the muscles, that Still suggests that the tendency to involvement of the muscles in certain cases of rickets may be a family proclivity.

The weakness of the muscles seems to be only temporary and to follow the well-known course of rickets. Children who have suffered from rickets in infancy manifest no signs of weakness when they have reached the age of three to four years. Hunter is stated to have possessed the skeleton of a rachitic dwarf who earned a living by performing feats of strength and Sir Charles Bell mentions two other instances.

INVOLVEMENT OF THE EYE AND EAR IN RICKETS.

The eye is rarely involved in rickets, but it is of interest that even this organ may be affected. Many years ago, Arlt noted that individuals suffering from *zonular cataract* frequently gave a history of convulsions in infancy. Horner of Zürich described this form of cataract in 1865 in connection with dental deformation of rachitic origin; in more than one-half of his 189 cases, convulsions had occurred. The literature of this interesting subject may be found in Michel's article on "Diseases of the Lens" in Gerhardt's Handbuch. More recently Dick has revived interest in the subject, and states that among 35 cases of zonular cataract, hypoplasia of the dental enamel was present in 30. He believes that an association, in minor degree, of these two clinical conditions is far more common than is supposed. From a clinical point of view this complex must be regarded as one of the exceptional manifestations of rickets. It gains added interest, however, from the fact that tetany is accompanied by a lowered concentration of calcium in the blood and that disturbances of calcium have been associated by some with the occurrence of cataract. Stoeltzner has carried out an experimental study of the so-called "tetany cataract." In this connection mention may be made of the fact that Eckstein and Szily recently have claimed that when rats are deprived of fat-soluble vitamin during lactation, cataract not infrequently develops in the young.

Nystagmus associated with spasmus nutans has been described by Henoch as a sign of rickets.

The *ear* is involved occasionally. In his study of otosclerosis, Mayer refers to this condition as resulting from rickets, and supports this opinion by a description of osteoid tissue in the temporal bone of a nine-months-old infant. A more recent report, that of Kauffman and his collaborators, records and portrays the occurrence of osteoid tissue in the petrous bones of animals fed a rickets-producing diet; they draw an analogy to the well-known clinical complex, characterized by otosclerosis, brittle bones, and blue sclera.

CHEMICAL CHANGES IN THE BLOOD IN RICKETS.

The main alteration in the blood is a *decrease in inorganic phosphorus*, a sign described a few years ago by Iversen and Lenstrup and by Howland and Kramer. This observation has been of the greatest value in the early recognition and diagnosis of rickets, and will be discussed in detail in the chapter on Diagnosis. If the Bell-Doisy method, or the Briggs modification, is used, concentrations below 3.75 mg. should be regarded as indicative of rickets, as the normal content is between 4 and 5 mg. per 100 cc. of plasma. With the Tisdall method the figures range 1 mg. higher, so that

about 4.75 mg. indicate rickets. As will be brought out in the chapter on Diagnosis, the chemical examination of the blood is not an infallible criterion in infants. The tendency has been to overrate its value and, more especially, its significance. At times the level of inorganic phosphate is within normal limits, in spite of the fact that undoubted clinical signs of rickets are present. The calcium concentration remains unchanged or but slightly lowered except where tetany is present either in manifest or latent form, under which circumstances the normal concentration of about 10 mg. falls to a greater or less degree, as will be described in considering tetany.

For many years there has been a difference of opinion as to whether *anemia* should be regarded as one of the symptoms of rickets. There is no doubt that many rachitic infants are anemic, but it is equally true that many of them have a normal percentage of hemoglobin and a normal number of red blood cells. Marfan, who believes that changes in the marrow constitute a constant lesion of rickets, has always maintained that anemia is an important and characteristic sign of rickets. On the other hand, Findlay, as the result of a careful study of 30 cases of active and uncomplicated rickets in children varying between the ages of twelve and forty-two months, concluded: "(1) In active and uncomplicated rickets anemia is not the rule, but is to be regarded as exceptional and, when it occurs, due to adventitious causes. (2) On the contrary, in rachitic children the amount of hemoglobin and the number of red cells in the series examined are notably in excess of the normal average. (3) The red blood corpuscles, as a rule, vary more in size than in normal individuals of similar ages, but otherwise there is no abnormality. The leukocytes may be normal, slightly increased or diminished in number. The mononuclears more frequently than the polymorphonuclears show an absolute increase in number per cubic millimeter." Morse examined 20 uncomplicated cases and found the red corpuscles approximately normal in number, but the hemoglobin both absolutely and relatively diminished. Still writes: "Another manifestation of rickets which may be altogether out of proportion to the bone changes, and which therefore is sometimes not recognized as rachitic is anemia." Such conflicting observations are due probably to the fact that one investigation comprised uncomplicated rickets, whereas as Naegeli suggests, in another "very often other diseases complicated the clinical picture." In my experience, which embraces mainly rickets of mild or moderate degree, anemia was not present more often or in greater intensity than in similar non-rachitic infants When anemia did accompany rickets, the anemia was greatly improved by giving large doses of iron, although there was no improvement in the signs of rickets. It has frequently been found

that where anemia and rickets are associated, the hemoglobin will remain low (even as low as 50 per cent), notwithstanding the fact that a cure has been brought about by means of cod-liver oil. It is probably true that severe rickets is generally accompanied by anemia. But whether this alteration is to be attributed to the rickets or to the malnutrition occasioned by associated errors of hygiene and diet remains to be determined. As Still has observed, there is no parallelism between the degree of anemia and the intensity of the rickets.

There is likewise a difference of opinion as to involvement of the white blood cells, especially as to the occurrence of a leukocytosis consisting largely of an increase in the mononuclear cells. Most observers believe that when a leukocytosis exists it is the result of a complication. Assuredly, it is not a regular sign of rickets, and one on which any reliance can be placed. In a consideration of blood changes, cases of the von Jaksch type of anemia should be left out of account, as the marked abnormalities in the red and white cells associated with this syndrome cannot be ascribed to uncomplicated rickets.

URINARY CHANGES IN RICKETS.

The urine shows no constant change and urinalysis plays no part in symptomatology. The chemistry of the urine is now being carefully investigated, so that it is possible that some characteristic quantitative or qualitative alteration may be established. Recently Hottinger has stressed the increased excretion of organic acid in rickets. The increase in diastase has been referred to in the chapter on Metabolism.

NUTRITION AND GROWTH IN RICKETS.

Although rickets must be regarded as a nutritional disorder, it is difficult to define its exact relationship to the general nutrition of the child. In this respect it differs essentially from infantile scurvy, which almost always is associated with evident malnutrition. The rachitic child, however, may be either well nourished or poorly nourished. From a clinical point of view it is desirable to distinguish two types of rickets, the one associated with normal or excessive weight, the other with marked underweight—*the "fat" and the "lean" rickets.* That well-nourished infants may, nevertheless, be rachitic was known to Glisson, and has been emphasized in connection with diets rich in carbohydrates. The newer and more refined methods of diagnosis have served to emphsize this fact, demonstrating that even the well-nourished breast-fed baby not infrequently shows definite signs of this disorder. Rickets, therefore, cannot be regarded as a disturbance characterized by undernutrition, but rather as one which is associated with a faulty or abnormal nutrition.

The relationship between *rickets and growth* is somewhat clearer. In general, it may be stated that the more rapid the growth, the greater the tendency to the development of rickets. In other words, there is a direct relationship between growth and rickets. This is well illustrated by the observation made many years ago by Thomson and others to the effect that cretins, in whom growth of the extremities is relatively small, very rarely develop rickets, and that they are peculiarly susceptible to this disorder when given thyroid extract and growth is stimulated. The case of the premature baby may be cited in this connection, although the heightened predisposition to rickets of these infants may be due to more than this cause; however, one of the main factors tending to this susceptibility is excessive growth during the first six months of life. Animal experiments confirm this general point of view. In his experiments with puppies Mellanby found that growth played an important rôle in the development of rickets—those animals which grew rapidly, either due to a diet rich in carbohydrates or to peculiarity of breed, manifested rickets more readily and in greater intensity. All investigators who have used the rat as the experimental animal have reported similar experiences. Indeed, healing may be brought about "spontaneously by unfavorable circumstances, such as a low caloric diet or infection occasioning a loss of weight." Nevertheless, the distinction between the young rapidly-growing animal and the adult must not be regarded simply as a difference in growth. In addition there is a difference in the factors which regulate evolution, for example, in the activity of the endocrine glands.

Another aspect which must be considered is whether rickets impedes growth in length, whether its development in a baby brings about a retardation in this respect. *A priori* one might imagine that there would be an increase rather than a decrease in growth, judging from the pathological picture which shows an increase in the width of the proliferating cartilage of the long bones. However, such is not the case, as this increase is compensated for by other factors. In considering this question, we have not in mind such a stunting in stature as is occasioned by curvatures of the bones, for example, extreme degrees of bow-legs or knock-knees, which should be regarded as false or apparent retardation of growth. There can be no doubt that in extreme forms of rickets impairment of growth may be encountered. The cases of rachitic dwarfism are instances in point. It would seem that quite apart from the various factors, such as bending of the extremities, coxa vara, bowing of spine, flat-foot, etc., which induce a condition of false dwarfism—there is true retardation of a constitutional nature. The more important question, however, is whether the common mild or moderate case of rickets is accompanied by an impairment of the growth impulse. In my experience, such has not

been the case. Some years ago, the opportunity was afforded for a study of this phenomenon in a series of infants measured in a routine way month by month, during the course of the first two years of life. It was found that intercurrent rickets rarely caused any decrease in the rate of growth. The accompanying figure (Fig. 28) illustrates this point, showing the steady growth of an infant for sixteen months in spite of the fact that it experienced two attacks

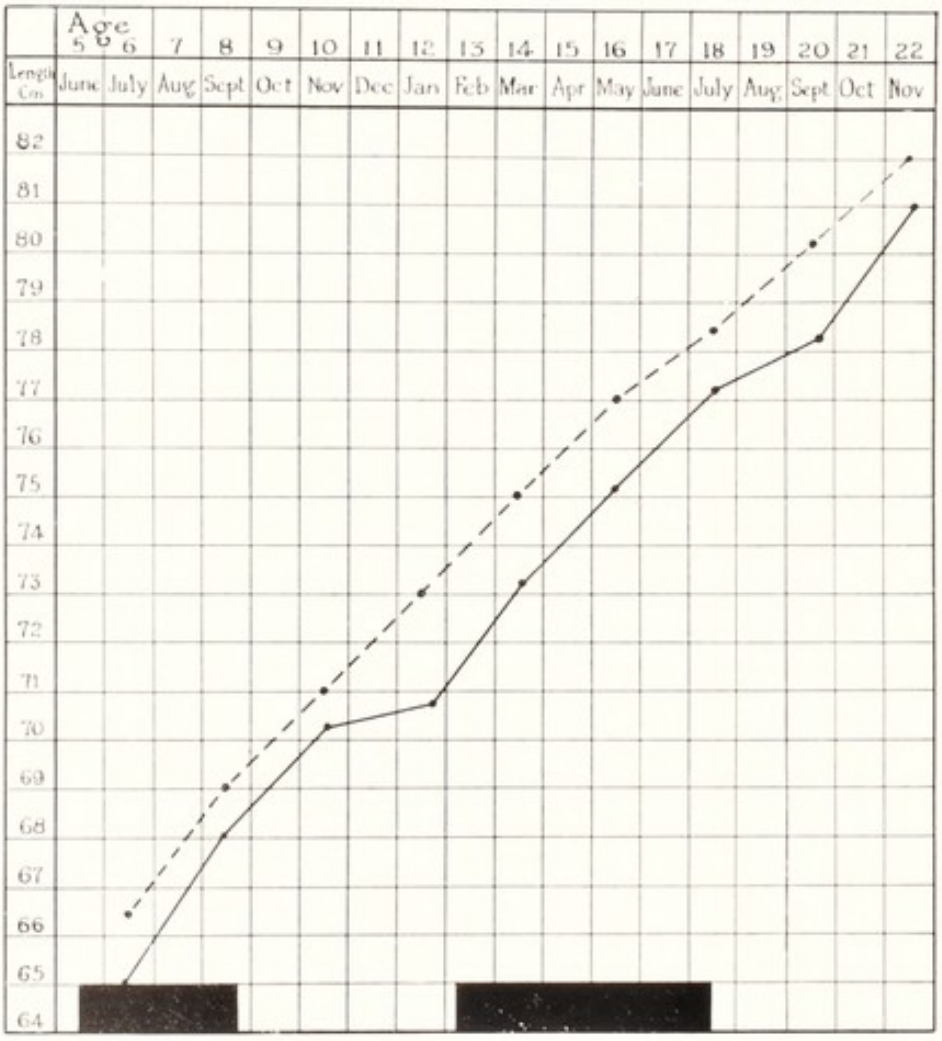

FIG. 28.—Growth in relation to rickets. In spite of "recurrent rickets" growth was not impeded. (Black squares indicate periods of active rickets. Broken line represents normal growth curve.) Cessation of growth at ten to eleven months, due to intercurrent infection. First attack of rickets occurred during the summer.

of rickets during this period; the first of these attacks was mild and the second of moderate severity. On the other hand, infants which developed infections, especially if these infections persisted or recurred during a period of several months, showed a definite decline of the growth curve far more regularly. Cessation of growth may come about from a lack of vitamin A, as in the cases reported by Wengraf of children who had been deprived of this dietary factor during the World War. Experiments have shown that, although a

lack of this vitamin does not bring about rickets, it does induce a retardation of growth.

As we shall point out in the following chapter, Wimberger has approached this problem in a different way. He studied the rate of growth of the long bones, particularly of the tibia, by means of the Roentgen rays, taking radiographs serially month by month. As the result of this study, he came to the conclusion that "growth does not suffer any impairment through rickets," and that there is an excessive growth during convalescence. It should be borne in mind, however, that there are almost insuperable difficulties in connection with a study of this kind, such as the well-known influence of the various seasons, of the action of fresh air, of the caloric value of the food, of the race of the infant, of the individual growth-rate, and probably numerous other variables.

In taking a broad view of the relation of growth to rickets, the outstanding and characteristic feature would seem to be that in this nutritional disorder, in contradistinction to all others, normal or excessive growth tends to induce and to intensify the condition, rather than to render the process less marked.

In this connection, it should be borne in mind that there are two intense growth periods in the postnatal life cycle of man, one embracing the first two years of life, the age of susceptibility to rickets, and the other puberty, the age when osteomalacia occurs most frequently. During these periods, as Aron pointed out, there is an increase in the growth of the skeleton out of proportion to that of the muscles and internal organs. The growth impulse is so intense during the first of these cycles that there are few nutritional disorders that are able to slow down its rate. Furthermore, bone is a tissue highly favored by the organism as a whole, and in times of stress and deprivation is suffered to grow at the expense of the fat and the muscle of the body. For example, in cases of marked infantile athrepsia, although the infant may be markedly underweight, its length generally is found to be normal. On the other hand, if the nutritional disturbance is extreme, or perhaps brings about peculiar pathological changes, growth may be impeded or even inhibited. This is true of infantile scurvy, of diabetes in the young, of "coeliac disease" and of "renal dwarfism," disorders of nutrition which are frequently associated with osteoporosis. In scurvy the retardation is quickly repaired, growth responding with remarkable promptness to the addition of food containing the antiscorbutic vitamin.[1]

[1] In this respect there is a fundamental difference between rickets and scurvy. In infantile scurvy, we found that growth in length was impaired even in latent and subacute cases, and that the normal rate was resumed as soon as orange juice was given. This distinction cannot be ascribed to a difference in duration of the two nutritional disorders, for they generally persist for about the same length of time. In scurvy, the reaction to specific therapy is so sharp and striking that it gives one the impression that we are supplying some factor which is essential for growth, in addition to one which is required for general nutrition.

CHAPTER IX.

THE RADIOGRAPHIC SIGNS OF RICKETS.

The Roentgen rays have been one of the significant factors in the recent advance in our knowledge of rickets. Today the use of radiographs in the clinic, as well as in laboratory studies of experimental rickets, is a routine procedure. The application of radiography to rickets has followed a somewhat unusual course. As a rule, a new method of diagnosis, especially if its technique is simple and readily available, quickly finds its way into clinical practice. With radiography the case has been different—fully twenty years elapsed between its introduction and its application. Rickets was one of the first diseases to which the Roentgen rays were applied. In 1895 Roentgen announced his epoch-making discovery and three years later Gocht published his text-book on Roentgen-ray examination, which contained a clear account of the characteristic changes of the epiphyses associated with rickets. In 1901 appeared Koehler's book on "Bone Diseases as Portrayed in Radiography," where good illustrations of active and of healed rickets were reproduced. These writers were orthopedists. A few years later (1908), Reyher wrote a monograph on "The Application of Radiologic Diagnosis to the Diseases of Children." Finally, in 1910, Fraenkel and Lorey published their classic "Atlas and Study of the Radiology of Rickets," describing in the minutest detail the various changes observed in the course of its development and healing. Wohlhauer's "Atlas and Principles of Rickets" appeared during the following year. With this extensive background, one might expect that radiography would have been employed promptly in the diagnosis of rickets, especially in the European university clinics. We find, however, no mention of its applicability in the text-book of Heubner published in 1903, nor in the article on rickets by Stoeltzner in Schlossman and Pfaundler's voluminous "Handbuch" which appeared three years later, nor in the excellent treatise on rickets by Schloss in 1917, nor again in the "Handbuch" of Czerny and Keller of the same year. This indicates a rare lack of coördination between two closely related branches of medicine, which is all the more striking in view of the fact that these writers had for many years made a special study of rickets and were justly regarded as authorities in this field. Outside of Germany and Austria still less attention was paid to the possibilities of the Roentgen rays in rickets. In France we find that Marfan in 1912 mentioned the characteristic

"mushroom or excavated" appearance of the epiphyses, but evidently did not make extended use of it in his clinic. In England and America one searches in vain for any mention of radiography in the pages of the standard text-books on pediatrics. The first reference to its application in the diagnosis of rickets seems to have been a short article by an orthopedist, Jacobsohn, published in 1916, which contains satisfactory illustrations.

The main cause of this unusual torpidity was the general lack of interest in rickets. A static phase had been reached, where interest was confined to the few, and these few were concerned more with its metabolic than with its clinical aspects. Another factor which tended toward its neglect was the prevailing opinion that rickets could be diagnosed so readily by simple clinical methods that the Roentgen rays were unnecessary and superfluous. The tone of several of the pioneers is frankly apologetic. It was only when fresh interest in rickets was aroused by the fact that it could be induced readily in animals, that investigators and clinicians sought to avail themselves of every method of diagnosis. In England, in 1919, Mellanby used radiographs to demonstrate that he had produced in puppies lesions characteristic of rickets and that healing could be brought about by cod-liver oil. In the same year Huldschinsky radiographed the infants he treated with ultra-violet rays. In this country Park and Howland (1921) demonstrated calcification of the epiphyses in infants treated with cod-liver oil. Today radiography is employed in clinics in a routine way, much as is the blood count or the Wassermann reaction; in all pediatric clinics, deserving the name, it is resorted to where the diagnosis is doubtful. As the result of this wide-spread application, and the many studies of rickets which have been carried out by its aid, knowledge of the radiographic changes that take place in the course of its development and its cure has become widely diffused. Although, as we shall see, the radiographic interpretation of rickets has inherent limitations, and is at times difficult, it has also inherent advantages. One of its outstanding advantages is the fact that it enables us to chart an individual case through its course of development to the stage of final healing. It provides the opportunity for visualizing and comparing the successive stages of development of the disorder—an exceptional opportunity for the physician, who usually has to rely on his recollection of symptoms which are evanescent. In general, it has tended toward an appreciation of the labile nature of bone tissue, of its quick response to favorable or adverse influences, and to overthrow the time-worn conception of bone as a fixed and inert tissue.

From 1919 to 1924 radiographs were taken every month of all infants under eighteen months of age in my clinic. This formed a part of the routine study of rickets, which included a complete physical examination and an analysis of the blood for inorganic

phosphorus. As a rule, only the wrist-joints were radiographed, but where the picture was atypical, the knees, ankles and other joints were taken. The films were filed as a permanent record and, as the infants remained in the institution for many months, we obtained serial pictures of a large number of infants who were living under identical hygienic conditions.

In order to avoid movement on the part of the infant, it is naturally important to have the period of exposure as short as possible; in this respect there has been great advance in technique. Furthermore, the rays should be soft, so as to portray in sharp outline the rachitic bones which are poor in inorganic matter and tend to cast faint shadows. If a series of radiographs is taken for the purpose of comparison, for example, in order to determine whether rickets is progressing or healing, it is essential that the duration of exposure and the quality of the tube should be uniform. Unless this precaution is taken, differences in intensity of the shadows, resulting merely from diversity in technique, may readily be construed as variations in the degree of calcification.

Rickets can be detected by the Roentgen rays first in the knee- and the wrist-joints—the lower end of the femur, the upper ends of the tibia and fibula, and the lower end of the ulna are the epiphyses which are the first to give evidences of rachitic changes. However, the very first epiphyses to be affected by the rachitic process are those at the sternal ends of the ribs. This has been proved by the histological studies of Schmorl and is evident by direct clinical examination, by the appearance of beading. Unfortunately, the costo-chondral junctions are not accessible to radiological investigation, for their silhouette is markedly blurred or even obliterated by the ribs that form the posterior wall of the thorax. On this account, as well as for other reasons, radiology is not the method of choice for the early diagnosis of rickets. It would be a decided advance and of clinical value if the technique could be perfected so as to enable us to obtain a clear picture of the costo-chondral articulations.

A few words in regard to the structure of the long bones may not be out of place. As is well known, the ends of the long bones consist of a cartilaginous epiphysis and a bony metaphysis. The former does not offer sufficient resistance to the rays to cast a definite shadow. The metaphysis, or bony end of the shaft, is composed of primary spongiosa, in other words, of newly-formed bone, which is bounded at its distal end by the preparatory zone of calcification. The normal healthy metaphysis is sharply demarcated in radiography from the epiphysis by a thin transverse band, which histological methods show to be composed of the inorganic salts of calcium and phosphorus. Emphasis is laid on the architecture of this portion of the bone, because this is the area which shows the

earliest radiological changes in rickets. The metaphysis, which is always sharp and clearly stencilled, may be almost horizontal or of a wavy, undulating outline. For example, at the distal extremities of the ulna and radius, it is almost transverse and straight, whereas at the lower end of the femur it is separated from the epiphysis by a wavy band. For this reason, and in spite of the fact that rachitic changes in the epiphyses of the femur sometimes antedate those in the epiphyses of the ulna and radius, it has been found of advantage to use the latter for routine examinations. It is hardly necessary to stress the normal picture of the shaft of the bones, but it may be well to call to mind not only that the shaft is composed of dense, compact bone, but that its cortex is decidedly thicker than its body and stands out sharply in the radiographic picture. In rickets this intensification becomes less marked and less sharply defined early in the disease and the shaft itself tends to induce a less intense shadow, owing to its diminished content of inorganic matter.

It should be emphasized at the outset that *all radiological examinations are in part subjective and in part objective.* This is especially true of the radiographs of early rickets. Time and again one is in doubt whether to regard some slight alteration in the contour of an epiphysis as a rachitic lesion. This has been the experience of all who have been engaged in the study of incipient rickets. A similar difficulty is met with in the interpretation of the earliest beginnings of the healing process. On the other hand, it is probably true that the radiographic picture is more objective than the other signs or symptoms of rickets. In order to test the anatomical basis for the interpretation of roentgenograms in rickets, Weech and Smith cut slices from the epiphysio-diaphyseal junctions and radiographed as well as examined them microscopically. It is clear from the numerous illustrations which accompany their paper that, with experience, one may draw histological deductions simply from the evidence obtained by the Roentgen rays.

A serious criticism of the value of the Roentgen rays in the diagnosis of rickets is that they fail to detect lesions until they are fairly well developed. As will be brought out in the next chapter in discussing the comparative value of the various signs of rickets, it is a common experience that the diagnosis can be made from the clinical signs, especially from the beading of the ribs, a month or more before radiographs of the epiphyses show any evidence of change. Wimberger, who has carried out the most refined radiological studies in this field, writes in 1928: "From investigation of postmortem material in which Roentgen ray pictures and histological sections were made from one and the same bone, it was shown that the interval of time between the first histological rachitic change and the first radiographic change is certainly as long as several weeks."

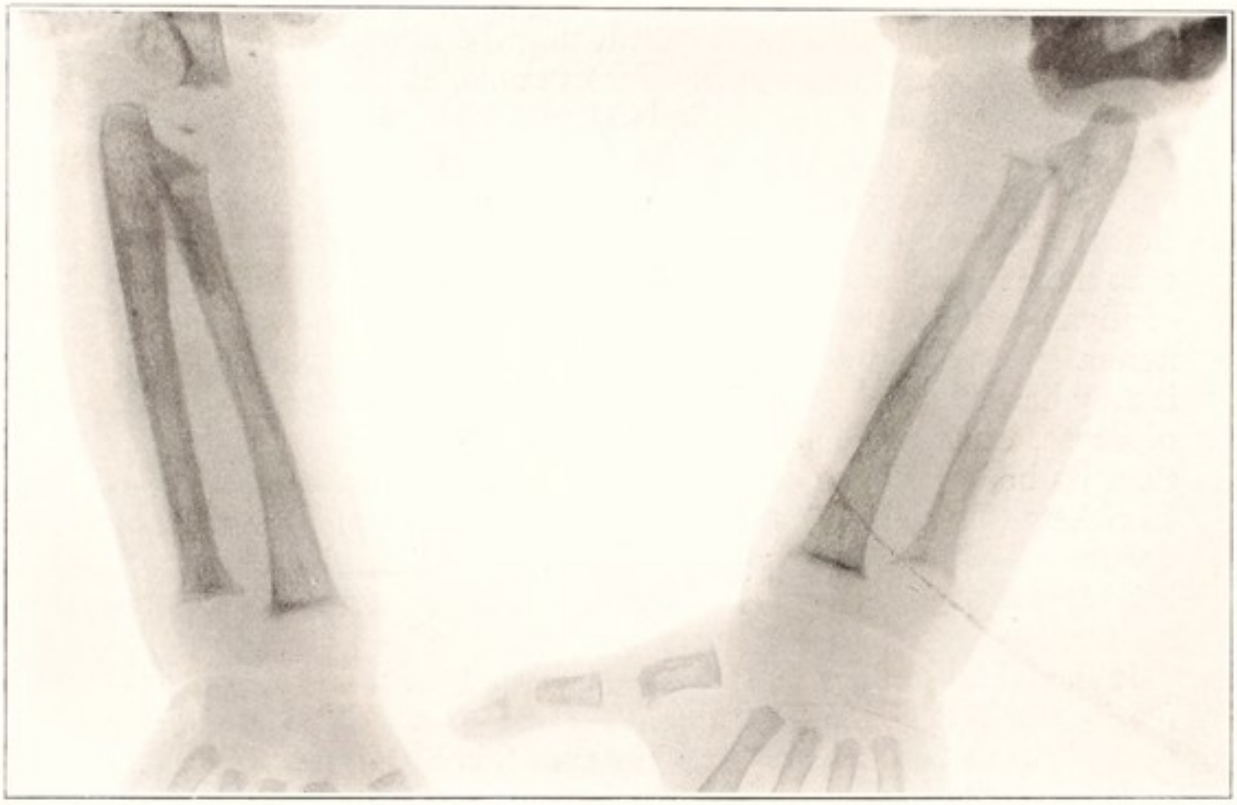

FIG. 29.

FIGS. 29 to 32.—Cure of rickets by heliotherapy: Fig. 29. Mild rickets and osteoporosis. Fig. 30. Marked healing of epiphyses and development of two carpal centers. Fig. 31. Further healing. Fig. 32. Final stage, rectification of epiphyses.

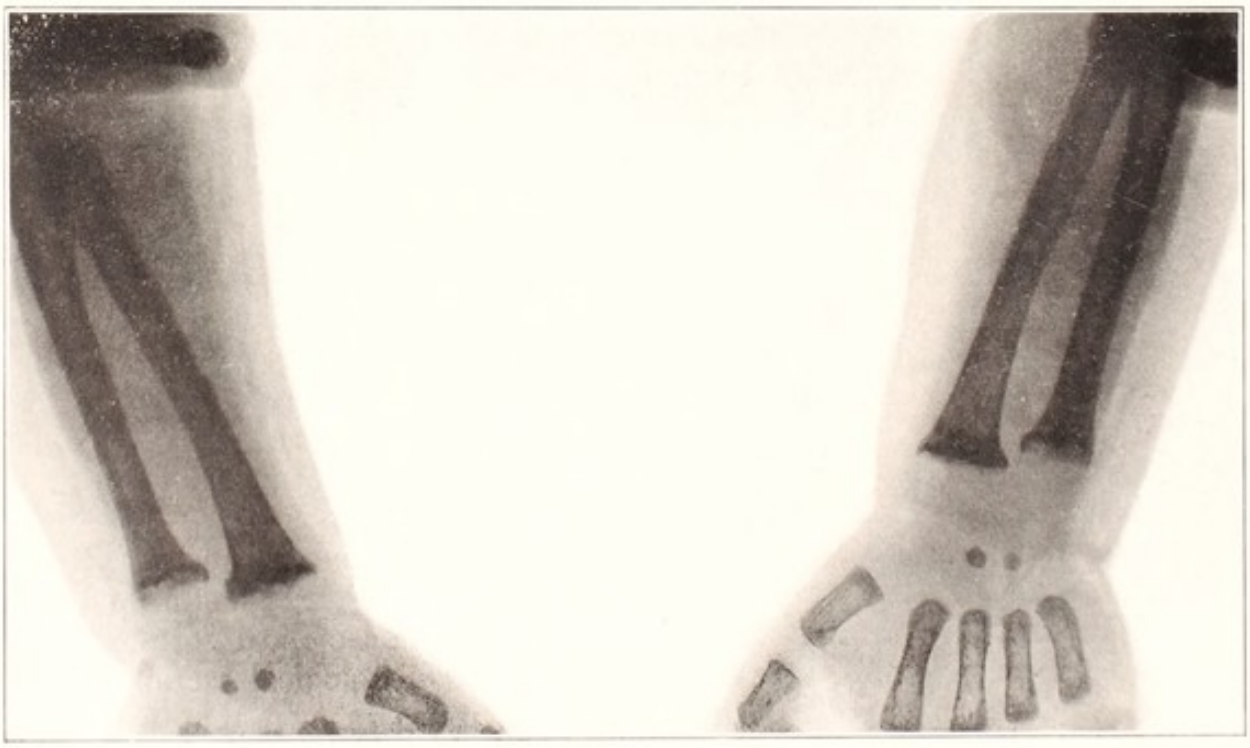

FIG. 30

The earliest indication of rickets by the radiograph is in the preparatory zone of calcification—the thin transverse band which sharply demarcates the bony metaphysis from the cartilaginous

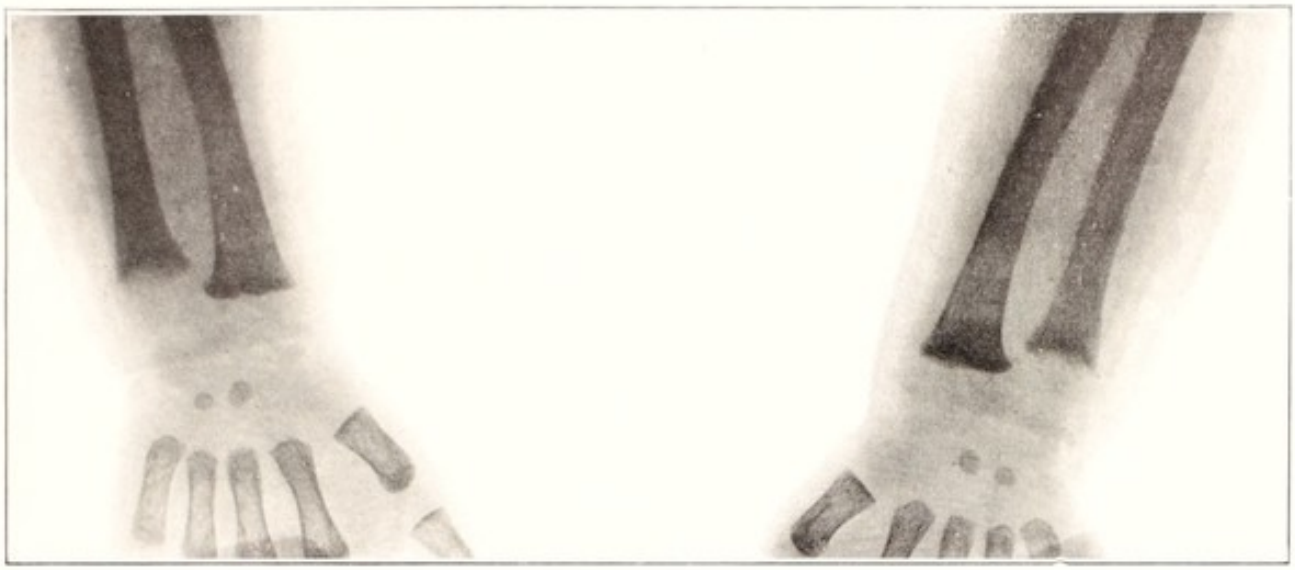

FIG. 31

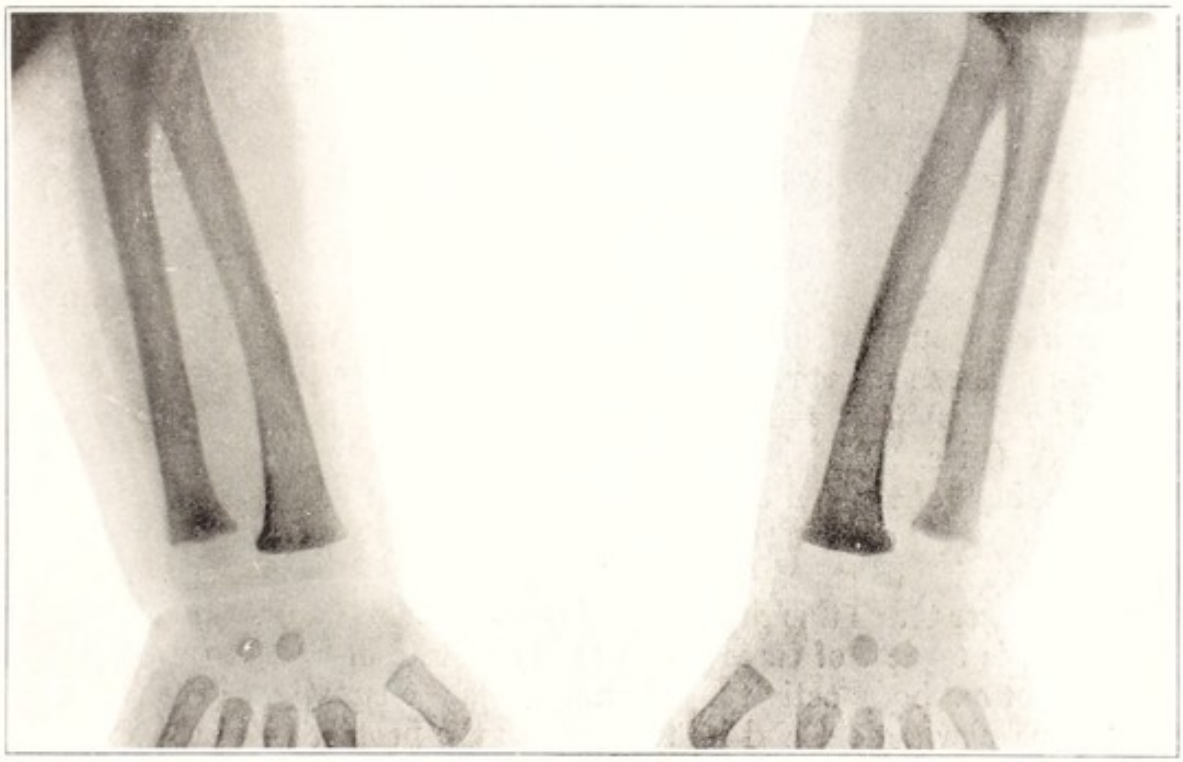

FIG. 32

epiphysis. This zone, or rather its respective shadow, becomes less intense and distinct and gradually fades and disappears. At the same time, or somewhat later, it is noted that the shadow of the

cortex of the shaft has become less intense and that the shaft itself gives a less well-defined picture. However, these changes in the shaft are difficult to interpret unless we can compare them with previous radiographs taken under precisely the same conditions. At the wrist these changes are noted at the lower end of the ulna weeks or months before they are apparent at the corresponding end of the radius. The same holds true at the ankle-joint, where changes in the fibula always precede those in the tibia. In passing, it may be mentioned that this same peculiarity in the distribution of lesions occurs in the epiphyses of rats in which experimental rickets has been induced. The next change is a very slight "cupping" or concavity in the epiphysis of the ulna, accompanied by a blurring of the edges. These deviations from the normal suffice to enable one to make a definite diagnosis of incipient or early rickets. There is, however, a lesion which precedes this cupping, one which we have been accustomed to designate in our records as "slight spreading" or "spreading," which consists of a broadening of the end of the ulna, especially at its external part. This early deformity presents the greatest difficulty for interpretation and I am unable to state whether this "spreading" should or should not be regarded as an indication of incipient rickets. I have had two opportunities to compare this radiographic picture with the associated histological lesions. In both cases the microscopic picture of the ulnæ did not show sufficient changes to warrant the diagnosis of rickets. One of these was accompanied by definite beading of the ribs, whereas in the other this sign had been slight and indefinite; in the one the concentration of inorganic phosphorus in the blood had been 3.7 mg. and in the other, 3.84 mg., in other words, just on the border-line of the rachitic plane by the Bell-Doisy method. It is evident that a far larger number of histological examinations will be necessary before we can interpret this picture.

The *moderate case* of rickets is typical and can be diagnosed at a glance (Figs. 29–32). The characteristic feature is the so-called "cupping" of the end of the metaphysis, a term which implies that its extremity becomes concave, instead of being flat or gently convex. This cupping or concavity grows deeper as the disorder progresses. Wimberger terms this the "active form of metaphysis," and believes that it is typical of cases which are in a state of healthy nutrition and normal body activity. He interprets the cupping as the result of muscular action, and its function as the protection of the weak rachitic zone, which it shields by means of its calcified margins. Cupping may also occur in the poorly-nourished infant who has lain inactive on his back, although crawling or walking tends to increase the deformity through pressure on the ends of the bones. Cupping is a change which is characteristic of the distal ends of the ulna and tibia, and the proximal and distal ends of the fibula.

It occurs with far less frequency at the distal end of the radius; it is not uncommon to note even a moderate degree of cupping at the distal end of the ulna with no cupping whatsoever at the neighboring epiphysis of the radius. The distal end of the humerus and the proximal ends of the radius and ulna never show this concavity; therefore, the elbow-joint is a site not suited for the study of rickets. In addition to the metaphysis becoming cup-shaped, its margin becomes "frayed." In other words, instead of the margin being represented by a sharply-defined shadow, it appears slightly blurred, irregular and fringed with small, frayed, thread-like projections. Sometimes these projections are so regular and so evenly distributed along the distal surfaces of a metaphysis that a "brush-like" appearance is brought about. At the same time the epiphyseal line which, as stated, corresponds to the preparatory zone of calcification, becomes decidedly fainter or disappears. In some instances one can note a delicate shadow extending distally from the outer margin of the metaphysis, like a shadowy thread projecting into the cartilaginous epiphysis.

Although the lesions are more marked and certainly more apparent at the epiphyseal ends of the bones, changes in the shaft are taking place at the same time. The mesh of the body of the shaft, composed of the spongiosa, becomes coarser and its pattern more apparent, due to increase in osteoid and a diminished content of inorganic salts, which no longer obstructs the passage of the Roentgen rays. The cortex of the shaft becomes still thinner, a change which is especially evident at the distal ends of the bones where it is normally thick and heavy. Even in moderate cases, *fractures* of the shafts of the bones may occur. These are never complete, but of the green-stick variety described by Virchow. In the course of the routine radiological examination of rickets, one is at times surprised to come upon a fracture of this kind in a baby who is well nourished and shows only mild clinical signs of rickets. For example: Baby H., aged six months, the breast-fed baby of a wet nurse in the clinic, was radiographed January, 1920, and found to have a fracture of the right ulna (Figs. 33–37). This baby looked the picture of health and weighed 15 pounds (6.8 kg.). According to the radiological examination, the diagnosis was "mild rickets," in other words, slight fraying and slight cupping of the ulna were evident. There was also a moderate degree of beading of the ribs. Immediately after noting this fracture, we examined the baby clinically and were surprised to find no sign whatsoever of fracture of the ulna—no pain, no tenderness, no disability. Silent or latent fractures of this kind occur not infrequently and are not diagnosed or even suspected. In my experience, the most common sites of fracture are the middle of the shaft of the ulna and the upper end of the fibula, but almost any of the long bones may be involved, even

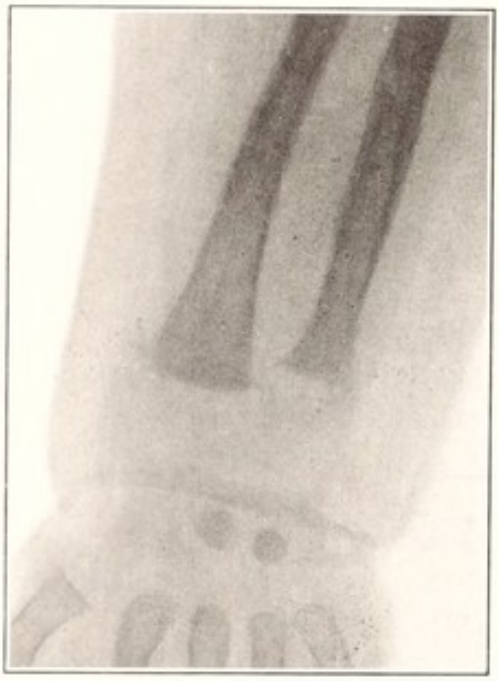

FIG. 33

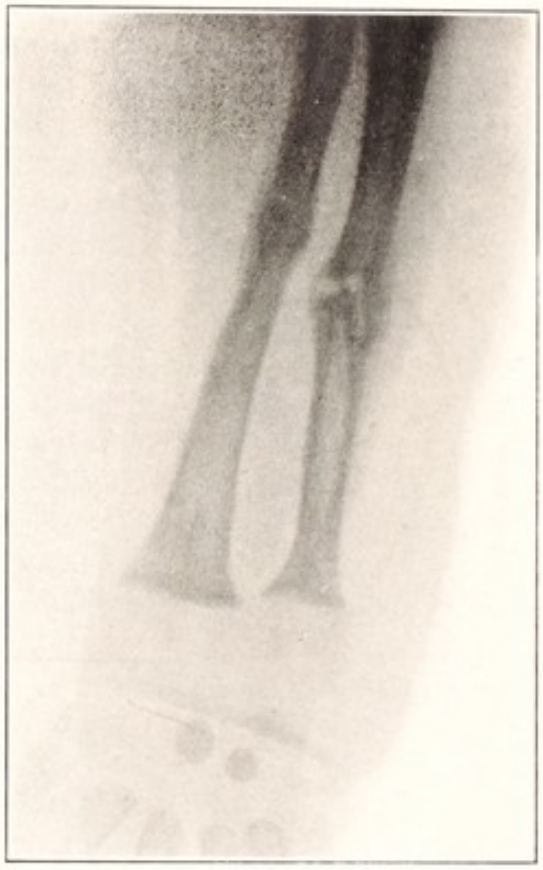

FIG. 34

FIGS. 33–37.—Rickets with fractures: Fig. 33. Very slight rickets. Fig. 34. Fractures of ulna and radius. Fig. 35. Fractures increased. Fig. 36. Callus formation and calcification of epiphyses. Fig. 37. Healed rickets, deformity at epiphyses.

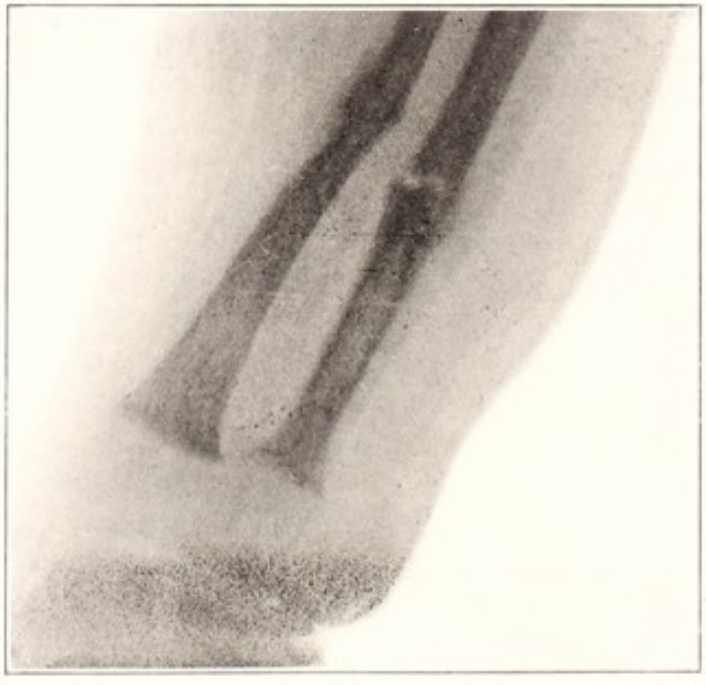

FIG. 35

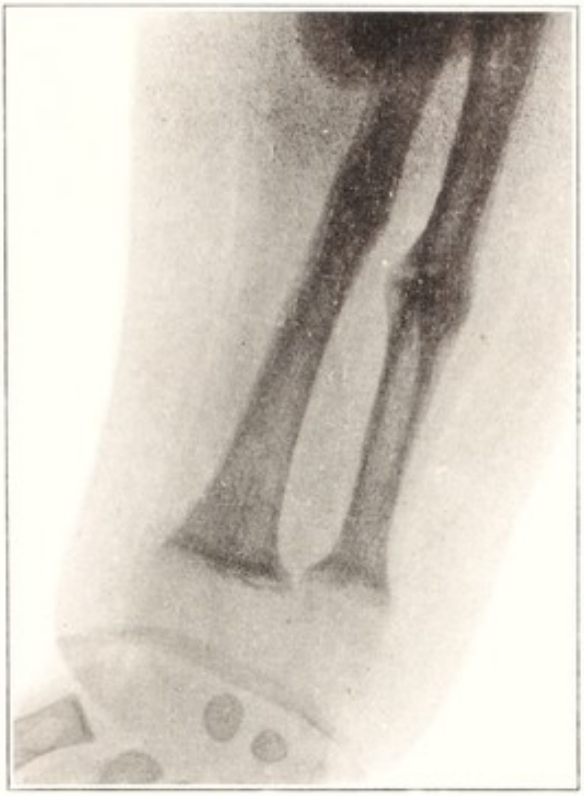

FIG. 36

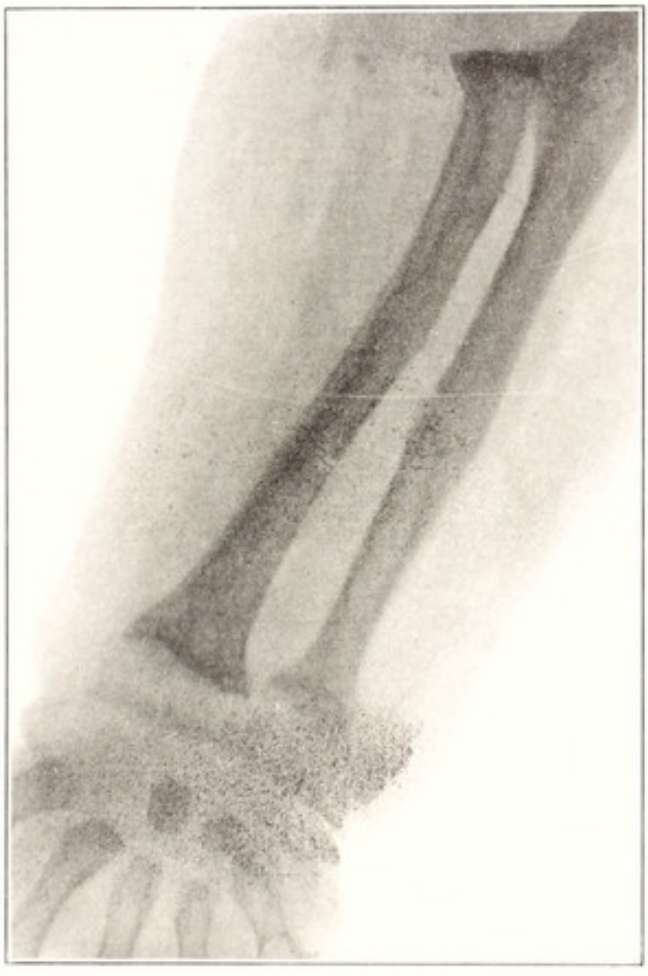

FIG. 37

the metacarpals. In a series of radiographs taken month by month, it was found that the first evidence of fracture may be a thickening of the shaft due to the formation of a callus. The fractures incline always toward the inner and never toward the outer side of the limb; the fibula is deflected toward the tibia and the ulna toward the radius. The angle formed by the fracture is soon filled in by a callus, composed of osteoid tissue and therefore but dimly visible. If the course of the callus formation is followed by serial radiographs, it is found to melt away gradually until it disappears and the bone assumes its normal contour. But months after the rickets is completely healed and the epiphyses have regained their normal appearance, a diagnosis of healed rickets may be possible from the abnormal contour, generally a slight fullness, of the shaft at the site of previous infraction.

In 1910, Looser described a phenomenon associated with rickets, late rickets and osteomalacia, and fragilitas ossium, which is characterized by one or more *horizontal transparent zones in the shaft of the long bones* (*Umbauzone*). The light area traverses the bone more or less completely and gives the impression of a break in continuity or as if a narrow slice of bone had been excised. This lesion will be discussed in the chapter on Late or Juvenile Rickets, where an illustration of the condition may be found.

The signs of *the marked case* of rickets differ only in degree from those of the moderate case (Figs. 38 and 39). The cupping of the diaphysis becomes increasingly deep. The diaphysis itself spreads and enlarges, becoming a hollowed-out, bulbous structure, which may surround the cartilaginous epiphysis like a socket; this is particularly evident in the lower extremity of the tibia. The shaft shows a very marked coarsening of its mesh and the trabeculæ are blurred and indistinct, due to the fact that they are composed largely of osteoid tissue. In very severe cases, such as have been termed the "osteomalacic form of rickets," the shaft may be almost entirely devoid of structure, showing merely irregular shadows of scattered trabeculæ. The cortex becomes abnormally thin, especially on its convex aspect, with corresponding thickening on the concave side. Occasionally a shadow may be noted leading into the marrow from this area of thickening, and almost, or even completely, dividing the marrow cavity.

In severe cases unusual sites may be involved. For example, the head of the humerus and the metacarpals, as in the accompanying illustration. Recently I saw an instance in which the lower angle of the scapula showed an irregular epiphyseal border.

Frequently the course of rickets is irregular, progression alternating with healing. This is manifested in histological preparations of the bones, as illustrated so clearly by Schmorl. As a result of this *intermittent healing*, a series of transverse lines representing suc-

cessive zones of preparatory calcification may be seen in the metaphysis. Generally, not more than two such thin bands are evident, but at times three or four may be seen. The clear areas between

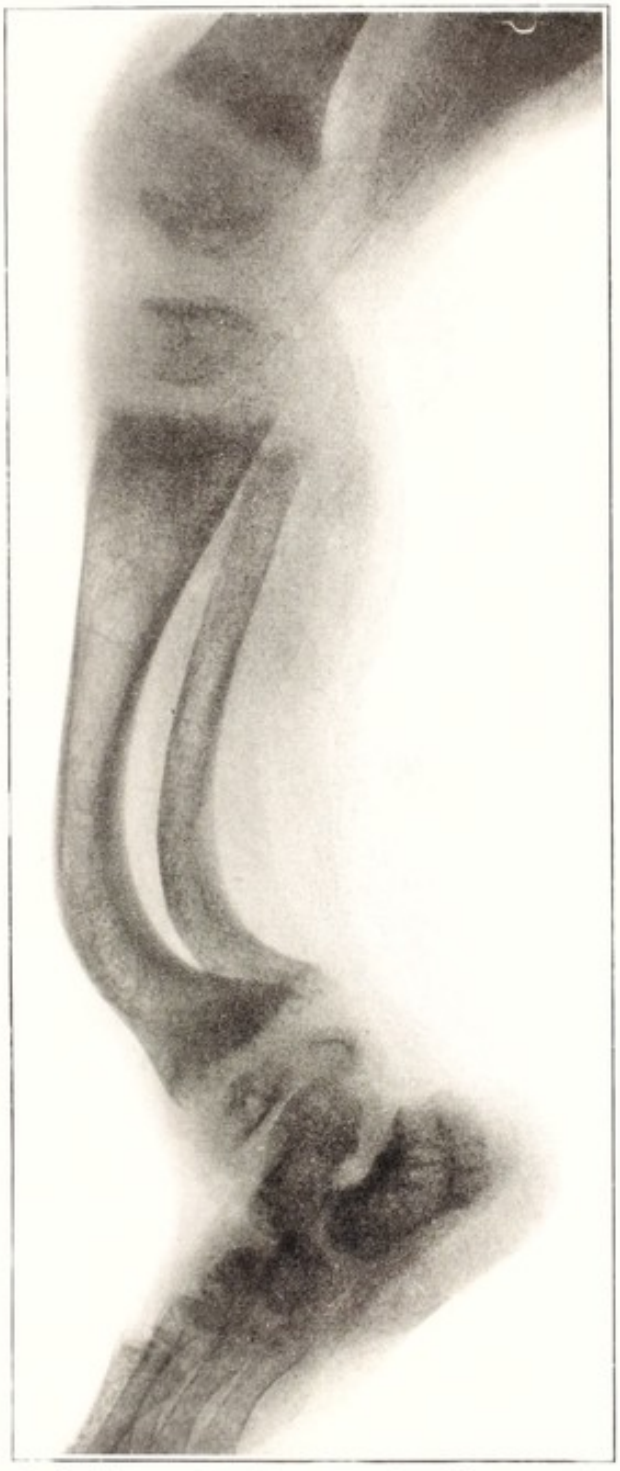

FIG. 38.—Marked rickets. Involvement of epiphyses at knee and ankle.

these tiers of calcification are composed at first of osteoid tissue. This irregularity in healing occurs most often in infants who have received cod-liver oil or ultra-violet therapy irregularly, or have

been taken out-of-doors only occasionally, and therefore it is seen more often in the out-patient department than in private practice or in institutions. However, these signs of intermissions or relapses have been frequently encountered in an institution where all curative factors seemed to have been stabilized—where the ingredients of the diet were known and where we could be certain that the infant had not received any specific antirachitic therapy. This same irregular course is met with in experimental rickets, where it

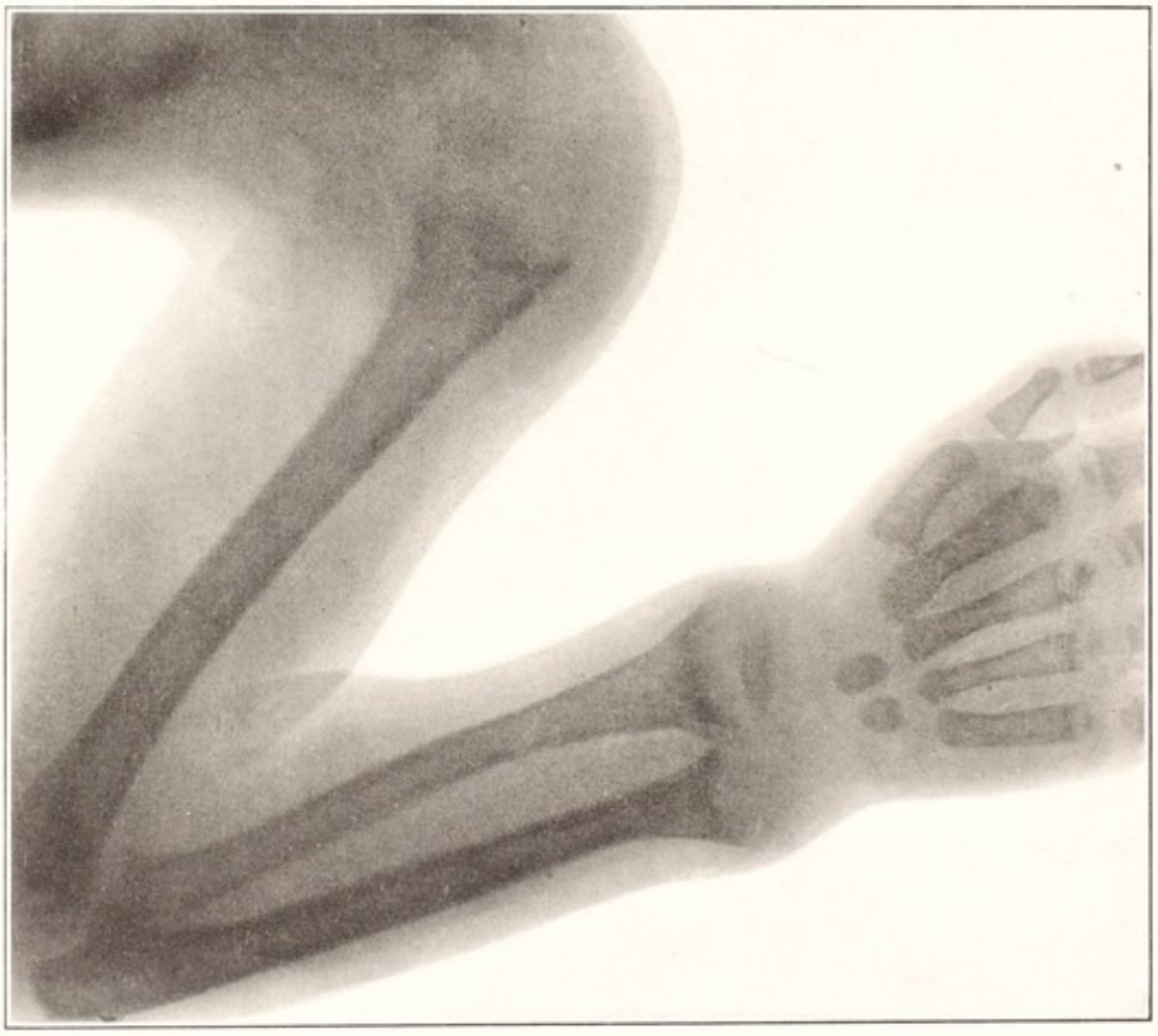

FIG. 39.—Marked rickets. Involvement of head of humerus, wrist and metacarpals.

has been possible to control the ration even from a chemical standpoint. It would seem that Schmorl is correct in believing that, irrespective of the occurrence of a remission, calcification may take place in the uncalcified tissue formed during the course of the disorder. Pommer and Ziegler also held that a deposition of calcium may come about in rachitic tissue during the phase of active rickets. Radiographs and histological examination of the bones of experimental animals confirm this point of view.

The *healing* of the rachitic epiphysis is a striking phenomenon and never fails to excite wonder at the remarkable reparative power of Nature. In a moderate or marked case of rickets, following treatment with cod-liver oil, activated ergosterol or ultra-violet light, faint indications of healing may be noted in even a week or ten days. Such a favorable result is still more common when a specific drug as well as irradiation have been given in adequate amounts. The first sign of healing is the appearance of a faint shadow distal and almost parallel to the metaphyseal margin. This phenomenon corresponds histologically to the beginnings of a new zone of preparatory calcification. It is generally a finely serrated or wavy line, somewhat resembling the appearance of a vibrio lying horizontally within the cartilaginous epiphysis. This new shadow appears at a varying distance from the margin of the metaphysis, the distance depending upon the duration of the rachitic lesion. As healing progresses, this faint transverse shadow becomes increasingly dense and more definite. It will be noted that this description of the radiographic picture of the healing process is merely an affirmation of the description of the histological changes which occur in the course of reparation. In addition to this horizontal shadow, and almost simultaneously with its advent, longitudinal shadow-bands make their appearance within the wide rachitic zone, and become gradually denser until they completely replace, with calcified tissue, the transparent zone of proliferative cartilage. On the other hand, the healing may first be evident along the brim of the "rachitic cup." The shaft of the bone shares in this healing process; there is a deposition of calcium into the cortex which gives it once more its sharp definition. The periosteum may be overlaid with a faint osteophytic layer, giving rise to a picture similar to that associated with periostitis. This had led to errors in diagnosis. Close examination of this osteophytic layer may disclose fine trabeculae running at right angles to the shaft. In addition, if there has been an infraction of the bone, a callus will be seen of increasing extent and density. The medullary area of the bone also takes part in the calcifying process and casts a denser shadow as the osteoporosis and osteoid become less marked. The most striking indication of healing is to be noted in the texture of the bone—the change from a mesh which is poorly defined and coarse to one which is increasingly delicate and sharply outlined.

Little by little the formation of osseous tissue is noted at the epiphyseal end of the bone, corresponding to the gradual calcification of the entire area lying between the new zone of preparatory calcification and the margin of the metaphysis. This newly-formed structure is finely meshed and can be clearly differentiated from the bone of the metaphysis which was less markedly involved in the rachitic process. This distinction between areas of old and new

bone furnishes us not only with a measure of the extent of the rachitic process, but many months thereafter, when the bones have returned to their normal state, it may furnish the clue to the previous existence of rickets. Other significant signs of former rickets are abnormalities in the contour of the ends of the long bones. In spite of the fact that the rachitic process may have been healed for

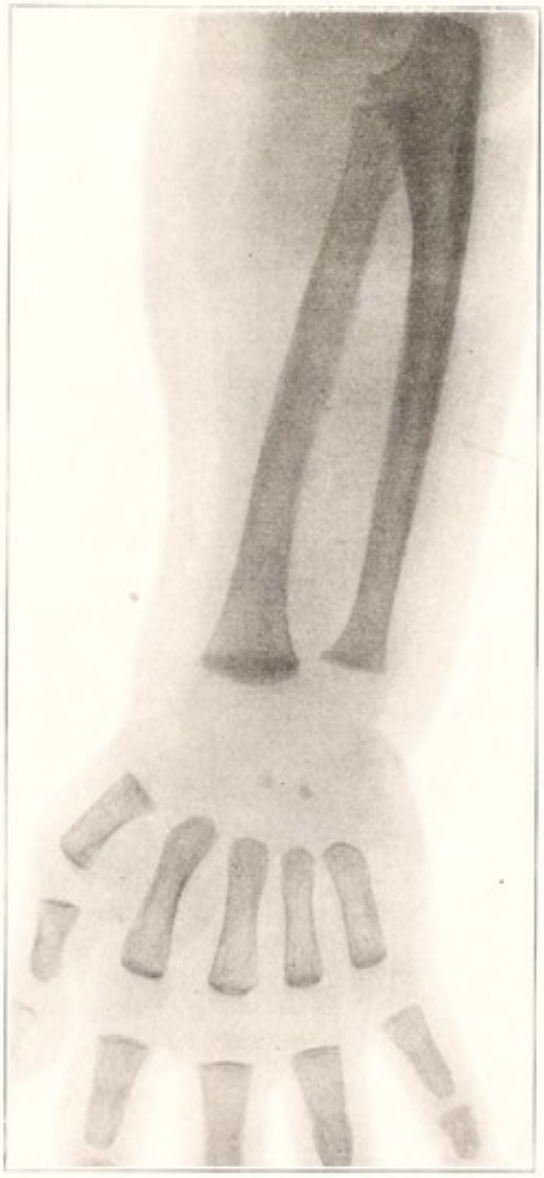

FIG. 40.—Hypercalcification of epiphyses after giving large doses of irradiated ergosterol to normal infant.

many months, the distal end of the radius may not have regained its normal shape, but present a somewhat club-shaped appearance. Again, although the metaphysis of the ulna may be quite as sharply defined as normally, it may show vestiges of cupping. Too broad a marginal border, hypercalcification in the course of healing, may also be a sign of previous rickets. On the other hand, it may be

merely the sign of hypercalcification which has occurred in a normal epiphysis from large doses of irradiated ergosterol or excessive exposure to the ultra-violet rays (Fig. 40).

As would be expected, the occurrence of rickets has an effect on the evolution and development of the *centers of ossification*. This is a factor which it is difficult to gauge, as the time of appearance of the carpal centers is subject to great variation, in male white babies it was observed at birth in 10 per cent of a large series, and in female white babies in somewhat over 22 per cent.[1] The epiphyseal center of the lower end of the femur is always present at birth in full-term infants. Plaut found a delay in the appearance and a decalcification of the carpal centers, resulting from rickets. Recently a study of some of my cases from this point of view has been made by Goldberger and Mellion, who conclude: "The appearance of carpal centers in infants with rickets was later than in infants free from rickets. Twenty-two of the 40 infants with rickets, or 55 per cent, developed their first center during the first six months of age, whereas 18 of the 22 infants free from rickets, or 82 per cent, developed carpal centers during a corresponding period." "The development of second or subsequent carpal centers in infants with rickets was delayed, compared to their appearance where rickets was absent." "Although delayed, new calcification centers appeared during the active stages of rickets. Thirty-three, or 82 per cent, of the infants with rickets showed new calcification centers during the active stages of the disease."

Accompanying the healing process, discrete granular bodies may be noted within the carpal centers—little pin-point dots of calcium scattered throughout the cartilaginous tissue. This phenomenon is of interest in affording a demonstration of the physico-chemical process associated with calcification and especially in differentiating it from ossification which is characterized by a diffuse laying down of bone from calcium salts which are in solution.

In 1923, Wimberger published an interesting study of the growth of the bones in a series of normal and in 19 rachitic infants. The tibia served as the gauge of growth, which was followed by radiographs, for the entire yearly cycle. Wimberger's conclusions in regard to rickets may be summarized as follows: The rate of growth becomes diminished somewhat before rickets is apparent by the Roentgen rays. During the period of healing, growth attains not only the

[1] A few words may be added regarding the appearance of the epiphyses of the new-born infant. In the course of the study of the carpal centers by Miss Weinstock and myself, approximately 500 radiographs of the wrists of new-born colored and white infants were taken. In almost all instances the epiphyses appeared to be normal—clear-cut and straight or slightly convex in outline. In two or three instances, however, there was a slight "cupping," a definite concavity at the end of the ulnae. The pathological significance of this exceptional picture remains to be determined.

normal rate, but becomes even excessive. The maximal impulse is manifested, however, in the autumn rather than in the spring. As the result of these counteracting phenomena, growth does not suffer because of rickets. Of course, this conclusion does not refer to extreme grades of rickets, which may result in permanent retardation of growth and dwarfism.

Mention must be made of the so-called "*transverse lines*" which are apparent so often in the metaphyses of the long bones, and attract attention in the course of the examination of radiographic films for evidences of rickets. They are seen more often at the end of the radius than of the ulna, and more often in older children than in young infants. As far as is known, they bear no relationship to rickets but merely indicate that at some period there has been a temporary cessation of growth. If the growth impetus has been checked several times by infection or other cause we may note a series of four, five, or even more of these lines running parallel to each other and to the end of the bone. Eliot, Souther and Park, who have studied this phenomenon most carefully, from both the clinical and histological points of view, believe that these lines result from "the bone-building energy of the shaft concentrating" at these levels. Histologically they found "that the formation in the bone responsible for the line in the Roentgen ray plate consists in an irregular lattice-work which extends transversely across the bone, and that the lattice is produced by the enlargement and cross-branching of the trabeculæ."

The radiographic phenomena of rickets may be summarized by the statement that they are focussed about the border which separates the bony metaphysis from the cartilaginous epiphysis. Instead of this boundary maintaining its normal sharply-defined outline, it becomes less distinct, then appears frayed and finally acquires the typical "saucer" or "cup-shaped" appearance. In addition to this gamut of changes which takes place along the epiphyseal line, the shafts of the bones become unduly transparent to the Roentgen rays, and bent and deformed as the result of the tugging of the muscles and their tendons. The joint itself, however, remains intact, periostitis is almost always absent, and no subperiosteal hemorrhages develop.

RADIOGRAPH OF RICKETS COMPARED TO THAT OF CONGENITAL SYPHILIS, OF INFANTILE SCURVY AND OF CHONDRODYSTROPHY.

The differential diagnosis of rickets will be considered in detail in the chapter which follows, but it would seem of advantage to compare, in this connection, the radiographic picture which we have sketched, with those of some disorders with which rickets is

at times confused. Among these conditions, congenital syphilis, infantile scurvy and chondrodystrophy stand out most prominently. As might be expected, the radiological distinctions between these various disorders are due to essential differences in the pathological lesions. The basis underlying the radiographical changes in rickets is the softening of the bones due to a prolonged deprivation of inorganic salts; this deficiency leads to a lack of stability which paves the way for deformity. In *congenital syphilis* a process of general softening does not take place, but a localized destruction of bone due to the action of a specific virus. Here we are dealing with the results of an inflammatory disease and not with the inroads of a nutritional disorder. The favorite site of this "osteochondritis" is the humerus at the elbow-joint. Accordingly, no saucer-like spreading of the soft epiphyses occurs, no atrophy or bending of the shafts, and rarely fractures; but, instead, localized foci of destruction are formed, which appear like punched-out areas in the shaft of the bone. Periostitis is generally also present, showing itself as a more or less regular film coating the cortex. In its early stage this exudate may be almost transparent and resemble the osteoid laid down on the surface of the shaft in rickets, in the later stages it forms an abnormally dense cortical layer, due to the calcification of the granulation tissue. The difficulty in making a diagnosis by the Roentgen ray rests on the fact that syphilis, as well as rickets, involves the epiphyses; syphilis leads to an inflammatory process—epiphysitis—which broadens the epiphyseal border and makes it irregular. As may be imagined, this gives a silhouette which may be difficult to differentiate from the rachitic lesion. The broadened epiphysis of syphilis bears an especially close resemblance to the calcified band seen in healed rickets which has been brought about by full doses of cod-liver oil or ultra-violet rays. In congenital syphilis a lighter area, of indefinite outline, may be apparent above the dark band; this is due to a partial destruction of the diaphysis at this site and its replacement by granulation tissue. It is this necrosis, associated with deficient calcification, which may lead to the characteristic separation of the epiphyses. The radiographic picture by itself, not taken in conjunction with the previous history, age of the patient, and various clinical signs, may be insufficient to establish the differential diagnosis between congenital syphilis and rickets. Nor should it be forgotten that the two pathological conditions may coexist; in fact, as has been previously mentioned, Marfan is of the opinion that syphilis constitutes one of the important etiological factors of rickets.

There is a similarity between the radiographic picture of rickets and that of *infantile scurvy* (Fig. 41). The main distinction is in the difference in involvement of the epiphyses. In rickets the changes are most marked at the epiphyseal line, in infantile scurvy this line

remains intact and the changes take place in the metaphysis just distal to the border. A dark shadow, more or less intense, and resembling a second epiphyseal line is formed a few millimeters behind the boundary. This conforms with what has been termed by pathologists the "Truemmerfeld," an area of destruction composed of broken-down bone trabeculæ, connective tissue, etc. There is no saucer-like depression at the epiphysis, no fraying, nor, on the other hand, any localized areas of softening as in congenital syphilis. Another phenomenon which is characteristic, when present, is the subperiosteal hemorrhage. When this effusion is recent it casts little or no shadow, but when organized, it may assume the density of compact cellular tissue (tumors). Frequently the uplifted perios-

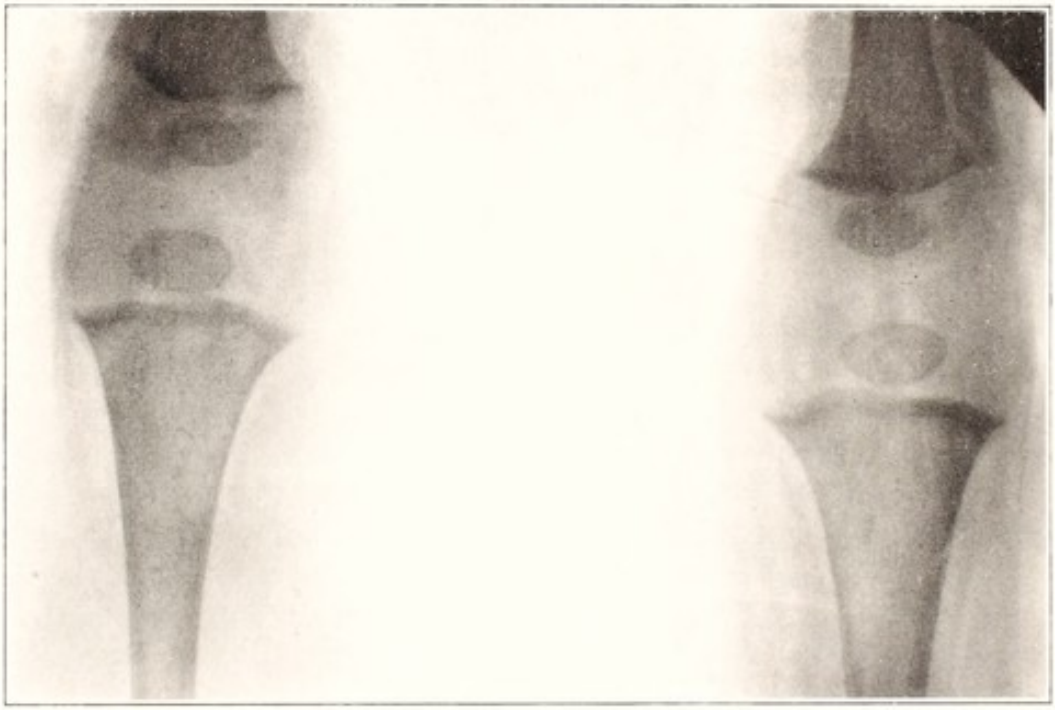

FIG. 41.—Radiogram showing "white line" at epiphyses in *scurvy*. (Courtesy of Dr. Charles Gottlieb.)

teum undergoes calcification and can be traced along the surface of the hemorrhagic area. The hemorrhages may result in separation and dislocation of the epiphysis. When typical, the radiograph of the epiphysis in infantile scurvy is readily differentiated from that in rickets. Unfortunately, the picture is frequently not clear-cut nor characteristic; furthermore, scurvy may be present in moderate degree without presenting any change visible by the Roentgen rays. The greatest confusion arises in distinguishing between the picture of scurvy and that of healed rickets, with its intense epiphyseal shadow. It is commonly stated, and it is quite true, that in scurvy the band is at some distance from the epiphyseal border and does not form an integral part of the border; in practice this distinction

may not be definite or convincing. A valuable guide is the irregularity of the epiphyseal line in rickets which may persist even when healing is far advanced. Of course, the differential diagnosis between these two nutritional disorders is greatly facilitated if one takes into account the history of the case and the presence of other signs and symptoms; this aspect will be considered in the subsequent chapter.

Rickets has been confused radiographically with some of the dystrophic disorders of infancy, especially with *chondrodystrophy*, formerly termed "fetal rickets." The diagnosis of this remarkable disorder is more readily made from the general appearance of the child than from radiographs. Mistakes have occurred owing to the fact that in chondrodystrophy the distal ends of the long bones are "mushroomed," so as to bear a certain resemblance to the saucer-shaped deformity of rickets. The epiphyseal line is, however, generally clearly outlined and "fraying" is not present. If the films are examined hastily, an error may readily occur. Careful examination of the entire shaft will disclose marked distinctions between the two disorders, resulting from the essential difference in their pathology. The fundamental characteristic of chondrodystrophy is the more or less complete cessation of endochondral ossification, associated with normal periosteal ossification. It results in an abeyance in the longitudinal growth of the bones accompanied by a persistence in their lateral growth. This leads inevitably to the production of bones which are broad and short. This perversion is to be noted especially in the femur and the humerus; the heads of these bones as well as the olecranon process become abnormally large. The metacarpal bones and phalanges are typically short and stubby; the carpal centers do not, however, show delayed calcification. In older children these cases are rarely overlooked, but, as Reyher points out, the circumstance that this disorder has been diagnosed so rarely in infants suggests that the early cases have been confused with rickets. In addition to the fact that they have many clinical manifestations in common (Chapter X), it should be borne in mind that, in infancy, differences in growth and in the relative proportions of the body are by no means striking. Unlike congenital syphilis and infantile scurvy, chondrodystrophy is rarely associated with rickets, as the one is characterized by an overgrowth and the other by a lack of growth of proliferating cartilage.[1]

Another prenatal disorder of infants to be considered in this connection is *fragilitas ossium* (osteogenesis imperfecta, osteopsa-

[1] This disorder, as well as rickets, furnishes an excellent illustration of the fact that calcification and endochondral growth are two distinct processes, going on independently, and controlled by different mechanisms. In rickets calcification is defective, but growth of the cartilage is not inhibited; in chondrodystrophy, on the contrary, calcification is normal but growth is in abeyance.

thyrosis fœtalis). This condition is characterized by fractures which may be mistaken for evidences of rickets. In cases where the fractures are numerous it is safe to infer that some disorder other than rickets is present. The fractures in fragilitas ossium are complete and not mere infractions. Furthermore, the epiphyseal line is unaffected and normal in outline. The essence of this disturbance is a lack of both endochondral and periosteal ossification. Consequently the bones become thin and brittle. The cortex may be evident merely as a thin boundary line, and the trabeculæ of the shaft may be so thin and sparse that it is difficult to obtain a satisfactory radiograph. Stunting in growth may be noted to a moderate degree. The picture of this pathological condition should not present diagnostic difficulties unless it is complicated by rickets.

The differential diagnosis of all of these disorders—congenital syphilis, infantile scurvy, chondrodystrophy and fragilitas ossium—can be made more readily from a consideration of the previous history and the clinical symptoms than from a mere study of radiographs. These clinical distinctions will be considered in detail in the following chapter.

CHAPTER X.

THE DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF RICKETS.

Rickets is the most common nutritional disorder of infants which occurs in the temperate zone. It is impossible to gauge its incidence accurately, but it seems safe to estimate that during the first two years of life one-quarter to one-half of the breast-fed infants, and approximately 75 per cent of the bottle-fed infants, develop rickets to some degree. I refer to rickets found by simple clinical or radiological examination without the aid of a chemical analysis of the blood. With these figures in mind it must be evident that a comparatively small number of cases are recognized in private practice, in the hospital ward, or in the out-patient department. If we include all degrees of rickets, even the milder form, I think it is no exaggeration to estimate that probably not more than 25 per cent of the cases are diagnosed. Even if we confine our consideration to the moderate cases, it is still probable that fully one-half escape recognition. We should add, however, that there has been decided improvement in this regard during the past few years, since physicians have begun to realize the prevalence of rickets. From this point of view rickets occupies an exceptional status, for no other disorder of infancy or childhood is overlooked fully as often as it is recognized. This failure in diagnosis is not due to a confusion of rickets with other nutritional disorders, but simply to the fact that it passes unsuspected and unnoticed. The average physician has a faulty conception of rickets. He has the severe case in mind; he pictures it as a disturbance which presents striking symptoms, or at any rate one which is evident on superficial examination. To him rickets is synonymous with poor nutrition, a square head, delayed teething and walking, and a large abdomen (pot-belly). Where these signs are absent he does not suspect. And yet the mild, unobtrusive case is representative of the great majority. There are still other cases which escape diagnosis due to errors in the technique of examination, or to a faulty interpretation of the physical signs.

As in all nutritional disorders, the most frequent manifestation is the early case. It is equally true that the incipient forms present the greatest diagnostic difficulties. In discussing symptomatology, it was pointed out that little weight should be attached to such early

but indefinite symptoms as sweating, flabbiness of the muscles, and restlessness. The signs which must be considered in particular are craniotabes, beading of the ribs, the percentage of inorganic phosphorus in the blood, and the radiographic picture of the long bones.

CRANIOTABES IN THE DIAGNOSIS OF RICKETS.

Craniotabes has been fully discussed in the previous chapter, especially as to whether it may come about as the result of simple osteoporosis. It was accepted as an early manifestation of rickets, which might appear at a time when other indications, such as the diminution in the inorganic phosphorus of the blood and the roentgenological changes in the epiphyses had not yet developed. It was pointed out that the difficulty in this connection is that there is another clinical condition which simulates true craniotabes, the so-called "congenital bone defects" of the skull, which does not result from rickets. Fortunately these defects often can be distinguished clinically from the rachitic lesions by their location, which is generally in the upper part of the parietal bones along the sagittal suture. It should be borne in mind, however, that it is one thing to diagnose the nature of cranial softening when it has been observed week by week, or even month by month, and the opportunity has been presented of noting whether it is diminishing or growing in extent, and quite another matter to determine its significance, when, as is usually the case, we have the opportunity of making but a single examination. It has been my custom to question the rachitic origin of areas of softening which are situated in proximity to the sagittal suture, unless there are other evidences of cranial softening in the lower areas of the parietal bones. The greatest difficulty, however, is in regard to isolated foci situated in the parietal bones in the neighborhood of the lambdoid suture. If there are other signs of rickets—for example, beading of the ribs or a diminution of the inorganic phosphous of the blood—the clinical picture can be viewed as a whole, and the cranial softening considered merely a link in the chain. But if there are no complementary signs of rickets, and the craniotabes exists as the sole symptom, it has been my rule to be guided somewhat by the age of the infant. In full-term infants under two or three months of age, isolated cranial softening, unaccompanied by other signs, cannot at present be regarded as pathognomonic of rickets. In older infants, those three or four months of age, softening of the skull must be interpreted as an indication of a true rachitic lesion. As stated in the previous chapter, it may be necessary to modify this point of view when the entire question can be reappraised in the light of the pathological histology of the cranial lesions.

In this connection attention must be called once more to the

tendency to overlook craniotabes. Unless the entire skull, especially its posterior portion, is palpated carefully inch by inch, small areas of softening are readily overlooked. This is the experience of the most expert. The common site of residual softening is the parietal bone posteriorly.

BEADING OF THE RIBS IN THE DIAGNOSIS OF RICKETS.

To my mind the most valuable clinical aid in the diagnosis of rickets is beading of the ribs, *the rachitic rosary*. It is, however, a sign which has to be studied in order to be understood and is, therefore, to a certain extent subjective. But this is a criticism which is applicable to all signs and symptoms including those which are elicited by laboratory methods.[1] Only clinical experience can be the guide to the degree of beading which should be disregarded clinically and the degree which should be interpreted as a sign of rickets. Pathology has furnished but few histological controls in regard to beading of the ribs—few instances where the clinical sign has been compared with the microscopic picture of the costo-chondral junctions. The British investigators in Vienna were able to make this important comparison in some cases. It is worthy of note that they found that their tendency had been to give a negative clinical interpretation to degrees of beading, which subsequent pathological examination proved to be rachitic. In other words, they had erred on the side of requiring too marked a degree of beading. This has been my experience. On examining my clinical records, I find that almost invariably when doubt existed as to whether the beading should be regarded as rachitic, the subsequent course of events showed it to have been an early manifestation of rickets.

Slight degrees of enlargement of the costo-chondral junctions should not be considered as evidence of rickets. A certain degree of beading may be felt not infrequently at the rib junctions of new-born infants or of those a few weeks of age. In some, this is a mere angulation, but in others it does not differ essentially from rachitic beading. Its exact pathological nature has not been determined. From a clinical point of view, however, it may be disregarded, in view of the histological investigations of Schmorl and others who failed to discover in the new-born the characteristic lesions of rickets in costo-chondral junctions. Angulation of the ribs is

[1] Beading of the ribs is no more a subjective phenomenon than the respiratory or cardiac sounds, or the palpation of the various organs. It is an error to regard phenomena which we appreciate through the sight and hearing as inherently more objective than those which we elicit through the sense of touch. Frequently I experience quite as much difficulty in deciding whether the epiphyses pictured in a radiographic film should be considered indicative of rickets, as in making a decision in regard to beading of the ribs.

encountered also in older infants, and should be clearly differentiated from beading. In general two types of beading can be differentiated, the one where the junction is round and formed mainly by an enlargement of the costal cartilage, and the other which we have designated as "angular" and which is occasioned by the enlargement of the bony, rather than of the cartilaginous terminal of the junction. The latter type will be described in connection with the differential diagnosis of rickets from infantile scurvy.

A word may be in place in regard to the technique of the examination for beading. In the first place, one should be sure to palpate the costo-chondral junctions and not areas on a plane either anterior or posterior to the junctions. Furthermore, palpation should be firm and not superficial, a precaution that is especially important in infants which are fat or have heavy musculature. Finally, it rests with the individual to acquire the simple method of eliciting this sign and of learning to distinguish between a degree of beading which is of no clinical significance and one which is indicative of rickets.

DIMINUTION OF INORGANIC PHOSPHORUS IN THE BLOOD IN THE DIAGNOSIS OF RICKETS.

Another sign which is of great value in diagnosis is the diminution in concentration of the inorganic phosphorus of the blood. The value of this sign has been discussed in the chapter on symptomatology, in connection with the interpretation of craniotabes and of the blood changes associated with rickets. As might be imagined, this contribution to our knowledge is of recent date—a product of "the newer rickets." The normal concentration of inorganic phosphorus in the blood varies from about 5 to 3.75 mg. per 100 cc. of plasma, when determined according to colorimetric methods, such as that of Bell and Doisy, or its modification by Briggs. When the Clark and Collip, or a similar method is used, the averages are about 1 mg. higher. Naturally, no rigid line can be drawn between the normal and the pathological level of inorganic phosphorus. The main disadvantage of this test is that it requires laboratory facilities and technique, which render it inapplicable to the average case. As a sign it is very reliable, and is of special value where the diagnosis is doubtful or as part of investigative studies. It has been employed extensively in ascertaining the incidence of rickets and the effect of various therapeutic agents.

From time to time the question has been raised as to whether this chemical change in the blood is the earliest clinical phenomenon of rickets; whether with its aid we can establish the diagnosis before the direct clinical and the radiological signs have become evident. In 1922, incidental to an investigation of the seasonal variation

of inorganic phosphorus in the blood, a comparative study was made of the earliest signs of rickets—of the development of beading of the ribs, of the diminution in the inorganic phosphorus, and of the radiological changes in the epiphyses. Once a month, throughout the autumn, winter and spring, the data were gathered and compared. The accompanying Table 19 shows the relative time of their appearance in a small group of infants. It shows that, generally, beading of the ribs preceded a definite fall of phosphorus, but that in some instances the reverse was true—the chemical change preceded all other evidences by a month or more. It should be borne in mind, as has been emphasized elsewhere, that none of these signs is a true indicator of the early stage of rickets, but that one and all should be regarded as the result of a rachitic disturbance which has existed for weeks or even months in the cells and tissues.

TABLE 19.—EARLIEST SIGN OF RICKETS (51 CASES).[1]

	Dried milk.	Raw milk.	Protein milk.	Total.
Rosary	14	9	1	24
Roentgen ray	1	0	1	2
Blood phosphorus	4	2	1	7
Rosary + roentgen ray	1	0	0	1
Rosary + phosphorus	5	2	1	8
Roentgen ray + phosphorus	2	0	0	2
Rosary + Roentgen ray + phosphorus	2	3	2	7
Total	29	16	6	51

[1] Am. Jour. Dis. Child., 1922, **24**, 327.

There is another question which arises in connection with diagnosis, namely, whether the inorganic phosphorus may be normal in concentration and rickets nevertheless exist. In discussing craniotabes, it was shown that this undoubtedly occurs in premature infants, who, as a rule, have an exceedingly high concentration of inorganic phosphorus. The same may occur exceptionally in full-term infants. This phenomenon indicates that the phosphorus level is a secondary rather than a primary manifestation of the rachitic disturbance. An instance of active rickets, associated with a normal concentration of inorganic phosphorus and calcium, is the following:

C. B., an infant admitted to the institution August 31, 1927, when one month old, weighed 7 pounds, 5 ounces (3.3 kg.). He was given protein milk and at two months had marked craniotabes. At three months he weighed 11 pounds 10 ounces (5.3 kg.) and still had marked craniotabes. In addition, moderate beading of the ribs,

some bowing of the legs, and rachitic changes, as shown by the Roentgen rays, had developed. The inorganic phosphorus of the plasma was 6.8 mg. and the calcium of the serum was 11.2 mg. per 100 cc. Irradiated yeast was given November 4 and healing was noted in radiographs on January 2. The diagnosis of rickets was established, therefore, by the Roentgen rays, during both the active and the healing stage.

It should be understood that this is an unusual case and that a high level of inorganic phosphorus almost always is an indication that active rickets is not present. An exception to this rule is the hyperphosphatemia associated with nephritis, which, however, does not occur in infants, and will be considered in the discussion of late rickets. A low concentration of inorganic phosphorus may be accepted as a sign of rickets, provided that an acute condition such as pneumonia, as Gerstenberger has pointed out, does not exist. It is evident, therefore, that this new test is of great service in clinical medicine.

The product of the calcium and the inorganic phosphorus in the blood normally exceeds 40 ($Ca \times P > 40$). It has been suggested by Howland and Kramer that when this product is between 30 and 40, active rickets is probably present, and that rickets is to be expected when the product is below 30. In general this rule holds true, but it is subject to exceptions, as in the case of rickets described above with a product of 76. It also fails in renal rickets, where the concentration of inorganic phosphorus may be so great as to render the calcium-phosphorus product abnormally high. In infants I have never found a multiple below 35 in the absence of rickets, but this does occur in animals. For example, if a small amount of phosphorus (75 mg. per 100 gm. of diet) be added to the Sherman-Pappenheimer rickets-producing ration, rickets will invariably be prevented, but the inorganic phosphorus concentration will remain low and the $Ca \times P$ product frequently as low as 35. This device, therefore, is not based on a principle which underlies the pathogenesis of rickets. It would seem that it offers little more than a statement to the effect that a concentration of less than 4 mg. of inorganic phosphorus (by the colorimetric method) indicates rickets and that a concentration of less than 9 mg. of calcium indicates tetany.

THE ROENTGEN RAYS IN THE DIAGNOSIS OF RICKETS.

As stated in the previous chapter, the Roentgen rays are of limited value in the early diagnosis of rickets, the lesions becoming apparent by radiographs some weeks after the beading of the ribs or the decrease in the blood phosphate. Possibly when we learn the pathological and metabolic significance of minor changes in the

epiphyses, more especially of "spreading" of the distal end of the ulna, the radiograph will acquire added value. The radiological changes associated with rickets have been described in detail, so that it seems unnecessary to review them again. The expert may suspect the existence of rickets by the general appearance of the bones—their translucency and texture, the lack of definition of the epiphyseal lines, the thinness of the cortex at the metaphyses, etc., but a definite diagnosis generally will hinge upon the presence or absence of the well-known changes at the epiphyses. These are more particularly the beginning of fraying at the border of the epiphysis, and somewhat later the development of a "saucer or cup-like" concavity.

The relative values of Roentgen-ray examination, beading of the ribs, craniotabes and inorganic phosphorus are entirely different, according to whether they are considered from the standpoint of diagnosis or of healing. Although radiographs cannot be relied upon to disclose incipient rickets, they furnish early and valuable evidence that the healing process has begun. In fact, *calcification or healing noted in the radiograph may be the first indication that the infant has been suffering from rickets.* Beading of the ribs, so valuable for diagnosis, not only cannot be depended upon in this connection, but may be misleading. The rosary often becomes firmer and more prominent, due to the loss of fluid which is associated with the healing of the costo-chondral junctions. This change may be followed only later by the gradual disappearance of the rosary. The inorganic phosphorus of the blood rises during the early stage of healing, but the increase often is within the margin of technical error. By the time the increase is well defined, calcification generally has been noted by the Roentgen rays.

THE FONTANEL, ENLARGED EPIPHYSES, AND BOW-LEGS IN THE DIAGNOSIS OF RICKETS.

The typical picture of moderate and of severe rickets has been outlined in the chapter on Symptomatology, but it may be of value to consider briefly the diagnostic significance of some of the well-established signs. Before doing so, mention should be made of a phenomenon which no doubt has been noticed by many clinicians. Not infrequently one is convinced from the general appearance of the infant that it has rickets, but a careful and complete examination fails to reveal definite rachitic signs. Beading of the ribs is absent, as is enlargement of the epiphyses, the radiographic film shows a normal picture and the concentrations of phosphorus and of calcium in the blood are not diminished. Such cases are by no means rare; my records contain numerous instances. The striking features are the square head and prominent frontal and parietal bosses, and

perhaps the slightly misshapen thorax. The Wassermann reaction is negative. A month or two later the development of one or more of the orthodox signs of rickets substantiates the diagnosis. Of course, it might be maintained that this later development was quite independent of the early signs. In one case we had to wait for corroboration from the middle of December to the middle of March.

It is true that the fontanel is often exceptionally large in rickets, and that its borders are apt to be thin and unduly pliable. But there are other conditions which may lead to delay in closure of the fontanel. The most common of these is hydrocephalus. Furthermore, occasionally one meets with a case which does not fit at all into established categories. For instance, not long ago I saw a child, aged four and a half years, with open fontanel and no signs of rickets. It was underweight, small, and had cyanosis which was due to congenital disease of the heart. On the other hand, occasionally rickets may be associated with premature rather than with delayed closure of the fontanel, as illustrated by the following case:

A baby, aged seven and a half months, was admitted in good condition and without signs of rickets. The circumference of its head measured 43.5, its chest 42 and its total length was 68.3 cm. At nine months of age it showed signs of definite rickets, especially marked beading; it weighed 16 pounds, 7 ounces (7.5 kg.), had one tooth, and the fontanel was almost closed. A month later, in February, the fontanel had closed. The inorganic phosphorus of the blood at that time was 3.7 mg.; in March it was 3.75 mg. (Bell-Doisy method). The baby had 4 teeth and sat up at thirteen months. It was not microcephalic, and its mental development was normal.

Many of the text-books stress the enlargement of the epiphyses in diagnosis. In my experience this sign has been conspicuously absent early in the disorder. The British investigators in Vienna found it "of little value in indicating the onset of the disease." Possibly there is a difference in the incidence of this sign among various races, for there is no doubt that epiphyseal enlargement is present more often and is far more pronounced in the negro than in the white child.[1] It is brought about in part by pressure and is often induced by crawling or by supporting the weight of the body on the hands. No significance should be attached to the absence

[1] The signs of rickets in the negro are so exaggerated that, from a clinical standpoint, it is virtually a distinct type of disorder. To appreciate this striking difference one has merely to compare the rickets in the average hospital in New York City with that in a hospital in the negro district. The deformities of the legs, the sinking in of the chest, the fractures and calluses, coxa vara, etc., in the negro baby are of the type which was depicted fifty years ago. The frequency and intensity of tetany parallel the degree of rickets, a fact which is interesting in view of the fact that syphilis tends to spare the central nervous system in the negro.

of enlargement of the epiphyses. Hypertrophy of the epiphyses is a valuable vestigial sign of rickets.

A few words must be added concerning some changes in the skeleton which are commonly regarded as distinctive of rickets, but which may come about independently of this disorder. In the first place, bow-legs. It is true that rickets is by far the greatest etiological factor in inducing this deformity, but it is not the only factor, so that bowing should not be accepted *ipso facto* as an indication of rickets, past or present. The cases from my clinic, published in 1924 by Barenberg and Bloomberg, clearly demonstrated this point. This holds true to a still greater extent in regard to two well-known deformities of the thorax—*the "pigeon-breast" or "chicken-breast" and the "funnel-shaped chest,"* both of which are regarded as specific lesions of rickets. The nature of these lesions has been fully discussed in the chapter on Symptomatology. Finally, just as these deformities of the anterior chest wall are not always the result of rickets, so the allied clinical phenomenon which I have termed "softening of the ribs" may arise quite independently of this disorder. In this condition the chest wall is unusually compressible, due to a lack of rigidity of the ribs. It is to be ascribed largely to atrophic changes, and is especially marked when infantile atrophy or marasmus is associated with rickets.

Frequently it is possible to diagnose rickets years after it has healed. Oddly enough, this is possible less often in premature infants than in those born at full-term, owing to the fact that the skeletons of the former usually are poorly developed and show less tendency to hypertrophy. In children under the age of five years a careful examination of the bony frame will often disclose that the child has suffered from rickets in infancy. The beading of the ribs may persist for years, even into adult life; the clavicles may be unduly curved and have an S-shaped contour; the head may still be square and present frontal and parietal bosses; the lower extremities may show signs of knock-knee or bowing. Residual bowing should be looked for especially at the lower end of the tibiæ just above the malleoli, where the shaft may give the appearance of having been bent inward. Flanging of the lower border of the chest wall is a tell-tale sign of rickets, as well as the vestiges of a transverse furrow (Harrison's groove) which may be associated with it.[1] The condition of the teeth, whether carious or sound, is of no value in determining whether rickets has existed. Radiographs may furnish evidence of slight bending of the long bones which had escaped clinical examination. Although these various changes, especially when considered in their entirety, may constitute circumstantial evidence of past rickets, they must be used with caution

[1] Recently I saw a young child in whom moderate "flanging" had been diagnosed as a fracture of the lower ribs and had been treated by "strapping" the chest.

as the basis of statistical studies in regard to the incidence of rickets. I mention this point because scattered through the literature may be found reports on the prevalence of rickets, based on the residual changes in the skeleton. In some instances it would seem that these investigations were carried out by inexperienced observers in the course of a routine examination of school children.

THE DIFFERENTIAL DIAGNOSIS OF RICKETS.

There has been considerable advance in the differential diagnosis of rickets owing to the fact that, during the past fifty or seventy-five years, conditions such as congenital syphilis, chondrodystrophy, osteogenesis imperfecta, etc., have been segregated and been recognized as distinct pathological and clinical entities. In regard to the purely clinical diagnosis of rickets, apart from its differentiation from other diseases, little advance has been made since the classic description by Glisson in the seventeenth century. Almost all the signs and symptoms which are sought for in the clinic today were clearly described by this great clinician. The one great exception is craniotabes. Definite advance has been made, however, by the utilization of laboratory methods—the estimation of inorganic phosphorus in the blood and the appreciation of characteristic lesions by means of the Roentgen rays. Nevertheless one feels increasingly the need for newer methods for the early recognition of rickets and the realization that at present we make the diagnosis only at a stage when the disease has existed for a considerable period. We are identifying it by the tissue changes which it has wrought, rather than by the metabolic disturbances which characterize it. The scope of rickets, what to include and what to exclude, is not yet definitely determined, and it is quite possible that our point of view may be altered as the result of clinical or experimental investigations. If this happens, the diagnosis of rickets will, naturally, have to be reshaped and adapted to harmonize with the new conception of the disorder.

Infantile Scurvy.—In connection with the differential diagnosis of rickets, the diseases to be borne in mind are chiefly infantile scurvy (Barlow's disease) and congenital syphilis. The subacute type of scurvy is no doubt often confused with rickets in localities where cow's milk is not supplemented by the addition of antiscorbutic food. This confusion extends even to the therapy of the two disorders, and it is not rare to meet with a physician who believes that orange juice is of value in the treatment of rickets. In differentiating between these two nutritional disorders, the nature of the previous dietary, the clinical signs, and the therapeutic test are all of value. In order that an infant develop scurvy it must have been deprived, to a greater or less extent, of fruit juices and of fresh

vegetables and have been fed on cow's milk which has been heated one or more times. Vegetables or fruits may have been given, but in insufficient amount or irregularly. The scorbutic infant is almost always poorly nourished, unhappy and capricious in its appetite; its weight will be found to have been almost stationary for a considerable period. As we know, although these attributes may apply likewise to the rachitic infant, it is quite as likely to be well-nourished and gaining steadily in weight. Associated with infantile scurvy is tenderness, which often becomes manifest when the thorax is subjected to pressure in lifting the baby, or when the lower end of the femur is pressed. A fine hemorrhagic line may be noted on the gums, if the teeth have erupted or are in the process of eruption. Petechiae of the skin, especially about the neck, will often be found if carefully searched for. Red cells may be present in the urine. A "rosary" may exist, but, as Hess and Unger pointed out, this beading of the ribs differs in character from the typical rachitic beading. It is angular rather than round and knobby, and is due to infractions at the costo-chondral junctions. It is owing to the fact that beading is common both to rickets and scurvy that confusion between these two disorders has persisted for so many years and that the belief is current that they are related. They have nothing in common from a pathological or etiological standpoint, and, in my opinion, rickets does not tend toward the development of scurvy, nor scurvy toward rickets.[1] The value of the radiographic picture in this connection has been discussed in the previous chapter. It will be remembered that the characteristic change in scurvy is the appearance of a band (the "white line" of Fraenkel) just at the epiphyseal boundary, and that "cupping" or "fraying" of the epiphyses does not develop. Too much reliance should not, however, be placed on the presence or absence of the "white line," as it is often missing in straightforward cases. If a subperiosteal hemorrhage is noted—the common site is at the lower end of the femur—the diagnosis of scurvy is established. The concentration of inorganic phosphorus, which is diminished in rickets, is normal in scurvy. It must always be borne in mind, however, that the two nutritional disturbances may be present simultaneously. In such cases, the greatest weight must be attached to the history, to the various hemorrhagic phenomena of scurvy, and to the radiographic and blood changes of rickets.

Congenital Syphilis.—Fournier believed that rickets is due to syphilis, and Marfan still accords syphilis an important etiological rôle in this disorder. Marked similarities may exist between rickets

[1] Glisson's opinion on this question was as follows: "The scurvy is sometimes conjoyned with this affect; it scarce holdeth any greater commerce with this disease, than with other diseases of longer continuance." Elsewhere he writes, "this affect doth somewhat the more dispose to the scurvy."

and congenital syphilis. The large square head is found in both conditions, but is more marked in syphilis and is apt to be less symmetrical. The skull is frequently soft, resembling the craniotabes of rickets. Furthermore, the epiphyses are enlarged in both diseases, the hypertrophy occurring earlier in syphilis. It is evident that mistakes in diagnosis may readily occur, especially where congenital syphilis is prevalent. On the other hand, if we make a more careful and comprehensive examination, sufficient diagnostic criteria can be assembled to differentiate the one condition from the other. In the first place, beading of the ribs does not result from syphilis; if this sign is present, it is due probably to rickets, perhaps to scurvy. Syphilis is associated with bilateral enlargement of the epitrochlear nodes, a sign which is of definite diagnostic value, and not sufficiently used. There may be tenderness of the bones in syphilis due to periostitis, especially of the epiphyses at the elbow-joint; this tenderness is frequently accompanied by thickening. The epiphysis may be separated from the shaft, leading to crepitation and to a disability of the limb, a phenomenon which is termed Parrot's pseudoparalysis. The spleen is almost always enlarged and firm, but may be difficult to palpate. The presence of the rash, the typical maculo-papular copper tinted areas, will at once serve to establish the diagnosis. In fact, congenital syphilis can be diagnosed frequently at a glance from the facies of the infant—its peculiar color, the coryza, rhagades, scaly eyebrows, etc. Moreover, the history may be of decided help—syphilis in mother, father or other children, frequent miscarriages, a previous rash in parent or child. The age at which the signs develop differs somewhat in syphilis and in rickets; in the former the signs enumerated are frequently well-developed before the infant is three months of age, in the latter they tend to appear after this period. Radiographic examination may establish the diagnosis at a glance. The points of difference between the radiographic pictures have been described in the previous chapter. They may be summarized by the statement that in syphilis instead of finding the characteristic epiphyseal changes of rickets, evidences of periostitis are noted along the shaft, translucent foci may be seen in the spongiosa due to the presence of areas of granulation tissue, and there is the dark shadow of excessive calcification at the epiphyseal border. As stated, this band of calcification may resemble the healing brought about by specific antirachitic therapy; however, the age of the infant and the history of the use of cod-liver oil, ultra-violet light, etc., should aid in the differentiation. Finally, mention must be made of the Wassermann reaction. This test cannot be absolutely relied upon in young infants, as it is negative sometimes in spite of the existence of syphilis. As in the case of scurvy, congenital syphilis may be complicated by rickets; in fact such is not infrequently the case. Whether syphilis tends toward

the development of rachitic lesions is a question which cannot be definitely answered.

Chondrodystrophy.—Chondrodystrophy may be mistaken for rickets. Indeed it is probable that a large percentage of instances of this disease—of those which are not entirely overlooked—are at first regarded as rickets. This is a pardonable error during the first year or two of life—the eminently rachitic age. There are a number of clinical signs which these two disorders have in common and which contribute to this confusion. In both, the head tends to be larger than normal and the frontal and parietal tuberosities unusually prominent; there is delay in the closure of the fontanel, in fact in chondrodystrophy it may not close until the child is four or five years of age. Furthermore, there is beading of the ribs, enlargement of the epiphyses, bending of the shafts of the long bones and frequently genu valgum. The main clinical distinction lies in the general appearance of the infant, in the fact that in chondrodystrophy an abnormal relationship exists between the length of the limbs and that of the trunk. In the normal individual the tips of the fingers extend down as far as the level of the middle of the thighs when the arms hang by the side, in chondrodystrophy they may extend no further than the level of the groin. The navel is not situated at the mid-point of the body, but, as the result of the shortness of the legs, it is at a much lower plane. Although this abnormality in the relative proportions of the body is recognizable at a glance in the chondrodystrophic child of four or five years of age, it is readily overlooked in the infant. This tendency is abetted by the rarity of the disorder. A case in point is the following:

A few years ago I saw a physician's child, aged six and a half years, with evident chondrodystrophy. This child had been apparently normal at birth except for a very large head. He grew rapidly and at one year was 32 inches (82 cm.) tall and weighed 28 pounds (12.5 kg.). He was under the care of a children's specialist who considered him "a beautiful baby." He did not walk until twenty months of age, but played squatting. When I saw him, his walk was somewhat rolling. At two years he was 35 inches (89 cm.) in height and weighed 35½ pounds (16 kg.). Between his second and third years he grew but 1 inch. At this time it was noted that his feet were abnormal, and he was taken to an orthopedist who diagnosed flat-feet due to rickets, and prescribed plates in the shoes. When four years of age he was 37½ inches (95 cm.) in height and a disproportion between the length of the body and legs was noticed. The diagnosis of chondrodystrophy was then made for the first time.

The nose is flat and sunken at its base, and the stubby fingers give a somewhat typical shape to the hand, which has been termed the "trident hand" (main en trident). If the condition is suspected

at an early age, the diagnosis may be substantiated by the Roentgen rays. The comparative shortness and breadth of the long bones, especially of the metacarpals and phalanges may be apparent and clinch the diagnosis. At an early age the appearance of the epiphyses may be confusing rather than helpful, owing to the irregularity of the zone of preparatory cartilage and to the spreading or "mushrooming" of its border. The confusion of chondrodystrophy with rickets is attended with no unfortunate results as we are absolutely helpless when confronted with this extraordinary pathological condition. In this respect the relationship differs essentially from that between rickets and infantile scurvy or congenital syphilis.

The two conditions do at times occur together. We have a child in the institution which was admitted three years ago at the age of one month; at six months of age this child had undoubted signs of rickets which were confirmed by the radiographic picture.

Osteogenesis Imperfecta (Osteopsathyrosis).—Osteogenesis imperfecta is often mistaken for rickets, especially before the fractures become so numerous as to excite doubt and suspicion. When fractures occur during the first few months of life and are numerous, especially if they are not accompanied by definite signs of rickets, the existence of osteogenesis imperfecta should be suspected. Generally, the difficulty in differentiating the two conditions is not great, and arises in the second half of the first year of life. It should be remembered that in osteogenesis imperfecta the skull may be very soft, resembling the "Weichschædel," the "parchment-like" or "celluloid" skull. Radiographs are of great assistance in enabling us to appreciate the nature of the pathological condition, as in the congenital dyscrasia the bones show merely a thin cortex and poorly ossified shaft—a deficiency in inorganic matter—and none of the lesions of the epiphyses which should accompany rickets of such intensity. The therapeutic test may be of aid, for osteogenesis imperfecta is not benefited by any of the agents which have proved themselves to be specific in rickets. On the other hand, the fractures associated with rickets respond rapidly to such therapy.

Myxedema (Sporadic Cretinism.)—Occasionally myxedema is regarded as rickets. There is very little justification for this error as the two conditions have but few signs in common. In the first place, cretinism is a form of dwarfism; if the infant is normal in length, it probably is not a cretin. Like rickets, it is characterized by a lack of ossification of the skeleton, which may be shown by delayed closure of the fontanel, and retardation in calcification of the carpal centers. The signs which both disorders have in common are: marked delay in teething and in walking, pot-belly and umbilical hernia. Beading does not occur, nor does enlargement of the epiphyses, nor the typical radiological picture of rickets. As a matter of fact, a myxedematous condition inhibits the development of

rickets, as do all processes which impede growth. The diagnosis of cretinism can be made from the general appearance of the child, its facial expression, flat nose, large protruding tongue, fat pads in the suprascapular region and especially from evidences of dwarfism.

Pott's Disease.—There are some lesions of the bones seen most often by the orthopedist, which at times present difficulties in diagnosis. Pott's disease or tuberculosis of the vertebræ is one of this number. The main distinctions between them are that the kyphosis of rickets is less marked, that it is not painful or tender, that it is rectified promptly when the infant is laid upon its abdomen, and that it is more diffuse and not localized to one or two vertebræ. At times the question cannot be dismissed so summarily, and must be decided by the presence or absence of other signs. I may add that in moderate and severe rickets I have noted a few instances of definite localized tenderness of the dorsal vertebræ which persisted for a few days or a week. In the case of a baby, aged thirteen months, there could be no doubt that pain was occasioned whenever it was placed in the sitting posture. All of these infants were under observation for at least a year and showed no signs of tuberculosis or of scurvy. It should be borne in mind that lesions of the vertebræ have been found in rickets and in osteomalacia.

Coxa Vara.—In severe cases coxa vara may result from rickets and be confused either with congenital dislocation of the hip or with curvature of the femur. A careful examination of the acetabulum, combined with radiographs of this region, and a comparison of the standard measurements of the lower extremities will enable a differentiation. Fig. 26 shows a mild instance of this condition.

Hydrocephalus.—In a young infant it may be difficult to decide whether enlargement of the head is due to simple hydrocephalus, to rickets or to rickets combined with hydrocephalus. If rickets is present and the head is abnormally large it may be impossible, for a time, to make a diagnosis, and incidentally, a reliable prognosis. Bohle found an increase in pressure in the ventricles in rickets, as shown by an abnormally high pressure in the spinal fluid; in one-third of the cases this sign persisted as a hydrocephalus occultus. The best that can be done, under the circumstances, is to follow the course of events, to measure periodically the growth of the head and to compare its increase with that of the circumference of the chest and the total length of the infant. For example: In December, 1919, I had under my care a baby, aged four months, which weighed 4.3 kg. Its head measured 39.2, chest 36.8 and body 58.8 cm. The fontanel was patent to the lambdoid suture, there was marked craniotabes and a moderate "rosary." As the winter progressed all signs of rickets increased and it presented the text-book picture. By March, the circumference of the head had increased to 44.3, the chest to 38.3, and the length to 63 cm. The question

arose as to whether a true hydrocephalic condition was developing. Cod-liver oil was given and the rickets rapidly disappeared. The rate of growth of the head became decidedly less—it measured only 46 cm. by October—the fontanel closed at twenty months and the child sat at thirteen months. This baby was under observation for some years and showed no further signs of hydrocephalus.

This case illustrates the value of the therapeutic test in differentiating the nature of the hydrocephalus; if the enlargement is rachitic in origin it should respond to specific antirachitic therapy, and if syphilitic to antisyphilitic therapy. Whereas if it is a simple obstructive condition, neither of these measures will prevent its increase. Direct irradiation or irradiated milk or ergosterol should be used in these conditions where rapid action is highly desirable.

Anterior Poliomyelitis.—Muscular weakness may become so extreme in rickets as to resemble that of anterior poliomyelitis. I have seen an error of this kind made in connection with rickets, as well as with infantile scurvy. It would seem to be sufficient to bear this possibility in mind but in point of fact the differentiation, at the time of an epidemic, may present considerable difficulty. The diagnosis will rest on the presence of the associated signs of these diseases. If in spite of a careful clinical examination of the nervous and osseous systems, one cannot arrive at a satisfactory conclusion, recourse will have to be taken to the radiological picture, and to a determination of the inorganic phosphorus of the blood. This should rarely be necessary. Such profound muscular weakness is generally accompanied by signs and symptoms of rickets of corresponding intensity.

CHAPTER XI.

THE PROGNOSIS OF RICKETS.

LIKE all chronic disorders, rickets is characterized by an insidious onset and ill-defined termination. It is never acute—acute rickets is generally scurvy or some inflammatory process. Its course is not definite nor regular and may run for weeks or for months. Most cases are very mild, pass unobserved, and progress at a varying pace until they are checked spontaneously by the advent of spring and its increasing flood of ultra-violet light. The course depends upon a large number of factors, many of which we now appreciate, but some of which doubtless we still fail to recognize. In view of the fact that rickets is eminently a seasonal disorder, much will depend upon the period of the year when the infant is born. If born in the early spring, in March or April, the prognosis is most favorable, for an abundance of sunshine will be available during the first half year of its life, so that rickets is not apt to develop until the following winter. The most inauspicious season to be born in respect to rickets is the early autumn, the months of September and October. Infants born at this time of the year almost invariably develop rickets unless protected by specific therapy. The prognosis of the disease will depend furthermore upon the predisposition of the infant, a conception which is indefinite and comprehensive, including all the prenatal factors which play a rôle in connection with this disorder. Prematurity and twinship not only predispose to rickets, as has been stated, but render its course more rapid and severe. To a certain extent the progress of the disease will conform to the growth of the infant, although this factor may be submerged by still more potent influences. The nature of the diet, especially whether the infant is breast-fed or bottle-fed, determines whether advance is slow or rapid, mild or severe. But the dominating factor, which more than anything else shapes events, is the advent of spring. Some years ago, before the rôle of light was recognized, in reviewing the records of a large number of cases of rickets, which had developed during a period of several years, it was remarkable to find the regularity with which the signs and symptoms disappeared in April, May and June.

A characteristic feature of rickets is its irregular progression, a more or less continuous advance interrupted with periods of quiescence or of healing. This phenomenon, which has been emphasized

in relation to the moderate and the severe case, is quite as characteristic of the mild type which we have recently learned to recognize. Schmorl described the histological evidence of partial healing and stated that it was found in 40 per cent of his cases. Most relapses can be recognized during life only by means of roentgenographs, but in some instances, where the periods of progression are separated by distinct intervals, a relapse is evident by direct clinical examination.

It is unnecessary to cite examples of this type of rickets. Those who have had an opportunity to follow mild cases by means of radiographs, as well as clinically, have had ample opportunity to observe instances of this kind.

RECURRENT RICKETS.

In addition to the relapsing type, with its irregular course throughout the winter, there is recurrent rickets. This is to be distinguished from the relapsing form by the fact that the attacks are unrelated and that an interval of months or even a year or more separates them. Numerous writers have called attention to these recurrences, which generally are regarded as exceptional and distinctive of rickets of the severer type. I believe that recurrences occur with great frequency even in the mild form of the disorder. They may take place, entirely unsuspected, in well-nourished babies, which are under close observation, and indeed are apt to occur unless prophylactic therapy is used. It is clearly impossible to state even the approximate frequency of recurrences. In 1926 I published a record of 31 such cases which were noted within a period of a few years, and no doubt others escaped attention. During the past years the infants under my care have received some form of specific therapy as a routine measure, so that recurrences have been forestalled. In view of the importance of this aspect, it may be of value to record in detail a few cases of recurrent rickets:

F. W. was seen in September, 1918, when she was two months of age. She was well-nourished and presented signs of rickets even at this early period. These signs increased on a diet of raw milk, to which 2 ounces of 20 per cent cream were added later. She was treated with ultra-violet light which brought about marked healing. Radiographs were taken every month throughout the spring, summer and autumn. They were all negative until December when signs of rickets were again evident. At this time she was a particularly well-nourished baby, weighing $22\frac{1}{4}$ pounds (10.1 kg.) and having 8 teeth at sixteen and a half months. Her muscles were good and she walked. Ultra-violet therapy was again given.

The recurrences of rickets may be of different types; the first attack may be associated with a low concentration of phosphorus

in the blood, and the second with a low percentage of calcium. For example:

W. L., when four months old, showed signs of mild rickets in the month of March. He was a poor baby, weighing about 10½ pounds (4.8 kg.) at that time. His condition greatly improved and when fourteen months of age he was a fine baby, weighing 25¼ pounds (11.5 kg.). All signs of rickets had decreased during the summer, but in October, when he was twenty-three months of age, they were again evident by radiograph and by chemical examination of the blood. The interesting point is that in the first attack the calcium was 10 mg. and the phosphorus 3.47 mg., whereas in the second attack the calcium was 7.55 mg. and the phosphorus 4 mg. per 100 cc. of blood. It is impossible to account for the low phosphorus in the spring and the low calcium in the autumn. The diet during both periods was the same. Carbon-arc light treatment was given.

The reverse may happen; the first attack may be characterized by a diminished amount of calcium in the blood, and the second by a diminished concentration of inorganic phosphorus. The following case may be instanced:

I. C. was seen in May when three months of age, with signs of mild rickets. There were marked craniotabes, a blood phosphorus content of 4.18 mg., and calcium content of 7.5 mg. per 100 cc. of serum. The calcium rapidly rose to normal (10.5 mg.) under treatment with the carbon-arc light. There were no definite signs of rickets throughout the succeeding autumn and winter, but the next April, when the infant was fourteen months of age, bow-legs and enlargement of the epiphyses developed. This time the rickets was accompanied by a diminished concentration of inorganic phosphorus, 3.4 mg., whereas the calcium was normal, 11.2 mg. per 100 cc. of serum. In this case also there had been no change in the diet, except the addition of cereal.

It is quite possible for a series of recurrences to take place—that winter after winter, if environmental conditions are favorable, a mild attack of rickets develops. In my opinion this phenomenon is more common than is suspected. I have seen one case in which there were two recurrences, in other words three attacks of rickets—one at six, another at fourteen and a third at twenty-six months. We have no means of determining whether the recurrence is to be attributed to incomplete healing, or whether these attacks arise entirely *de novo*.

In the course of an analysis of the cases of recurrent rickets it was found, much to my surprise, that of the 31 infants which comprised the group, 25 were males and only 6 females. The difference in the sex ratio is so great that it raises the question of whether males are not more predisposed to rickets than females, an aspect

which has been discussed in connection with etiology. As stated in 1926, "it is possible that the incidence of recurrences may, to some degree, serve as a delicate indicator of the comparative susceptibility of the sexes to rickets, and that males are somewhat more susceptible than females."

Children never die of rickets, so that it does not enter into mortality statistics. Nevertheless, it is a factor in infant mortality. As in the case of all nutritional disorders, the greatest danger lies in the heightened susceptibility to infections; the infants do not die of rickets, but of the infectious disease which it has incited and intensified. This holds true to a greater extent of adult scurvy and of infantile scurvy (Barlow's disease). Years ago, the sailors in the navy and in the mercantile marine who developed scurvy died by hundreds and thousands of pneumonia and bowel disorders. When the fat-soluble vitamin A is lacking in the dietary, infants as well as animals develop the well-known infection of the eyes, termed xerophthalmia. Even in conditions occasioned by metallic poisons, such as phosphorus, the local lesions, as well as the fatal outcome, is due to infection. In regard to rickets the distinctive feature is the peculiar vulnerability of the respiratory tract. There is no doubt that this is true for the severer cases of rickets; it is clearly in evidence among the negro infants seen in New York City in the home or in the hospital. The high mortality of Italian infants from respiratory diseases, an unquestionable fact, has been ascribed to the marked incidence and severity of rickets among the offspring of these people in our larger cities. It is possible, but by no means certain, that this deduction is warranted. But, as emphasized in discussing symptomatology, the interrelationship between rickets and respiratory diseases holds true for the severe type of the disorder.

Quite apart from this kind of susceptibility is the susceptibility of the respiratory tract which is brought about by *deformity of the thoracic wall.* This predisposition also applies only to the severer case. It is due to a loss of elasticity of the ribs, as the result of which the thorax may become so rigid that respiration becomes largely diaphragmatic. Added to disability of this kind, continuous pressure may be exerted on the lungs by the deformed ribs, leading to atelectasis and compensatory emphysema. In severe cases such deformity is usually associated with kypho-scoliosis of the spine, which impedes still further the normal function of the organs within the chest. The heart may be displaced, may hypertrophy and dilate, especially the right heart, and dyspnea result. In this way severe rickets, which in this country is limited largely to negro and Italian infants, may lead to recurrent attacks of pneumonia and to death. In the study of rickets, which Unger and I carried out several years ago in a negro district in New York City, several instances of this kind were observed. This tendency of children

having rachitic deformities of the spine to develop fatal pulmonary complications was a point stressed by Glisson.

Involvement of the intestinal tract must also be mentioned in considering prognosis. In my personal experience diarrhea has rarely developed in the course of rickets and has influenced the prognosis but little. But in the very severe cases, such as are encountered only in negroes nowadays, a stubborn enteritis or colitis occasionally develops. The typical pot-belly is an evidence of a derangement of the intestinal tract; whether simply of increased fermentation, as is generally believed, or of faulty innervation remains to be determined. In general, however, the involvement of the intestinal tract is metabolic and functional rather than inflammatory.

In considering the prognosis of rickets, one naturally is curious as to *the outcome of the numerous bony lesions which form the essential residuum of the disorder.* What is the prognosis of the deformed pelvis, of the extremities, of the spine, etc.? In order to answer these questions, we must learn the experience of various specialists—of the obstetrician, gynecologist, orthopedist, as well as of the internist. The danger associated with rachitic deformity of the pelvis has been stressed in the chapter on symptomatology. It is the gravest complication of rickets, and, during child-birth, often leads to the death of mother or child, especially among the negro women in the United States. Its importance cannot be emphasized too greatly in appraising the seriousness of rickets and the value and necessity of prophylactic treatment.

As is well known, the most common deformities resulting from rickets are those of the lower extremities, the bow-legs and the knock-knees. Ruhe found bow-legs in about 3 to 6 per cent of the school children in Madgeburg, without distinction of sex. The importance of these deformities is generally esthetic, but some believe that many of the muscle and joint pains, which are attributed to rheumatism and gout, are due to mechanical disturbances resulting from rickets. Happily, there is a marked tendency for these deformities to right themselves. Kamps, who carefully followed these pathological conditions by means of a series of casts taken at intervals for years, found that among 32 cases, 24 underwent spontaneous healing and that in only 3 instances was there no improvement. Schanz came to the same conclusion and states that "even very marked bowing has completely disappeared by the fifth or sixth year of life." On the other hand, in some cases there is a tendency for bow-legs or knock-knees to increase at the time of puberty. This is an interesting phenomenon and possibly should be linked with the development of late rickets at this period.

Coxa vara should be mentioned in reviewing the prognosis of rickets and its deformities. It is an infrequent complication but by no means rare in the orthopedic clinics of the large cities. As is

true of all rachitic deformities, it is encountered with especial frequency among negroes.

If one carries out a careful examination of school children, it is surprising how many show definite evidences of past rickets. The head may be misshapen, the chest deformed or the legs bowed or bent. The figures which Ruhe recently published, as the result of an examination of 30,000 school children, give a fair idea of the frequency of such deformities of the skeleton. Among children

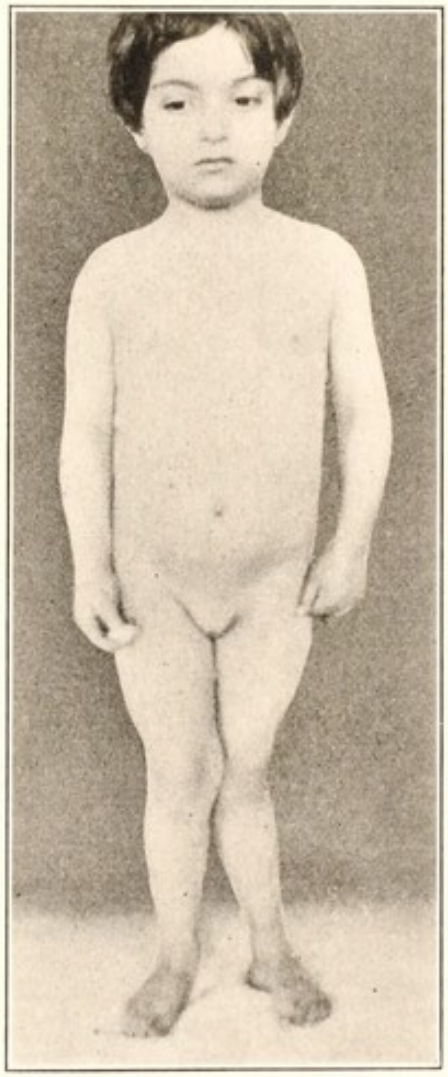

FIG. 42.—Knock-knee following rickets (more marked on one side).

six to fourteen years of age, he noted signs of rickets in 75 per cent among the boys and in 69 per cent among the girls. In other words, during the school age only about 20 to 30 per cent of the children were free from rachitic deformities, and the girls were spared oftener than the boys. A few years ago, as the result of a study carried out in Dortmund, Engel concluded that among 50,000 school children, 5000 had suffered from severe rickets, and that 10 per cent of this number, namely 500, were handicapped as the result of this disease.

The prognosis of rickets is rendered grave by the occurrence of tetany which may complicate even the mild case. In its manifest form tetany is characterized by convulsions which may be single, few in number, or numerous. As will be described in a subsequent chapter, tetany may lead to death as the result of convulsions or cardiac or respiratory failure. There is no means of ascertaining what percentage of the deaths which are associated with convulsions are attributable to infantile tetany.

Familiarity with rickets must not breed contempt for the consequences which may follow in its wake. It is true that its severity is steadily diminishing and that we no longer encounter the monstrosities which are pictured in the text-books of fifty or more years ago. But it should be remembered that rickets still leads to deformity, disability and indirectly to death. It is also worth bearing in mind that we have no means of judging what insidious disturbances rickets may bring about which may become manifest only years after the original disorder has disappeared and been forgotten. Studies in this regard may change our attitude toward rickets and many of the nutritional disorders which, at present, are regarded lightly and considered unimportant. It is an aspect that can be illuminated only by long-continued clinical observation, and cannot be solved by animal investigation.

1561 Ollet. Rachitisme tardif.

CHAPTER XII.

LATE OR JUVENILE RICKETS (RACHITIS TARDA.)

WHETHER rickets is exclusively a disorder of infancy or occurs also in later childhood and adolescence has been discussed by children's specialists, surgeons, and orthopedists for many years. Such authorities as Rehn, Henoch, Kassowitz and Monti doubted the existence of late rickets, or stated that they, at least, had never encountered such a disorder. The first case reported in England—the supposed birth-place of rickets—was presented by Drewitt in 1881 before the Pathological Society in London. It is worthy of note that the society considered the case sufficiently rare and important to appoint a committee of investigation. The committee agreed in the diagnosis of late rickets, which two years later was proved to be correct by Barlow and Abercrombie at post-mortem examination.[1] In 1908 Looser, who gives an excellent account of this condition with full bibliographic references, wrote that there were only 60 cases of late rickets and juvenile osteomalacia in the literature and that two-thirds of these had occurred in females. In 1914, Wieland stated that the reported cases numbered 70. Today its existence is generally accepted, largely as the result of nutritional conditions resulting from the World War, which led to an unprecedented number of instances in Germany, Austria and Poland. It is still, however, a subject concerning which there is a sharp difference of opinion in regard to frequency, clinical importance, the phenomena to be included in this category, and the pathogenesis of the lesions of the bones. Questions relating to the pathology of osteomalacia have tended also to complicate the problem. As is well known, many have been of the opinion that rickets and osteomalacia are quite distinct pathological conditions, having followed the dictum of Virchow, who in 1853 stated that "in osteomalacia tissue is absorbed, what is firm becomes soft; in rickets nothing is essentially absorbed, the tissue merely does not become firm." In order to conform to this dual viewpoint, cases of rickets occurring in young adults were classed arbitrarily by some as "juvenile osteomalacia," by others as "late rickets." Indeed, the weight of Virchow's authority may be stated to have postponed a solution of the relationship between rickets and osteomalacia for fifty years or more. The later studies of Pommer and

[1] The necropsy of this child forms one of the two described by Barlow in 1890, in his article on Rickets in Keating's Cyclopædia of Diseases of Children.

of Schmorl made it clear that the two disorders are essentially one and the same pathological condition, the main distinction being the age of the individual. As the result of what may be termed clinical intuition, Trousseau, in the early part of the past century, had sponsored the identity of rickets and osteomalacia.

Occupying a position between rickets and osteomalacia, the one occurring in infants, the other in adults, is this intermediate group, termed late rickets. Naturally one cannot fix definite age limits for this clinical condition. The lower boundary has been set by Schmorl at the age of four years, which seems warranted in view of his extensive pathological studies. In a histological examination of 57 cases of rickets in children between the ages of two and three years, he found that more than one-half showed evidences of healed rickets, one-quarter healing rickets, and the remainder florid rickets. In children a year older, however, the percentage of healed and healing rickets rose to about 92 per cent, indicating that at the age of four, active rickets had become an exceptional disorder.

It is still more difficult to draw a line at the other boundary, between late rickets and osteomalacia. Usually, all cases up to the age of eighteen or twenty years are considered as belonging to the group of late rickets. Such a classification makes it necessary to regard instances of "puerperal osteomalacia" under the age of twenty years as late rickets, and all over this age as true osteomalacia —a procedure which is clearly artificial, arbitrary and not based on etiological, clinical or pathological criteria. The inconsistency of the present terminology becomes evident when one considers the large number of cases of puerperal osteomalacia in India, involving girls at the age of adolescence. One way out of the difficulty might be to do away entirely with the term "osteomalacia" and call all three conditions rickets—infantile, juvenile and adult—corresponding broadly to the existing subdivisions of infantile rickets, late rickets, and osteomalacia (puerperal, as well as senile). Such a classification would at least rest on a common basis of pathology, although the boundaries could not be sharply drawn.

Symptomatology.—From a clinical point of view *one must distinguish between a general type and a local type of the disorder.* In the former the symptoms are fairly uniform, and have been vividly sketched by numerous writers. The onset is very characteristic. The child, or adolescent, complains of *pain on standing or walking,* of tiring easily, and of vague pains in the legs, especially in the knees or in the feet. It is evident that these signs are not very definite or striking, and are readily overlooked or misconstrued. As a matter of fact, they are regarded generally as growing pains or as symptoms of rheumatism. Soon thereafter it is noted that the gait has become uncertain and waddling. If the patient is carefully examined at this time typical beading of the ribs may

be found, associated often with enlargement of the epiphyses. There may be also some deformity of the legs, the typical genu valgum or genu varum, bowing of the humerus and of the forearm, so that an S-shaped deformity is brought about. The spine may become curved—scoliosis, kyphosis, or a combination of both—with associated displacement of the ribs. The natural curvatures of the clavicles are at times accentuated, as has been described in connection with infantile rickets. Clubbed fingers, as well as toes, have been frequently observed, suggesting Swoboda's description of a form of infantile rickets associated with deformities of the thorax. When the condition has lasted for several years, a definite stunting in growth may come about, often associated with a retardation of development, an infantile habitus, or the general picture of infantilism. Menstruation is delayed or irregular, and the secondary sexual characteristics do not develop. Some have decribed a retarded mentality with psychic disturbances. The abdomen may be enlarged (pot-belly), but the spleen and liver are normal. It is of interest, bearing in mind the previous discussion of the relation of anemia to infantile rickets, to note that Tobler mentions specifically that, in his cases, there was no anemia. Generally there is a delay in the loss of the deciduous teeth, as well as in the eruption of the permanent teeth. The most convincing sign, however, is the radiographic picture which in marked cases closely resembles that of infantile rickets; we see the same fraying of the epiphyses and spreading of its borders, the same coarseness of the pattern in the shafts of the long bones, and a marked increase in permeability to the Roentgen rays. Osteoporosis is apt to be particularly marked in late rickets and is one of its distinguishing features, calling to mind the "rachitic consumption" which Guerin—the pioneer in the study of experimental rickets—claimed to result from long-standing rickets.

It will be noted that there is a striking resemblance between the picture of infantile rickets and that of late rickets. As will be evident from the description of osteomalacia in the following chapter, late rickets resembles this condition still more closely. This is true particularly in regard to pain. Infants suffering from rickets very rarely manifest signs of pain. I have met with but two or three instances where pain was evident when a rachitic infant was placed in the sitting or standing posture. In late rickets, as well as in osteomalacia, pain is the rule and constitutes one of the out-standing symptoms. It is difficult to explain this incongruity in pathological conditions which are supposed to be identical. Another sign in which late rickets differs somewhat from infantile rickets is in its slight degree of enlargement of the epiphyses. Too much, however, has been made of this difference. As pointed out by Schmorl, we should expect this distinction in view of the fact that the

epiphyseal cartilages are so much narrower when late rickets develops, endochondral ossification having almost ceased at this time of life. The undue stress which has been laid on this point reminds one of the old reiteration of the fact that bleeding of the gums occurs in adult scurvy but not in infantile scurvy, and the deduction that the two conditions should, therefore, not be considered as the same pathological disorder. In that connection it was shown that the discrepancy was due merely to a difference in age, to the fact that adults have teeth.

Tetany is a frequent accompaniment of late rickets, but probably does not occur more often than in infantile rickets. We shall find that it is very frequently associated with osteomalacia, which is generally characterized by a diminished amount of calcium in the blood. Schueller described latent, as well as chronic tetany, in the cases of late rickets observed recently in Vienna. Stapleton reported 30 instances of manifest tetany among 63 cases of late rickets occurring among East Indian girls. These observations serve to link late rickets closely to infantile rickets, in that both may be manifested by either the type of disorder characterized by a low concentration of phosphorus or the type low in calcium. In 14 of the 29 cases which were radiographed by Stapleton, "spontaneous" fractures were apparent, which had not been evident to ordinary clinical examination. It would seem that the incidence of tetany, as well as of fractures, definitely exceeds that met with in infantile rickets.

There is little difficulty in diagnosing florid cases with symptoms such as have been outlined. Moreover, now that it is established that there is no essential difference between rickets and osteomalacia, it is of little moment whether cases occurring at the threshold of puberty are designated as "juvenile osteomalacia" or as "late" or "juvenile rickets." A more important question is one which has been raised repeatedly since Ollier first distinguished "late rickets" (rachitisme tardif) from osteomalacia—namely, whether these cases should be regarded as rickets which has developed primarily in later childhood, or merely as instances of relapsing or recurrent infantile rickets. From a clinical standpoint it makes very little difference which point of view is adopted, whether we regard them as primary or secondary. In his presentation of this subject before the Lyons Medical Society in 1861, Ollier expressed the opinion that the majority of cases were of the relapsing type and that a comparatively small number were primary. It is clearly impossible to decide this point at the present time, when fully three-quarters of all children suffer from rickets in some degree during infancy, thus rendering it probable that any child who happens to develop "late rickets" has suffered from this disorder during the first years of life. The answer to this question may be forthcoming when infantile rickets becomes

rare or exceptional, instead of being an almost universal nutritional disturbance. This may come to pass when our knowledge of the beneficent effect of sunlight, direct and indirect ultra-violet therapy, etc., is applied to its fullest extent. My personal opinion, based on an experience with rickets in infants and with experimental rickets in animals, is that although older children are undoubtedly less susceptible, they will develop rickets primarily if the etiological conditions are sufficiently favorable.

A problem allied to that of the rôle of recurrence, is that of the relation between chronic relapsing rickets and late rickets. The matter may be stated as follows: Excluding the question of whether the child had rickets during infancy, has it been suffering from relapsing rickets year after year since that period, and is the late rickets merely the final manifestation of a chronic and persistent nutritional disorder? This conception has been crystallized by Schmorl in the term "rachitis inveterata," or progressive or relapsing rickets. A similar condition was described in 1685 by Harvey in relation to scurvy; he applied the term "inveterate scurvy" to cases which had persisted in a mild form for many years and which had developed disability and weakness. There are no data on which to base an opinion as to the frequency of relapses or of their relation to late rickets. As stated in the previous chapter in discussing prognosis, it has been my experience that recurrences are more frequent in rickets than has been supposed, and that they extend beyond the period of early infancy. There has been no systematic study of the incidence of rickets in children over four years of age, and it would be interesting to ascertain how many instances of relapsing rickets a routine examination of a large number of children of this age group would divulge. Radiographs taken recently of children of pre-school age have led me to suspect that mild or incipient rickets occurs occasionally during the winter months at this period of life. The instances of late rickets which Tobler reports are suggestive. He reproduces the photograph of a girl, aged thirteen and a half years, with a well-proportioned body, limbs perfectly straight, and no signs of residual or active rickets. Nevertheless, radiographs of this girl showed the typical rachitic changes. One wonders whether instances of this kind—cases completely masked except to the Roentgen rays—would not be discovered if a large number of poorly-nourished boys and girls were radiographed in a routine way.

Recently Sterling, of the U. S. Public Health Service, made a "Study of the Physical Status of the Urban Negro Child." In the course of this investigation she ascertained what percentage of negro children, attending the schools of Atlanta—a city of about 250,000 inhabitants—showed signs of rickets. Over 5000 children between the ages of six and fourteen years were examined. Two

striking facts emanated from this study. In the first place, there was a marked difference in the incidence of rickets between the boys and the girls. At the age of six to seven years about 12 per cent of the boys presented "two bony evidences" of rickets and 6.8 per cent of the girls, whereas at the age of fourteen the relationship had become the reverse, the incidence having risen to about 15 per cent among the girls and fallen to somewhat over 11 per cent among the boys. But what is of equal importance is that more than twice as many cases were found among the girls in the age group of fourteen and over, as in the age group of six to seven (Fig. 43). Such an increase must indicate that the signs of rickets were not mere vestiges of infantile rickets but signs of late or juvenile rickets. It may be added that the number of children having three bony evidences of rickets, although naturally much smaller, illustrated the same two significant phenomena. The sex incidence of the younger group was similar to that which I noted in relation to recurrent infantile rickets. But at the age of ten to eleven, as the

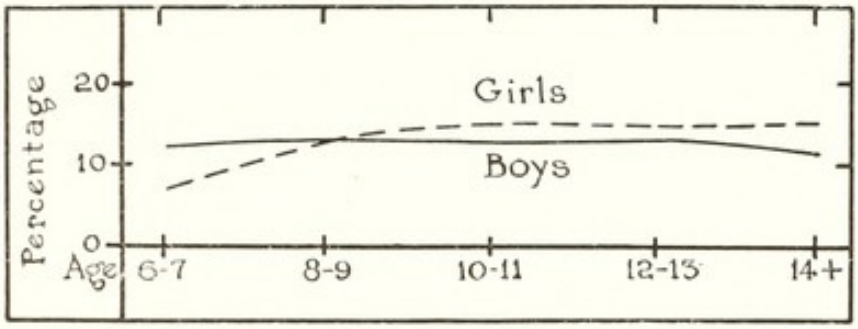

FIG. 43.—Percentage of children showing two bony evidences of rickets among 5170 negro school children in Atlanta, Ga. Increase of incidence among girls toward period of maturity. (Sterling, U. S. Public Health Report, 1928.)

graph shows, evidences began to preponderate in girls, which, as we shall see in the following chapter, is indicative of a transition from the period of late or juvenile rickets to that of osteomalacia.

Associated with the clinical condition known as Froehlich's syndrome, which is occasioned by a disorder of the hypophyseal gland, marked knock-knee develops. This malformation is not due to rickets, if we judge by the roentgenologic picture and the failure of specific antirachitic therapy.

Thus far I have considered the general form of late rickets. There is another type which may be termed *the local form* of the disorder. Deydier, a pupil of Ollier, differentiated this form in 1895, and expressed the opinion that it occurred more frequently than the generalized type. The chief credit, however, for calling attention to this pathological condition is due to the celebrated surgeon, Mikulicz, who reported a series of cases of this kind in 1879, some of which were verified by microscopic examination. His thesis was that isolated deformities of the long bones, for example,

knock-knee or bow-legs, were the result of rickets and were merely a local manifestation of a general disorder which was latent in other parts of the skeleton. In some of his cases the epiphyseal cartilages at the knee-joint, of the femur and of the tibia, were markedly broadened, as well as those of the costo-chondral junctions, which in one instance were enlarged and "showed the closest resemblance to the rachitic ribs of infants." As Mikulicz put it: "In marked cases a glance is sufficient to convince me of the presence of the rachitic rosary." This observation was supported by the clinical experience of other surgeons, for example Thiersch, Billroth and Macewen, who in the course of operations had noted lesions of the bones which they were unable to distinguish from mild rickets. Mikulicz's report met with antagonism and led to a controversy which has persisted to the present time.

The point at issue is in regard to the proportion of these "deformities of adolescence"—so common among boys and girls brought up even under the most favorable hygienic and nutritional surroundings—which should be considered due to rickets. As is well known, various deformities occur in children between the ages of ten and fourteen years. Among these may be mentioned especially flat-foot, accompanied by pains in the legs or feet, and various deformities of the spine associated with faulty posture; less frequently knock-knee and rarely coxa vara. A swelling of the inner extremity of the clavicle with subluxation of the joint is occasionally encountered.

Some have attributed such deformities to the carrying of heavy burdens which has caused the bones to give way, or to a weakness of the soft parts, of the ligaments and of the muscles. The great German orthopedist, Volkmann, believed in the harmful effect of carrying heavy burdens. He argued that the child assumed a faulty attitude while at work or at play, and that this changed the equilibrium of the vertebral column so that the weight was not transmitted equally to the entire surfaces of the vertebræ. As a result, faulty ossification ensued. It has been suggested that a weakness of the intervertebral ligaments plays an important rôle. The question arises as to why the condition does not occur more often, if this is the sole or the main cause of the pains and of the pathological lesions. Many orthopedists, however, do not believe that normal bones yield to superimposed weight, but that they give way only if the bony structure is of poor quality, in other words, that the deformity is fundamentally due to a constitutional weakness of the skeleton. The observations of Hoessly are of interest in this connection; he showed that in cases where there had been an amputation of one leg, there was as a rule no deformity of the remaining leg, nothing resembling the deformities supposed to be brought about by over-burdening the bony skeleton.

Still others have grouped cases of this kind in a category termed "essential or habitual or idiopathic deformities of the growth period." This designation would suggest that the deformities are due to growth, the "osteite de croissance" of the French, and that they have no connection with rickets.

The weakness may be hereditary in nature. Attention has been called to the fact that these deformities are found frequently in several members of the same family; for example, the children, as well as the parents, may develop late scoliosis or high shoulders at the same period of life. Eulenburg and Hoffa believed that a hereditary factor is evident in fully 25 per cent of the cases, and Kirmisson traced the histories of sisters, of parents and even of grandparents who showed scoliosis.

The question as to *the pathological nature of these local deformities* assumed a new aspect in 1905, as the result of the histological studies of Schmorl. Schmorl carefully examined the skeletons of 4 cases which presented the clinical picture of the localized type of late rickets. The individuals were nine, eighteen, nineteen and twenty-one years of age and showed no other clinical or pathological signs of rickets; some of them had slight spinal curvature or knock-knee. He was able to show not only that typical rachitic lesions were present at the sites of the deformities, but that such changes could be found in other parts of the skeleton which gave no clinical indication of rickets. For example, in a case of slight knock-knee, rachitic lesions were found at the costo-chondral junctions—there was the characteristic increase in width of the growing cartilage and the overabundance of osteoid tissue, which have been accepted as conclusive evidence of rickets ever since the classic description of Pommer. Such lesions were present most often in the costo-chondral epiphyses, as would be expected, for this junction is the last to fuse, its epiphyseal cartilage persisting sometimes well into adult life. This investigation of Schmorl's fully confirmed the clinical observations of Mikulicz. Since this time Looser and others have demonstrated similar rachitic lesions in various epiphyses of the body in cases in which late rickets had been manifested merely by deformity of a single joint. It is evident that these studies opened a new vista in relation to late rickets, and that henceforth there could be no question as to whether localized deformities may be rachitic in nature. They do not, however, completely solve the problem. Their main defect lies in the fact that the number of cases examined by Schmorl and by others are so few that they afford no idea as to the frequency with which rachitic lesions are to be found associated with local deformities. The microscope may or may not reveal signs of rickets. Frangenheim, Lange, and others found, in the course of operating for local disorders of the bones, for example of the neck of the femur, that the tissues showed no his-

tological evidences of rachitic lesions. On the other hand, Haedke reported typical changes in the epiphyseal cartilage of the head of the femur in a case which he operated upon for coxa vara, and which presented no external evidences of rickets. Only after we have at hand data concerning a large number of cases of this kind shall we be able to judge whether the majority of these deformities "of the growth period" should be regarded as rachitic. At present, although opinion is divided on this point, the majority incline to the view that only a small number of these cases are due to rickets.

There is still another aspect to be considered, namely, whether these deformities are due indirectly to rickets. Those who suggest this pathogenesis believe that the deformities come about gradually, following the rickets of infancy, and that as a result of strain and pressure they increase progressively during later childhood. Such an explanation makes rickets the primary, and mechanical forces the secondary cause. Here again, before judgment can be expressed, it will be necessary to carry out a histological examination in a large number of cases. If merely old lesions of rickets, or what Schmorl terms "healed rickets," are found, then this theory would deserve support, but if signs of recent rickets are found either in the bones at the site of the deformity, or elsewhere in the body, it would argue for an active rachitic process as the prime pathogenetic factor. Wieland, who wrote an excellent monograph on this subject in 1914, believes that most of the cases of late rickets are not due to a florid rachitic process, but to a residual rickets, to a deformity resulting from rickets in infancy. In his opinion true or primary late rickets is by no means a frequent disease.

Etiology.—The etiology of late rickets of the general type is that of infantile rickets. In most cases lack of sunlight plays the dominant rôle, in some, faulty diet. The numerous instances of late rickets reported by Stapleton among Indian girls, aged ten to fifteen years, who were brought up in Delhi under the purdah system and received almost no sunlight, furnish a striking example of the effect of deprivation of the sun's rays. The fact is all the more convincing as these girls were of the well-to-do class, and their dietary was above the average rather than below, in quality and quantity (Table 21). Many of them were on a vegetable diet. On the other hand, the occurrence of late rickets in endemic proportions following the World War must be attributed mainly to dietary causes and not to lack of sunlight. In spite of numerous studies, however, we do not know the chemical nature of the deficiencies or defects of the dietary within the "Central Empires" during the post-war period. The diet varied in different localities and was most dissimilar in urban and in rural communities. There can be no doubt that calcium, as well as phosphorus was lacking, due to the great scarcity of milk, cheese, eggs and meat,

and that the fat-soluble vitamins were inadequate. In addition to these qualitative defects the total caloric intake was insufficient, a condition which no doubt tended to the development of the osteoporosis which so frequently complicated the clinical and pathological picture. It is possible that there are other nutritional factors which are needed by the tissues—for example, the bones—of which at present we have no conception, or that there are substances which are harmful to the growing tissues. Although this wide-spread endemic failed to throw light upon the nature of the dietary deficiencies which induce late rickets, it furnished incontrovertible evidence in favor of the view that diet plays a rôle in the etiology of rickets, and that lack of sunlight should not be regarded as the sole predisposing or exciting cause.

There is one etiological factor which is associated especially with late rickets and is referred to repeatedly in the histories of cases occurring both in the pre-war and in the post-war periods. I refer to *the effect of occupations such as involve the carrying of heavy burdens* or standing or walking for prolonged periods. This observation was made years ago by Macewen in one of the first reports of a case of late rickets. It may be of interest to cite this case:

A boy, aged fifteen years, had scarlet fever, followed by an attack of marked bronchitis. After this illness he returned to his occupation and soon began to have pains in his legs, especially in the knees. His character changed—instead of being active, he seemed lazy and did not want to exercise, and soon gave up work. His pains became more marked when he attempted to walk, in fact, he was never without pain unless when reclining in a horizontal position. In the second month of his illness his legs began to be bowed. The epiphyses at the wrists enlarged and became sensitive to the touch, which was true also of the lower ends of the femora. His muscles were flaccid and his color poor. As the result of having to work at an occupation which necessitated his walking a great deal, he rapidly became markedly bow-legged.

A note in regard to the cases described by Tobler may also be of interest in this connection. He writes "after the school period 3 of the boys worked in a factory in poor hygienic surroundings, where they were occupied either sitting or standing in a close room ten hours daily." The fact that the great majority of cases of late rickets in the post-war years 1919 and 1920 developed in male adolescents, has been attributed by almost all observers to the comparatively heavy work to which they were subjected. It would seem, however, that stress and strain can be only the exciting cause which leads to knock-knee, bow-legs, flat-feet, etc., and that the primary or underlying factor must be an abnormal softening of the bones.

Stress and strain as well as pressure on the epiphyseal ends of the

bones, play a rôle in infantile rickets. The bowing of the legs in heavy infants, the enlargement of the epiphyses and bending of the bones of the forearm in rachitic babies who crawl, are manifestations of this mechanical factor. Müller's interesting experiments in this field have been discussed in the chapter on Etiology. It is evident that in the adolescent, whose bones are still growing rapidly and whose epiphyseal cartilages are as yet ununited, heavy work must lead to deformity. This explanation necessitates the inference that as the result of the deprivations of war, although female adolescents must have been afflicted with rickets to much the same extent as the males, the disorder was latent in the former and not manifested by deformity. Possibly such was the case. It is impossible to consider this interesting supposition further, as the newer criteria for diagnosing latent rickets—the estimation of the phosphorus and calcium of the blood as well as radiographs of the epiphyses—were not employed during this period.

Pathology.—The reports in regard to the pathology of the late rickets which occurred in the post-war period filled a lacuna in our knowledge of this disorder. Not that they essentially changed the pre-war point of view, but they greatly supplemented data, which previous to this time, had been exceedingly scanty and unsatisfactory. In general it may be stated that the lesions of the bones observed in the course of this endemic were very similar to those which had been described in the sporadic cases of peace times. In other words, viewed from the standpoint of pathology, infantile rickets and late rickets proved to be substantially one and the same process. The main difference in the bony changes was the greater incidence and intensity of osteoporosis in late rickets. But even in this respect we find a lack of unanimity in the reports of pathologists from various cities. For example, whereas Alwens found osteoporosis prominent in the histological picture of the cases which came to necropsy at the Pathological Institute of Frankfort, Partsch stressed the resemblance to true osteomalacia among his cases in Dresden. It would seem that just as there were differences in the clinical picture in various localities—for example Goettingen and Vienna—so a distinction could be recognized between the histological manifestations. Alwens noted an insignificant increase in the osteoid borders of the bones, and compared the condition to the pseudo-rachitic osteoporosis which can be brought about in animals by a deprivation of calcium and phosphorus, or to the lesions encountered in starved individuals. Others describe a typical increase in osteoid tissue, associated with proliferation of the growing cartilage. A consideration of the various reports gives one the impression that these differences were due largely to marked variations in the ages and in the nutritional state of the individuals. As is well known, in conditions of advanced atrophy, especially in old

age, there is a marked decrease in the apposition of bone. This decrease must be accompanied by a corresponding diminution in osteoid tissue. But that osteoporosis was present in exceptional degree even in younger individuals can be inferred from the high incidence of fractures reported among adolescents by clinicians as well as by pathologists.

In this connection mention should be made of the relation of late rickets to lesions of the parathyroid glands, a subject which will be discussed in connection with osteomalacia and with tetany. In 1920, Schmorl demonstrated at necropsy 2 cases of "hunger osteomalacia" having enlargement of the parathyroids; one of these was a girl, aged eight years. Furthermore, Erdheim, in 1903, in the course of his systematic study of the fat content of the parathyroid glands, reported the occurrence of a large tumor of one of these glands in a young man, aged eighteen years; genu valgum was present to such a degree that osteotomy was resorted to. In his monograph on rickets and the parathyroid glands, published some years later, Erdheim refers to another case of parathyroid tumors in a young adult, which was accompanied by pathological changes in the bones. These reports have since been multiplied and are interesting in view of the well-established relationship of the parathyroid glands to tetany and the frequent association of tetany with late rickets.

Treatment.—Little need be stated in regard to treatment, which consists in giving cod-liver oil, irradiated ergosterol or irradiated food, and in exposing the patient to the sun or to artificial ultraviolet radiations. The details of these various forms of therapy are given in the chapter on the Treatment of Rickets. In accord with what has been mentioned, it is evident that the dietary should also be rendered adequate in quality and that strenuous work should be forbidden until the bones have become strong and firm. Where late rickets is endemic it would be of benefit to give antirachitic therapy to all adolescents who complain of indefinite pains in the bones or joints.

LATE RICKETS AND DEFORMITIES OF BONE IN CONNECTION WITH THE WORLD WAR.

As is well known, after the World War was over, disorders of the bones began to make their appearance among the peoples of Austria and Germany. Some described this condition as late rickets, others as hunger osteopathy or osteomalacia, and still others by the noncommittal term "an endemic disorder of the bony system." The first reports of this unusual clinical condition came from Vienna in 1919, although it is probable that it existed in a mild form in 1918.

Edelman and Schlesinger were the first to call attention to this affliction, which threatened to become endemic in Vienna. Soon after these reports, German clinicians described a similar condition in adolescents, which closely resembled late rickets. Fromme, Bittorf and Simon published convincing papers which were soon followed by a succession of publications dealing with the clinical, pathological and etiological phenomena in relation to "hunger osteopathy" or "hunger osteomalacia." In 1921 Simon issued, under the egis of the German government, an official review or survey of the subject, bearing the title "Late Rickets and Hunger-Osteopathy." My description will follow largely this comprehensive report.

One of the first signs was pain in the legs which soon was associated with difficulty in walking and a peculiar inelasticity of gait. Climbing or descending stairs became increasingly difficult. These symptoms were generally overlooked or mistakenly diagnosed as rheumatism. Accompanying this pain there was tenderness of the bones, especially of the epiphyses at the knee-joints, or occasionally of the vertebræ on percussion. All reports are in accord that males between the ages of fifteen and eighteen years were particularly singled out. Bittorf states that all of his cases were males, and Simon estimates that three or four times as many males were involved as females. He attributes this to the comparatively hard work to which young male adults were subjected. This explanation of the peculiar sex distribution of the disorder is not satisfactory in view of the fact that a similar disease, osteomalacia, greatly preponderates among females. During the winter and spring of 1919 the endemic increased in extent so that the people themselves came to recognize it. They dubbed it quite expressively "marmalade Beine," that is to say "marmalade legs," implying that it came about from a diet consisting largely of the adulterated preserves which formed so large a part of their food. With the advent of summer, the intensity of the disorder abated somewhat but increased once more during the winter of 1920. After this period it rapidly declined owing to improved dietetic and hygienic conditions.

It is worthy of note that the endemic presented characteristics in Vienna different from those observed in German cities. In Vienna the disorder attacked women far more often than men, and mainly women of middle age or advanced in years. There does not seem to be a satisfactory explanation for this decided difference in age and sex incidence. Whether it was due to differences in quality or quantity in the dietary of the two localities, it is impossible to ascertain. The adult females showed some signs which rarely developed in the young males, especially involvement of the pelvis and of the spinal column, as well as tetany and occasionally struma.

Marked deformities of the spine were common, kyphosis, scoliosis and lordosis.[1] Simon's account, in translation, is as follows:

"When we turn to a consideration of the deformities of late rickets, or of the war osteopathies of adolescence, we find that bending of the diaphyses does not play a marked rôle at this age. It is to be found occasionally, especially the O-legs, but the frequency of occurrence is relatively slight and in this form we generally find either clinically, or in the previous history, that there has been infantile rickets, so that one is dealing with a relapsing rickets or a rachitis inveterata. The bending in these cases—whether primary or an intensification of a previously abnormal condition—is due to the fact that the soft bone is unable to bear the weight. In some of these cases which required a corrective osteotomy I have encountered a markedly unfavorable delay in consolidation, in fact once a true pseudo-arthrosis; relapses also were common. These mishaps occurred much more rarely in the course of operations for other deformities, for example genu valgum. Other deformities of the diaphyses can come about suddenly through bending of the bones or secondary fractures at sites at which the 'Umbauzone' or transparent areas are found. These unfortunate occurrences, as already mentioned, came about without warning."

Bittorf states that he could obtain no definite history of rickets during infancy and that his patients had all begun to walk at the normal time and never had shown previous deformity of the legs. In his experience the most prominent signs were tenderness at the knees, ankles, trochanters and wrists; some gave evidence of flat-feet, others of developing "X- or O-legs," in other words of genu valgum or varum. In almost all of his cases there was some indication of tetany. The Roentgen rays disclosed the typical picture of rickets.

In Simon's experience it was difficult to determine whether one was dealing with an osteomalacic or an osteoporotic process. There are some scattered observations in this report which are worthy of special attention: For example, that in Goettingen, one of the first districts in Germany where the endemic was observed, the soil is particularly rich in calcium; furthermore, that during this post-war period infantile rickets increased in Germany, more especially in the cities and in the great metropolitan centers. It is stated by Hirsch that "arthritis deformans" also increased markedly among

[1] In 1920, in the course of a visit to Vienna, I was struck by the number of older women to be seen on the streets with kyphotic deformities. They resembled the hunchback which we are wont to associate with tuberculosis of the spine. At this time the orthopedic clinics were overrun with cases of deformities of the spine and of the lower extremities. Dalyell and Chick state that between January and May, 1920, over 600 cases of "hunger osteomalacia" attended one orthopedic clinic in Vienna. Eighty-four per cent of these patients were between the ages of forty and seventy years. (Lancet, 1921, ii, 842.)

both women and men above the age of forty-five years, an observation to be noted in view of the fact that this form of arthritis has been linked by some with previous rachitic changes in the zones of ossification.

These cases of late or juvenile rickets which were one of the sequels of the World War, are of great clinical interest, but, unfortunately, have not served to advance our knowledge of bone disorders. Circumstances were such in 1919–1920 that they could not be studied by the newer methods; in fact the pathological investigations of the lesions are few and unsatisfactory. As a result *we are unable to classify the cases in this endemic, either from an etiological or a metabolic point of view.* In fact we cannot be certain that the disorder was of the same nature in all parts of Germany and Austria. A similar lack of definition exists in regard to the relationship of the war osteopathies to osteomalacia, a subject which will be considered in the subsequent chapter.

RENAL RICKETS.

There are two manifestations of rickets which are attributable to functional disorders of certain organs of the body—one, renal rickets, seems to be due to faulty excretion on the part of the kidney, of phosphorus, nitrogenous products, etc., the other the so-called cœliac rickets, mainly to a disturbance in the absorption of calcium by the intestines. Both occur most often in the period of juvenile rickets.

Renal rickets has come to be recognized only recently. It is true that Bright's disease, associated with albuminuria and with deformities of the extremities, had been noted by several clinicians fifty years or more ago, but the symptom-complex and more particularly the interdependence of disease of the kidney and of the bones were not suspected. This is true of the report published in 1883 by Lucas entitled, "A Form of Late Rickets Associated with Albuminuria" as well as that mentioned by Goodhart in his article on Chronic Bright's Disease; he cites the case of a girl, aged ten years, who entered the hospital with advanced nephritis and gave the history that "her legs had been crooked ever since she began to walk." These early accounts of what we now term renal rickets were almost all reported by English clinicians, and peculiarly enough most of the reports have emanated from England ever since. During the past few years several papers have appeared in the American literature and one from Germany, that of György, which has just been published. Hutinel reported a case in 1912 but attributed the renal symptoms to a secondary complication. It seems unnecessary to give in detail the history of this interesting form of rickets, as a complete review will be found in the communication of Hunt, who

has compiled a table which includes the clinical and laboratory data of some 42 cases, as well as in the recent papers of Parsons and of György. The first real appreciation of the disorder dates back only to 1911, when Fletcher presented a typical case before the Royal Society of Medicine. In the following year, Miller and Parsons published an account of several cases. The credit for showing the interrelationship between the renal disturbance and the bony deformities belongs to Barber, who since 1913 has published a series of papers on this subject. The evolution in the conception of this symptom-complex is well illustrated by the fact that it first was termed renal infantilism, then renal dwarfism and now goes by the name of renal rickets.

The time of onset of the disorder varies greatly. In general, it may be stated that the symptoms are first noted at the age of six to seven years. Paterson has described the case of an infant, aged twenty-one months, who never had stood and whose deformities were said to have existed since birth. On the other hand, Barber reported the case of a boy who was able to play football at school, and at fourteen years began to work as an errand boy. *The first signs which attract attention, and for which the physician is consulted are generally retardation in growth, or inordinate thirst, or the development of knock-knee*, a sign which is apt to develop about the time of puberty. The family history is generally negative, although Barber has reported two cases in one family. The skin is apt to be sallow, pigmented and abnormally wrinkled. The characteristic signs of rickets may be present, especially the enlargement of the epiphyses at the wrists and ankles, beading of the ribs and a failure of the fontanel to close. The knock-knee often develops with exceptional rapidity. It is this manifestation which frequently induces the mother to consult the physician, and which in turn has led the surgeon to resort to operative measures, with unfortunate results. In marked cases the thorax may be greatly deformed, and marked chicken-breast or a funnel-shaped chest develop. The ends of the long bones, especially of those of the legs, may give way and lead to exaggerated malformations which resemble those encountered in the so-called "infantile osteomalacia."

In addition to, or even preceding the involvement of the skeleton, there may be marked polyuria and polydypsia. These signs are generally disregarded or may lead to a diagnosis of diabetes insipidus. The urine is of very low specific gravity, and may contain a trace of albumin, but usually is free from casts. There have been but few functional tests of the kidney, but those which have been made have shown a disturbance of the excretory mechanism when tested by means of injections of phenolsulphonphthalein. The heart is found to be normal, as usually is the blood-pressure, nor is there definite thickening of the arteries.

The third important symptom is stunting in growth, which may reach the degree of dwarfism. The child is exceptionally small, a condition similar to that which is encountered in association with diabetes in children or with cœliac disease. In addition to this lack of growth, there is apt to be a lack of development in the primary and secondary sex characteristics—infantilism. The disease

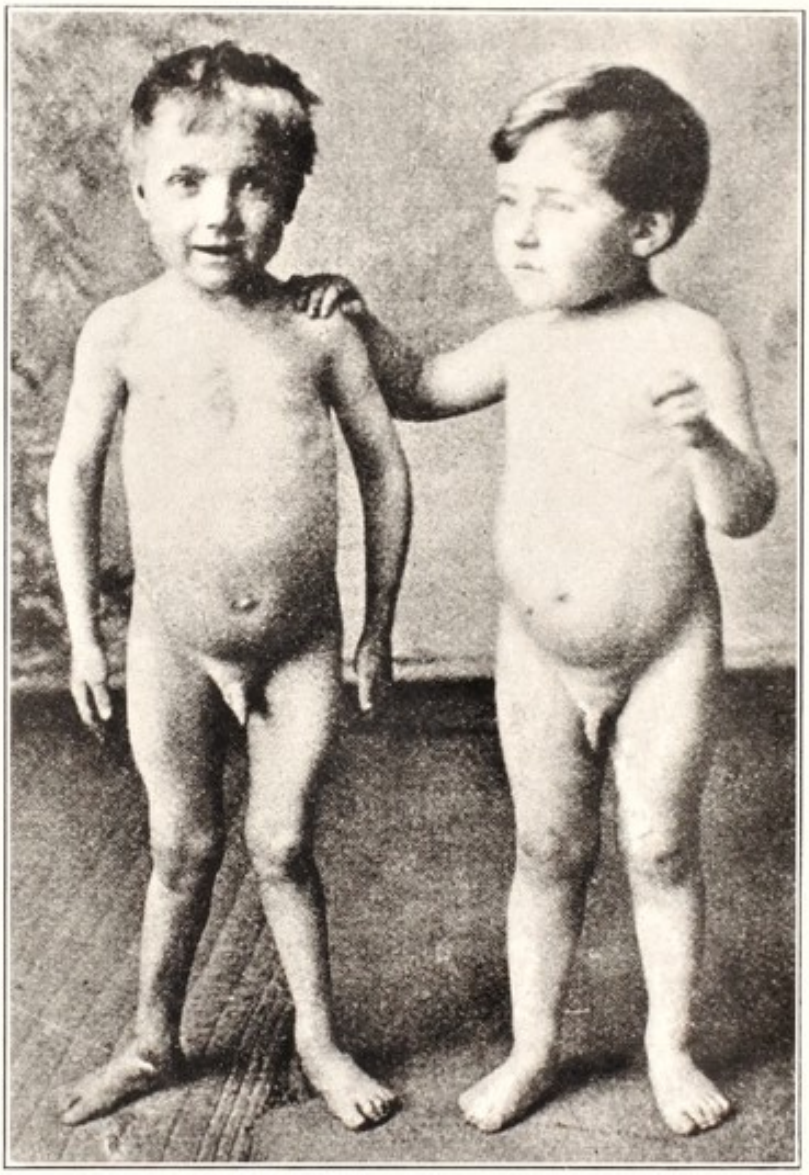

FIG. 44.—*Renal rickets.* Dwarfism and knock-knee. Child on left, aged nine years and nine months; normal brother on right, aged three years. (Miller and Parsons, Brit. Jour. Child. Dis., 1912, **9**, 289. Adlard & Son, London.)

almost invariably terminates in death from uremia, which occurs during the second decade of life.

Interesting and at times characteristic changes have been noted in the bones by means of the Roentgen rays. The picture may resemble that of infantile rickets or present peculiarities; in some cases the Roentgen rays show surprisingly little. Parsons has

contributed greatly to our knowledge in this field. He has divided the signs into three well-defined groups—the atrophic or osteoporotic type, the florid or infantile type and the woolly, stippled or honey-combed type, which he describes as follows: "This portion (the metaphysis) of the bone presents a curious appearance which sometimes suggests a honey-comb, at other times shows marked stippling, while at others it has a woolly appearance, the bone looking moth-eaten as if the shaft were being eaten away subperiosteally, and giving at first sight the suggestion of osteomyelitis or syphilitic disease." This stippling is due to the islands of cartilage in the metaphysis which Shipley, Park, and their associates have emphasized in their description of the histological picture. The skull may likewise be stippled and show markedly thick and thin areas, such as are typical of Paget's disease. Shipley and Park state that the "involvement of the skull appears to be out of proportion to the involvement of the bones of the extremities or of the thorax." One of the characteristic features of the radiological picture is the occurrence of "Umbauzone"—the transverse translucent areas in the long bones described by Looser, and mentioned in connection with the radiography of infantile rickets. In no other condition is this striking phenomenon so wide-spread or encountered so often.

Recently, *chemical examinations of the blood* have been carried out in conformity with the procedure now well-established in infantile rickets. The concentration of inorganic phosphorus has often been found to be unusually high, 13 to 14 mg., but at times may be normal. The calcium in the serum tends to be low, 7 to 8 mg., but likewise varies remarkably, rising to or even above normal. Parsons has emphasized the fact that the calcium is always low relative to the inorganic phosphorus, but this relationship is not constant. In spite of the low calcium, the occurrence of tetany is rare, especially when compared to its high incidence in cœliac rickets. Perhaps this is due to the fact that the concentration of ionized calcium is but slightly diminished. It is also worthy of note that the product of Ca $\times$ P is frequently above 40, in other words, well above the level which has been thought by some to exclude the presence of rickets. Accompanying the increased retention of phosphorus is an increased retention of nitrogen, and nitrogenous products; the non-protein nitrogen, urea and creatinin are all excessively high. In the case of an infant, aged sixteen months, which showed the "woolly type" of bone, Parsons found 19 per cent of fat in the serum. The urine is acid, in fact, there is a tendency to acidosis.

The histology of the bones has been studied in very few cases. Shipley, Park and their colleagues give the following description: "In the deep metaphysis were large islands of cartilage bordered on

one or more sides by dense calcium deposits. These islands of cartilage gave to the metaphysis, as seen in the roentgenogram, a honey-comb appearance. The trabeculæ were thin and the osteoid borders, comparatively speaking, narrow." They suggest that renal rickets "may belong to the low-calcium form of the disease" and that "rickets under certain conditions may have an endogenous origin." Paterson has described similar lesions of the bones. It will be noted that the osteoid tissue is but slightly increased, a lesion reminding one of that which develops in the low-calcium rickets of rats.

The kidneys have been found to be very small and to present the picture of advanced interstitial nephritis with marked destruction of the parenchyma and but little of the glomeruli. Microphotographs illustrating this condition will be found in Lathrop's report. In some cases malformations have been found. The changes in the heart and bloodvessels have been surprisingly slight when compared to those which are commonly associated with this type of kidney lesion in adults.

Renal rickets is but slightly understood. We do not know what brings about the disease of the kidneys nor why the disturbance in renal function should lead to these lesions of the bones. An infection of the kidney has been suggested. It is possible that the effect on the metaphyses is due largely to the fact that the nephritis occurs at a time when the bones are in the stage of active growth. This form of rickets is especially interesting in view of the fact that it is of endogenous origin and cannot be ascribed either to dietetic or to hygienic causes. It should be added that the disorder is not amenable to specific therapy, to ultra-violet rays or to cod-liver oil.

CŒLIAC RICKETS.

In 1908, Herter described a clinical condition which he termed "infantilism from chronic intestinal infection" resulting from an overgrowth of Gram-positive bacteria in the intestine. During the twenty years which have elapsed since that time, the symptom-complex has become established and clearly defined. Children suffering from this disorder generally have done well in early infancy, and during the second or third year develop a chronic indigestion associated with voluminous fatty stools. The derangement is very stubborn and the children lose greatly in weight and strength. The characteristic phenomena are the stunting in growth which always comes about if the disorder persists for a long time, the signs of tetany, the occasional edema of the limbs and face and the rarefication of the long bones. The occurrence of tetany varies greatly in the different reports and generally is manifested merely by prolonged carpopedal spasm. The wasting of the bones is clearly

evident by the Roentgen rays, which show marked osteoporosis and translucency of the shafts, and a peculiar tendency to develop the so-called "transverse lines" which have been referred to in the chapter on Radiography. In addition, there may be the typical evidences of rickets at the epiphyses, with a delay in development of the carpal centers and one or more fractures.

In 1912 and 1913, McCrudden and Fales carried out metabolism experiments in 2 cases of this disorder and found more particularly a negative balance of calcium, as well as an inadequate retention of phosphorus. In view of the fact that the urine contained a very small amount of calcium, they suggested that the concentration of calcium probably was lowered in the blood. This supposition proved to be correct. In 1925 Vollmer and Serebrijski reported a case in which the calcium concentration was only 5.4 and the inorganic phosphorus 2.9 mg. per 100 cc. of serum, and in 1927 Parsons showed that among 5 cases of severe cœliac disease, 4 had diminished calcium in the serum. The reports concerning the concentration of inorganic phosphorus are not so clear. In Parson's case, the phosphorus showed a tendency to be low, but was variable, and in the recent report of Fanconi, the phosphorus also frequently was diminished. It should be added, however, that Fanconi's figures for normal phosphorus are unusually high and that he made use of less than 1 cc. of blood for the determinations. In general, tests for inorganic phosphorus do not show the regularity which we are accustomed to meet with in infantile rickets.

The incidence and the degree of rickets vary greatly in cœliac disease. Some, as for example, Lehndorff and Mautner, who have written an excellent monograph entitled "Die Cœliakie," have failed to note any rickets. Others, especially Parsons, have encountered it frequently. My own experience has been that it is generally absent; in 2 instances it was evident in slight degree. Parsons explains this variability on the theory that "bone deformities do not occur unless the disease is severe in type and of long standing, and unless the child has passed the age of seven years." This explanation is not quite satisfactory as there are in the literature numerous cases of children under the age of seven where rickets undoubtedly was present. It seems rather that the development of rickets is, as might be expected, intimately linked with that of growth. First, rickets may come about before the cœliac disease has developed in marked degree; it will not arise while there is complete or almost complete failure of growth. Again, it may develop during the reparative stage of the disorder when growth has once more begun (Fig. 45). Lehmann has described several cases of this kind.

It should be added that there is a difference of opinion as to whether the specific curative agents of rickets are of value in this

condition. Parsons reported cures by means of ultra-violet light and of irradiated cholesterol, although the healing came to pass

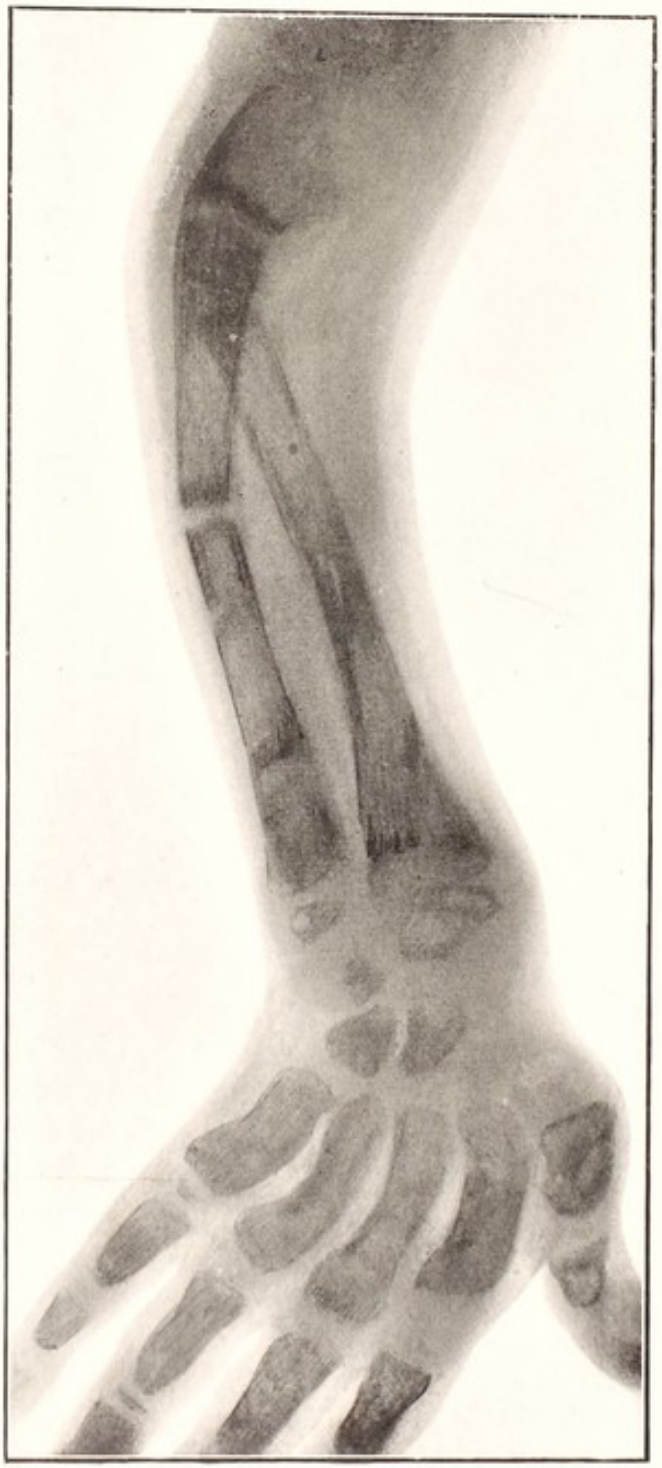

FIG. 45.—*Cœliac rickets.* Boy, aged ten years, serum calcium 6 mg., inorganic phosphorus 5.8 mg. Marked osteoporosis and "transparent zones" in shaft. (L. G. Parsons, Arch. Dis. Child., 1927, **2**, 198.)

exceptionally slowly. On the other hand, Fanconi failed to note healing from treatment with cod-liver oil, irradiated ergosterol and

ultra-violet irradiation. In my experience irradiation has been of little or no value.

There are broader aspects which must engage our attention in regard to the association of rickets with cœliac disease. In the first place, it has been suggested that we are confronted here with instances of tetany developing quite unassociated with rickets. This is a question which has led to much discussion in relation to infantile tetany. In connection with cœliac disease, it should be pointed out that consecutive chemical tests of the blood are lacking and that no investigation has been carried out to determine whether a phase of low inorganic phosphorus has preceded the development of low calcium and of tetany. This form of rickets seems to be generally of the low-calcium type and, therefore, we cannot be guided by the radiological evidences of rickets, for, as is well known to those who have had experience with experimental rickets, the rachitic lesions brought about by diets low in calcium are rarely evident in radiographs. From the standpoint of rickets, the lesions in the bones which accompany cœliac disease must be regarded as being the result of a deficiency of calcium. This happens in the first place, because the food is low in calcium, owing to the withdrawal of milk from the dietary. But of greater significance is the fact that the calcium is not absorbed, but is excreted in large amount in the bulky fatty stools which are characteristic of the disorder. It is this great loss of calcium which is one of the main causes of the rickets, as well as of the low calcium in the blood and of the accompanying tetany.

The second point which cœliac rickets raises is that of the relationship between osteoporosis and rickets. It is the same question which has been discussed in the chapter on Pathology and in connection with craniotabes—whether or not osteoporosis predisposes to the development of rachitic changes. Parsons believes that it does; in other words, he considers the bones in cœliac disease as being potentially rachitic. At present the question is a matter of personal opinion, for clinical observations are equivocal and there are no animal experiments to guide us. Indeed, it is by no means certain that osteoporosis should be regarded as a unit—that there may not be more than one kind of osteoporosis. For example, are we to consider the osteoporosis brought about by an acid diet to be the same as one which has been occasioned, as in the case of cœliac disease, by a deficiency of calcium? Are they of equal potentiality in regard to the development of rickets? This question must be left open, but in connection with the occurrence of rickets in cœliac disease, it seems certain that an important factor is the sudden change from almost absolute growth-stagnation to a condition in which the growth of the bones proceeds at an excessively rapid rate.

It is questionable whether the rickets associated with cœliac

disease should be regarded as an entity. It is exceptional, merely in that it is a form of late or juvenile rickets that develops in bones which are the seat of marked osteoporosis. Renal rickets, on the other hand, differs fundamentally from other types in regard to etiology. It is due to the action of one or more retention products which diseased kidneys are unable to excrete. This is a tissue reaction which is of importance from a pathogenetic point of view. Clinically it is characterized by a tendency of the bones to bend, whereas the osteoporotic bones of cœliac disease tend to break. This distinction must be due to differences in the chemical constitution of the bones.

CHAPTER XIII.

OSTEOMALACIA. (MALACOSTEON; MOLLITIES OSSIUM.)

Osteomalacia has always aroused great medical interest. The marked exaggeration of its deformities, which may border on the bizarre and grotesque, has been a favorite theme for description and illustration for hundreds of years. The fact that its course is attended with intense pain and that its deformities lead to dangerous obstructions to child-birth, a field which, from earliest days, has occupied much of the time and attention of the physician, has also tended to focus interest on its clinical phenomena. It is difficult to ascertain who first described this condition or where it was first observed. Lobstein, a French pathologist of the early part of the past century, states that an Arabian physician by the name of Gschuzins, described a case of this kind dating back to the time of Mohammed. All the bones of this woman were soft, so soft that she could not move; the only part of her body which was under her control was her tongue. Lobstein refers to cases which he had seen and to the typical "three-cornered pelvis." He mentions a number of the well-known cases of the eighteenth century, particularly the Supiot woman whose skeleton may still be seen in the Dupuytren Museum of Paris. This woman was so deformed that her left foot served as a pillow for her head, and at necropsy even the ossicles of the internal ear were found to be softened.[1] These early treatises were largely descriptive and considered these cases merely in connection with the general subject of monstrosities. The disorder has been termed "malacosteon" or "mollities ossium," on account of the frequent involvement of the ribs and the marked softening of the bones.

Osteomalacia belongs to the group of disorders which has become steadily less numerous with the advance of civilization and the application of our newer knowledge of hygiene and dietetics. Today it occurs sporadically probably throughout the world, but it is a comparatively rare disease in Europe and America. In 1861, Litzman collected 131 cases from the literature, 85 in pregnant or puerperal women, 35 in non-pregnant women, and 11 in men. Even as late as seventy-five years ago it played a rôle in the mortality statistics of almost all the European countries: of Italy, France,

[1] It is of interest to note that at necropsy all the viscera were found to be normal in spite of the extreme degree of malformation. The kidneys contained gravel; at the onset of the disease the woman had noticed in the urine a chalk-like deposit, which proved to be soluble in acid. This grotesque exhibit calls to mind the distorted skeletons of monkeys which may be seen in the museums of various zoölogical gardens in this country and abroad.

Germany, Switzerland, Great Britain, but not of Scandinavia. The gynecologist Gelpke states that in 1880, 24 deaths were ascribed to this disease in Great Britain,[1] and 25 in Bavaria in 1882, 30 in 1883, and 20 in 1884. Many have remarked on the endemic character of osteomalacia, on the fact that it showed a tendency for years to be associated with certain localities, for example, with the Rhine Valley, the Ergolz Valley in Switzerland, the Olona Valley and Calabria in Italy, and especially with the city of Vienna. Gelpke wrote an account in 1891 of "Osteomalacia in the Ergolz Valley," and commented on the fact that the people of this section belonged to the better situated communities of Switzerland. He believed that this endemic tendency was due to the gradual development of a race or strain of people who had osteomalacia in a latent form, and whose bones were deficient in inorganic salts. The diet of these people is stated to have been poor in phosphoric acid. On the other hand, the Italians attribute this endemic phenomenon to the invasion of a specific bacterium; according to Arcangeli, it is due to a diplococcus. Some years later, in 1903, Masueger, a student of Gelpke's in Basel, reported that the incidence of osteomalacia in this section of the country had markedly diminished. Brittany is another district which, for a long time, seemed singled out by this disorder. In a thesis on puerperal osteomalacia, published in 1909, Hudde reported that in Rennes (Brittany) 3 cases had occurred in the maternity service during the past six years, and that dystocia was frequent among the women of this district; among 880 deliveries during the past four years, 107 instances of rachitic pelvis had been noted. He remarks that the hygiene among the people was poor, the climate unfavorable, and the diet deficient in calcium. In this connection it should be mentioned that the famous Trousseau, in collaboration with Lasègue, was one of the first to study osteomalacia and carefully to depict its clinical features, especially those involving the nervous system. In America, osteomalacia has always been rare. Dock was able to collect but 10 cases occurring in the United States up to the year 1896, and Williams states that he has seen but 3 instances at the Johns Hopkins Hospital in Baltimore. This statement acquires added significance when we consider that, as mentioned elsewhere, negroes preponderate among the clientele of this clinic, and that the typical "rachitic pelvis" is unusually common.

THE OCCURRENCE OF OSTEOMALACIA.

Although osteomalacia has become an exceptional disorder among peoples living under a modern civilization, there are still large areas where it is of frequent occurrence and constitutes an important

[1] It is worthy of note that his inquiries disclosed that it was exceptionally rare in Glasgow, a city which always has been distinguished for the high incidence and marked severity of its rickets.

medical problem. Probably it is most widely distributed in *India*. It is difficult to estimate its incidence in that country as no classification such as "osteomalacia" exists in the hospitals which are subsidized by the government, the disorder being variously designated as "chronic rheumatism" or as a "disease of the organs of locomotion." One of the first reports from India, that of Scott in 1916, emphasized the frequency of rickets in northern India, in the mountainous district bordering on the Himalayas. This study was based on a wide-spread questionnaire and brought to light the fact that osteomalacia was observed almost throughout India. The investigations of Huchison and Shah a few years later, to which further reference will be made, was concerned with the Nasik district of the Bombay Presidency, a hilly, rather moist area about 100 miles from Bombay. Another report of this author, in collaboration with Patel, describes the marked incidence of osteomalacia in the city of Bombay on the west coast, a "subtropical climate, moist and hot." The most recent paper on this subject is one by Stapleton, who took part in some of the previous investigations, which shows the high incidence of late rickets and osteomalacia in Delhi, near the central part of the country. It will be noted in the course of the subsequent discussion of the etiology of osteomalacia that topography seems to play but little rôle in the incidence of osteomalacia in India, and that it is apparently of no moment whether the climate be dry or moist, cold or hot. Its frequency depends rather on the customs and habits of the people.

Another country where osteomalacia is still an important medical problem is *China*. That such is the case has been recognized only recently, since the investigations of Maxwell and of the Peking Medical School. The areas involved are fairly large but remarkably circumscribed. The heaviest incidence has been found in the northern three-fourths of the province of Shansi, the southern limits being Luanfu on the east and Pinguangu on the west. The entire affected area is a high plateau, 2000 to 3000 feet above the sea. In the latter district Maxwell states that in one week he saw 22 cases in part of the city and one of the suburbs. "This city and its suburbs contain about 15,000 inhabitants and it is probable that at least 1 in 50 of the women of child-bearing age have, or have had, the disease. We know of one family at Pingtingchow where three daughters-in-law died one after the other from obstructed labor due to osteomalacia. Probably 2 to 3 per cent of the pregnant women die in labor from the disease!" This is the country where it was commonly stated, until recently, that rickets did not occur.

In 1912, Ogata described a district in *Japan* in the Province of Toyama, where he found a large number of cases of osteomalacia. The symptomatology and pathology leave no question as to the correctness of the diagnosis.

Krajenska published in 1900 an interesting account of 50 cases of severe osteomalacia occurring in an isolated district in *Bosnia*. The population is Mohammedan. Girls marry at the age of twelve to thirteen years, and then lead a life of seclusion indoors. The district is mountainous and the diet consists mainly of corn bread and coffee. This report was amply confirmed by Januszewska in 1910. In the course of ten years this physician saw 3510 cases of osteomalacia in Bosnia, only 12 of which occurred in non-Mohammedans. This disorder developed almost exclusively among the dwellers of the large cities; for example, in Cazin, with a rural population of about 38,000 who do not practice seclusion (purdah), he did not meet with a single case.

No doubt osteomalacia is more wide-spread than has been supposed. The Mohammedan religion, or rather the seclusion which it imposes on women, is, as we shall see, an important etiological factor. When we bear in mind the vast number of Mohammedans dwelling throughout the East and the meagerness of our knowledge as to their physical condition, it seems probable that numerous foci of osteomalacia, such as have been described in India and Bosnia, exist in these countries. In regard to the United States and Europe, it may be added that latent cases of this disorder, such as we have learned to recognize in connection with rickets, infantile and adult scurvy and beriberi, no doubt occur in the course of pregnancy or the puerperium where hygienic and dietetic conditions are especially unfavorable.

THE ETIOLOGY OF OSTEOMALACIA.

Similar differences of opinion have existed in regard to the etiology of osteomalacia as in regard to rickets. Some have maintained that it results from faulty hygiene, others from a faulty diet, and still others have placed the blame on defects in both of these domains. The errors of hygiene have been summarized categorically as "indoor living," lack of exercise and damp quarters, little effort having been made, until recently, to analyze the individual rôles of these various factors. Similarly, the references to deficiencies in diet have consisted of suppositions rather than of evidence based on a study of dietaries. A lack of calcium or a lack of phosphorus in the food has been suggested frequently as the underlying cause—an inference obviously deduced from the extreme softening of the bones, which dominates the clinical picture. Such was the status of this question until some ten years ago when the study of osteomalacia was begun anew. Since this time a series of excellent papers have appeared in rapid succession from various sources, which have elucidated the etiology of osteomalacia

and, incidentally, have brought it into close harmony with infantile rickets.

Before discussing the respective rôles of hygiene and of diet, the fact should be emphasized that osteomalacia is preëminently limited to the female *sex*. Scott states that she has no record of a case in the male, and Huchison reports the same experience in India. There is no doubt, however, that males are sometimes affected. Maxwell records an instance in a boy, aged twelve years, who had been confined to a dark room for a long period on account of measles and its sequelæ. Lobstein performed a necropsy on a male while he was in Strassburg. In 1899 Hahn wrote a paper on this subject, entitled "Osteomalacia in the Male," in which he reviews the disorder from this point of view. He found that Vienna, which leads all the cities of Europe in the number of cases of puerperal osteomalacia, had the highest incidence among males. This sex peculiarity must not be lost sight of; it is so definite and well established that it must be given a prominent place in considering the pathogenesis of this disorder. In this connection it is well to remember that no distinction in regard to sex susceptibility has ever been established in connection with infantile rickets, although tetany, both in adults and in infants, preponderates in males.

Age is also an important factor in connection with the occurrence of osteomalacia. Here we meet with the difficulty referred to in the preceding chapter, namely, in differentiating between late rickets and osteomalacia. It is, I think, generally accepted at the present time that such a distinction or classification is purely artificial, that the difference between the two forms is merely one of age, and that they merge imperceptibly into each other. Stapleton recently has brought out this point in a convincing fashion in an analysis of 73 cases of late rickets and osteomalacia occurring in Delhi. She writes: "Very soon after commencing the investigation one came to realize that they formed a fairly complete series, leading gradually from the typical late rickets case in young girls of ten, twelve and fourteen years, through an intermediate stage in rather older patients in which the Roentgen ray signs of bony rickets were still present, but were accompanied by the deep-seated pains in the bones that are usually associated with osteomalacia and then on to the well-developed form of the latter disease that up to now has been thought to be mainly connected with pregnancy and lactation in young married women." In general the disease usually commences about puberty or in early adult life. Cases do occur occasionally in older women even past the menopause; one woman in Stapleton's series must have been at least sixty years of age, as she had been born a few years after "the great mutiny."

In considering etiology, a sociological aspect should be emphasized. Whereas rickets occurs in greatest degree and extent among

the children of the poor, *osteomalacia is least prevalent among the poor*. There is general agreement on this point among observers in different parts of the world. Scott states that in India among the patients who were visited, 28 were poor people and 30 "people in comfortable circumstances, some quite rich," and Huchison that "it is far more prevalent among the well-to-do." Maxwell gives it as his experience in China, an opinion in which Miles agrees, that the poor rarely get it; he adds "nor do the rich who have plenty of nourishing food," but it is the middle class which is afflicted. The explanation for this apparent incongruity will be evident when we bear in mind the influence of hygienic factors.

Apart from the fact that osteomalacia in India is almost entirely limited to the female sex and occurs largely in early adult life, there is a *peculiar caste incidence* which has been noted by all recent observers and which furnishes the key to the dominant etiological factor underlying this disorder. The Mohammedan women and the high-caste Hindus observe "purdah," a system of seclusion based on religious rites. According to this custom the women do not appear unveiled in public, and practically never leave their houses during the day, or if they do "they wear an uparana or cloak which covers the whole body while a fine net-work is left in front of the eyes, nose and mouth. They take but little exercise, and their houses are often badly ventilated and ill-lighted." Scott states that "a marriage or death in the family, or a religious festival, is almost the only occasion on which the women will go out-of-doors." The younger women leave the house still less and, moreover, are obliged to do most of the work of the house, washing, cooking, etc., all of which they do sitting or squatting on the ground or on a low stool. The low-caste women do not practice purdah. In other words, conditions of living, more particularly from a hygienic standpoint, are governed not as in western countries by the affluence of the individual, but by custom and tradition. The women who are rich and who eat the best of food, obtain less sunlight and fresh air than those who are poor. This state of affairs is almost unique and furnishes an exceptional opportunity for a separate study of the effect of hygiene and of diet. It establishes conditions similar to those which are artificially formulated in the laboratory.

TABLE 20.[1]—DISTRIBUTION OF OSTEOMALACIA ACCORDING TO CASTE AND ITS RELATION TO THE COMPLICATIONS OF CHILDBIRTH.

Class.	Total osteomalacia.	Frequency, per cent.	Total labors.	Total complications.	Frequency, per cent.
Mohammedans	84	5.60	1484	218	14.60
Hindus	24	1.04	2300	62	2.60
Other classes	0	0.0	3372	6	0.17

[1] Huchison, H. S. and Stapleton, Grace, On Late Rickets and Osteomalacia, British Jour. Child. Dis., 1924, **21**, 18.

The distribution of osteomalacia according to caste is well illustrated by the accompanying data (Table 20), which show the distribution of osteomalacia among the Mohammedans, who practice purdah, among the Hindus who observe purdah to a small extent, and among other classes who are not subject to this rite. It will be noted that among the 108 cases of osteomalacia which are recorded, about four-fifths occurred among Mohammedans, one-fifth among Hindus, and none whatsoever among "other classes." The reliability of these figures can in a measure be checked by noting the number or the percentage of complications which occurs in the course of childbirth among these various castes, a criterion which is of decided value in judging of the incidence of osteomalacia. Looking at the data from this point of view, it is found that out of a total of more than 7000 labors, there were 14.6 per cent of complications among the Mohammedans, 2.6 among the Hindus, and but 0.17 per cent among all other classes.

TABLE 21.[1]—RELATION OF LATE RICKETS AND OSTEOMALACIA TO THE PRACTICE OF SECLUSION (PURDAH) AND TO ECONOMIC STATUS.

	Late rickets.		Osteomalacia.	
	Total cases.	Percentage.	Total cases.	Percentage.
Hindus, high caste	28	70.0	27	55.1
Mohammedans	7	17.5	17	34.7
Hindus, low caste	4	10.0	5	10.2
Other classes	1	2.5	0	0.0
Seclusion practised	35	87.5	44	89.9
Seclusion doubtful	3	7.5	3	6.1
Seclusion not practised	2	5.0	2	4.0
Well-off	30	75.0	27	55.1
Not well-off or poor	10	25.0	22	44.9

As has been stated, no sharp distinction should be drawn between osteomalacia and late rickets. We quite agree with Stapleton in the opinion that the one condition merges imperceptibly into the other, and that they are essentially, therefore, the same pathological disorder. In judging the importance of purdah, in other words, of faulty hygiene, in the etiology of osteomalacia, it would seem to be of value to ascertain the influence of this practice on the development of late rickets. Table 21, which is a composite of several tables in an article by Huchison and Stapleton, shows that in late rickets, as in osteomalacia, there is a direct relationship between the practice of seclusion and the development of these forms of malnutrition. It illustrates also that the incidence of these disorders bears a direct rather than an inverse ratio to the affluence of the individual—75 per cent of the women suffering from late rickets were "well-off," as were over 55 per cent of those suffering from

[1] Huchison, H. S., and Stapleton, Grace, On Late Rickets and Osteomalacia, Brit. Jour. Child. Dis., 1924, **21**, 18.

osteomalacia. There can be no doubt, therefore, that the harmful effect of purdah is not dietetic, but hygienic. Some believe that the essential error is a lack of exercise, others that it is a lack of sunlight. Scott emphasizes the dampness of the clothing and of the ground in the houses which are "freshly plastered with wet mud and cow-dung before the cooking of each meal and, therefore, are damp." If we draw an analogy from the etiology of infantile rickets, the dominant factor must be regarded as a lack of sunlight. Similar living conditions probably prevail among the Mohammedans in Bosnia, who also are sorely afflicted with osteomalacia.

But how are we to account for the endemic osteomalacia in China, which Maxwell and others have described? It seems that the "kangs" of China take the place of the purdah of India. Maxwell describes the situation as follows: "The "kang" is a platform built of brick or mud which is used as a bed. It is heated by means of flues passing under it, the firing being done from inside or outside the room. In Shansi, where the disease is most prevalent, the "kangs" are heated by coal, the fumes to a considerable extent escaping into the room and thus vitiating the atmosphere. Cases of carbon-monoxide poisoning are not by any means unknown . . Finally there is the question of sunlight. Some of the courts get little, and if the woman stays in the room on the "kang" (and she tends to stay there more and more after the pains of the disease come on) she gets very little sunlight."

In China, as in India, the poor, who are agriculturists and work in the fields, rarely develop osteomalacia. However, in contradistinction to India, the rich "who have plenty of nourishing food with meat and fat" also seem to be spared. "The victims are, what one might call the 'genteel members of society'—too proud to work and not rich enough to afford the meat and fat."

Miles noted a marked *seasonal variation* in the severity of osteomalacia in all of his patients. This is of interest as it corresponds to clinical observations in regard to rickets and the so-called hunger osteomalacia which was observed in Vienna and elsewhere shortly after the World War. The remission in the summer is probably due to the action of the sun's rays.

The fact that osteomalacia is restricted almost entirely to women is convincing evidence that it should not be regarded as a dietetic disorder, that faulty *diet* is not the dominant etiological factor. The consensus of opinion that the well-to-do and the rich develop osteomalacia even more frequently than do the poor, is a further indication that we are not dealing with a simple deficiency disease. Fortunately there are detailed accounts of the dietaries, in India as well as in China, of those who develop osteomalacia. It may be stated at the outset that wherever osteomalacia has occurred in endemic proportions, cereals have formed the staple diet. In Bosnia the diet

consisted mainly of corn bread and coffee; in India the basis of the diet was wheat, in China, millet. There does not seem to have been a marked or general lack of fat. The Bhoris, according to Huchison and Patel, develop osteomalacia in spite of eating large quantities of "ghee" (clarified butter), whereas the poorer Indians generally remain well although fat is the one article which is deficient in their dietary. It should be added, however, that the use of sesame oil and cocoanut oil for cooking purposes is very general. The diet of the poor consists chiefly of rice as well as wheat cakes and pulses with a certain amount of ghee. Salt fish is also eaten regularly, but meat and milk only occasionally. That there is no decided lack of the fat-soluble vitamin A is amply attested by the fact that there is no mention of the occurrence of xerophthalmia in any of the reports which come from India. Maxwell specifically states that in China "none of the patients have exhibited either xerophthalmia or night-blindness." He found that the diet in the affected district consists in the main of "wheat meal, oatmeal, kaoliang flour, bean-flour, and millet with a little white cabbage and bean leaves and gourds. . . . During the winter the diet is in the majority of cases in the country limited to millet gruel, sometimes supplemented with a little cabbage or salted vegetable."[1] Viewing this ration as a whole, it is evident that it contains considerable of the water-soluble, the fat-soluble and antiscorbutic vitamins. It would seem to be lacking somewhat in proteins and to be especially poor in mineral elements, particularly in calcium. The fact that "prac-

[1] Miles and Feng describe the diet of the Chinese as follows: "In their homes these people live on a very meagre diet consisting entirely of cereals and a limited amount of vegetables with no milk, meat or eggs. The principal article of diet is millet which is eaten at least once a day in the form of a thin gruel made of the whole seeds, which have been partially hulled, boiled in water to which may be added a few chopped pieces of onion or garlic or some other vegetable in season. A small quantity of "salt vegetable," usually a variety of turnip or radish which has been preserved in salt brine is eaten with the millet gruel. Another vegetable eaten in the same way is prepared by placing green leaves of bean plants in brine, thus making a sort of 'sauer kraut' of the bean leaves. Its principal function is to furnish a flavor to the food and also salt as the cereals are cooked without salt. Very small quantities of this 'salt vegetable' are consumed at a meal, only about 10 to 15 gm. Millet is also prepared by 'dry steaming' the seeds producing a dish very much like steamed rice. Wheat flour products are eaten once a day by those who can afford the luxury. Steamed bread is made of wheat flour, or the dough is rolled out thin and is baked in large flat unleavened cakes. A third favorite way of eating wheat flour is in the form of noodles and usually in the noodles a certain proportion (usually about 25 per cent) of flour made from green soy beans is added. Of vegetables in the regular dietary we find very few varieties. The Pai Tsai, marketed in America under the name of Chinese celery-cabbage is eaten in large quantities throughout north China, but in the region affected by osteomalacia, which is on a high plateau, the season is short and this useful vegetable is not cultivated extensively. The supply is limited and the price high, as a consequence the poor people and the women, especially, do not eat much of it. The Pai Tsai is eaten boiled or fried and, as a rule, the valuable outer green leaves are stript off and thrown away, only the bleached inner leaves being eaten. Onions and garlic are eaten and also another variety of 'salt vegetable' prepared from the leaves and stalks of the mustard plant is used extensively. Small quantities of bean curd are eaten by those who can afford it."

tically all the patients at one time or another have tetany" is interesting in this connection. It is difficult to state whether the supply of phosphorus is likewise inadequate. Miles believes that there is a relatively large amount of phosphorus which leads to a disturbance of the phosphorus-calcium ratio in the dietary. These diets have an acid ash, which tends to decrease the retention of calcium and to further its excretion by the urine.

TABLE 22.[1]—RELATION OF ONSET TO MENSTRUATION, PREGNANCY AND LACTATION

Before puberty	16	Before first pregnancy	30
With or after puberty	50	During first pregnancy	14
Relation to puberty not noted (age twelve to fifteen years)	5	During successive pregnancies	10
After menopause	2	After delivery	4
		During lactation	12
		After weaning	1
		Many years after weaning	2
	73		73

One of the most striking and significant factors in relation to osteomalacia is the effect of *pregnancy* and, to a less degree, of lactation in its causation. There can be no doubt as to the influence of these factors. Recent authors have tended to stress the fact that osteomalacia not infrequently develops quite independently of pregnancy, that it may antedate puberty or appear after the menopause, and that the designation "puerperal osteomalacia" frequently given to this disorder is a misnomer. It is perhaps true that the rôle of pregnancy has been somewhat exaggerated; nevertheless, we must recognize it as an etiological factor of importance not only clinically, but also pathogenetically. A consideration of the influence of pregnancy gains added interest because it directs attention to an aspect which the study of rickets naturally cannot bring into view. The accompanying data (Table 22), compiled from the figures of Stapleton, show that the onset of the disease is intimately associated with the beginning of pregnancy, but that *the relationship between osteomalacia and puberty is even closer than that between osteomalacia and pregnancy.* The marked susceptibility during pregnancy cannot be explained on the assumption that calcium and other inorganic salts are withdrawn from the skeleton of the mother for the benefit of the fetus, for this withdrawal occurs mainly during the last two months of pregnancy. For example, according to Hoffstroem, the fetus contains about 5.39 gm. of calcium at the twenty-eighth week of pregnancy and 30.51 gm. at the fortieth week. Among the cases reported by Huchison and Stapleton, 25 of the 26 occurred previous to the seventh month, and 13 at or before the fifth month of pregnancy. In other words, if in these cases the osteomalacia were to be ascribed to the loss of calcium utilized in

[1] Stapleton, Grace, Late Rickets and Osteomalacia in Delhi, Lancet, 1925, i, 1119.

building up the fetal skeleton, one would have to postulate that the loss of about 5 gm. of calcium from the bony frame of an adult can bring about this nutritional catastrophe—a hypothesis which is clearly fallacious. Moreover, signs of the disorder manifest themselves not infrequently during the first two months of pregnancy. The effect is one which suggests rather the action of the glands of internal secretion.

The rôle of *lactation* is less definite. The fact that nursing is, in general, unduly prolonged among Indian women renders it difficult to appraise the significance of this factor. All classes of women nurse for exceptionally long periods in India, not only the Mohammedans. Yet this custom does not lead to the universal development of osteomalacia. Nor does this happen in Japan where a similar custom prevails. As Huchison and Stapleton remark: "The disease begins in a large majority of cases either during the first pregnancy, before lactation has commenced, or sooner or later after delivery, before lactation has been carried on for any length of time. Also, in many cases, the symptoms are alleviated after labor, when lactation begins." Lactation certainly should not be regarded as a primary etiological factor.

In China a contributing factor may well be the custom of starving the parturient woman during the last two months of pregnancy, of limiting her diet largely to millet gruel. The practice of foot-binding, insofar as it leads to a limitation of exercise, tends also to favor the development of osteomalacia.

A number of writers have inclined, to a greater or less degree, to the infectious origin. They have been led to this opinion as the result of the low fever which at time accompanies osteomalacia, as well as by the occasional suddenness of the onset and rapid softening of the bones associated with pains in the pelvis and the thighs. Huchison considers these clinical phenomena "suggestive." Arcangeli, who has written a most comprehensive account of osteomalacia in Italy, not only believes in its infectious origin but attributes it to a definite diplococcus. His work is very similar to that of Koch whose investigation has been considered in relation to the etiology of rickets. In our opinion such microörganisms must be regarded as secondary invaders which have gained entrance to the body following the disturbance in metabolism. The condition is similar to that which is encountered not infrequently in scurvy, in which latent or subacute scurvy permits the invasion of bacteria into the blood stream.

THE PATHOGENESIS OF OSTEOMALACIA.

As in rickets, almost every one of *the endocrine glands* has been associated by some investigator with the pathogenesis of osteo-

malacia. *The parathyroid glands* are probably involved in those cases in which there is a marked disturbance of calcium metabolism. In most instances the level of calcium in the serum is low. In some, however, especially those associated with gross lesions of the parathyroids, a condition of hypercalcemia is found (hyperparathyroidism). Recently Barr and his colleagues reported an instance of parathyroid tumor accompanied by hypercalcemia, a calcium concentration of 16 mg. per 100 cc. of serum. This condition resembles that which is brought about by injections of parathyroid extract and should be distinguished from that of typical osteomalacia. In view of the fact that it is now definitely established that the parathyroid glands are intimately concerned with the regulation of calcium, pathological reports, macroscopic as well as microscopic, must be carefully weighed and interpreted.

Among the glands of internal secretion which have been held responsible for the pathogenesis of osteomalacia, may be mentioned *the adrenals*, which Stoeltzner associated with osteomalacia as well as with rickets. Some have stated that a derangement of the function of the thyroid gland plays a part, and have cited the frequent occurrence of goiter in cases of osteomalacia. Scipiades believed that he was able to prove, by means of animal experiments, that osteomalacia can be brought about by extirpation of the thymus. Some have stressed the importance of the bone-marrow, regarding it as an organ of internal secretion. A pluriglandular causation of osteomalacia has been suggested, in which the functions of the parathyroid glands, the ovaries, in fact of almost all the endocrine glands, are supposed to be deranged. Oppenheim suggested the interesting theory that there is a center in the brain which regulates the metabolism and the functions of the viscera, and that although osteomalacia is under the influence of the endocrine glands, they in turn are controlled by the central nervous system. He reports having seen a case of osteomalacia develop in the course of v. Recklinghausen's disease—multiple neuromata—and cites 5 similar instances drawn from the French literature.

In 1879 Fochier of Lyons, in the course of Cæsarean section operations removed the pregnant uterus and ovaries in several cases of osteomalacia. Finding that this procedure had a favorable effect on the progress of the disorder, he suggested that this operation be tried in other instances of active osteomalacia. The well-known gynecologist, Fehling, attributed the improvement following this operation to the *removal of the ovaries*, and performed ovariotomy on a number of women suffering from osteomalacia. In 1884 he published a paper entitled "Ten Castrations: An Account of the Value of Castration," and a few years later recorded the subsequent course of a series of cases; 6 were well three years after operation, 2 had not been cured, and the others had either

died or their welfare could not be ascertained. Fehling, who wrote a series of articles on this subject between the years 1884 and 1894, suggested the hypothesis that osteomalacia is due to a pathological increase in the activity of the ovaries leading to a stimulation of the vasodilators or paralysis of the vasoconstrictors, followed by congestion or hyperemia of the bones and a consequent solution of their lime salts. Within the next few years this operation was performed by a large number of surgeons in many countries. In 1892, Truzzi reported 97 cases of osteomalacia treated by castration, of which 16.9 per cent failed to be cured. In 1913, Seitz published a report of 328 patients in whom the ovaries had been removed and stated that 87 per cent had been benefited. Benzel came to a similar conclusion as the result of an analysis of a series of operations in the Strassburg clinic. All of these reports have been based on clinical observations rather than on metabolic studies. Neumann was the first to carry out metabolism tests in women following ovariotomy; of his 2 cases a retention of calcium resulted in the 1, whereas in the other the calcium balance was not improved. McCrudden studied a non-puerperal case and found a retention of calcium a few months after operation, but a net loss when a balance test was carried out a year later.

There can be no doubt that pregnancy leads to the development of osteomalacia, and that ovariotomy tends to decrease its occurrence and severity. But the question is: Do the ovaries exert an effect quite apart from their rôle in pregnancy, do they secrete a hormone which leads to the development of osteomalacia, or does their removal halt the progress of the disorder merely by preventing subsequent pregnancies? This question is difficult to answer, and must be regarded as still *sub judice*. Those who, with McCrudden, believe that the effect of ovariotomy consists simply in putting a stop to repeated pregnancies, frequently cite the well-known investigation of Hanau in support of their view. This investigator, in 1892, described a "physiological osteomalacia," claiming that the catabolic processes are increased to such a degree in the course of pregnancy that the bones, especially those of the pelvis, normally undergo mild osteomalacic changes. According to this hypothesis, osteomalacia represents merely an abnormal intensification of the physiological drain of inorganic salts which takes place in the course of pregnancy. This striking hypothesis which was based on a post-mortem study of the bones of 20 pregnant women, who during life had been free from all symptoms or signs of osteomalacia, created great interest when advanced, but strange to say never has been confirmed or convincingly refuted. From our point of view little is to be gained by studies of this kind, for even granting the correctness of the data and their interpretation, one is justified in ascribing the osteomalacic process either to the activity of the ovaries or to

metabolic disturbances peculiar to pregnancy. The difficulty with a theory of this kind is that it makes a most complex syndrome—pregnancy—the criterion for judging the activity of the ovaries. As previously mentioned, osteomalacia is also intimately associated with the onset of maturity, a phase largely dependent on the functional activity of the ovaries and pituitary, and one far simpler to interpret than pregnancy. Table 22 illustrates the marked effect of puberty on the frequency of osteomalacia. Data which Ogata furnishes in connection with the endemic of osteomalacia in Japan lead to a similar conclusion, showing the increased incidence of this disorder as we approach the period of puberty. The recent report of Maxwell and Miles on the occurrence of tetany among girls ten to eighteen years of age in an orphanage of the Shansi district, also points in this direction. Using puberty rather than pregnancy as the gauge of function of the ovaries, it would seem that their activity predisposes to the development of osteomalacia, previous not only to pregnancy but to marriage. The answer to the question as to the effect of an ovarian hormone on the metabolism of the bones will be decided probably in the laboratory rather than in the clinic. Recent investigations—which have led to the elaboration of a purified ovarian or female sex hormone—are most promising in this connection. There are phenomena which should also lead us to keep in mind the function of the pituitary gland.

THE PATHOLOGY OF OSTEOMALACIA.

In 1853, Virchow made the following pronouncement in regard to the relation between the pathology of osteomalacia and rickets: "In osteomalacia, tissue is truly absorbed, what is firm becomes soft, gelatinous marrow is formed from bone rich in calcium; in rickets nothing is essentially absorbed, what is firm does not become soft. The osteoid layers which are free of calcium remain unchanged as do the layers of compact and spongy bone. Where can an anatomical resemblance be found between the two? In osteomalacia it is the bone itself which is changed; in rickets it is the cartilage and the periosteum, which in osteomalacia can hardly be considered as affected. In the latter we find only loss, atrophy, degeneration, and retrogressive metamorphosis, which does not progress beyond a certain point. Can we speak of an identity of these conditions?" This sharp differentiation between rickets and osteomalacia coincided with the current opinion of clinicians, and was generally accepted by pathologists. In 1889, however, Cohnheim questioned this point of view, drawing attention to the fact that in osteomalcia there is an increase of osteoid tissue similar to that regularly found in the bones in rickets. This report was the

signal for reinvestigation of this entire subject. Pommer, to whom we are so much indebted for our understanding of the physiology of bone, supported the view of Cohnheim, as did Kassowitz, and more recently Schmorl, Erdheim, Stoeltzner and others. In general, it may be stated that opinion veered sharply to the view that these two disorders, the one occurring in infancy and the other in adult life, are fundamentally the same from a pathological standpoint. In his article in Virchow's Festschrift which appeared in 1891, v. Recklinghausen promulgated his well-known dictum that the distinctive feature of osteomalacia is a destruction, a "halisteresis" of bone, and called attention to the abundance of osteoblasts and of Sharpey's fibers in the bones of those who had suffered from osteomalacia. Some have taken a mid-position, for example, Kaufmann and Marchand, who believed that rickets and osteomalacia are not quite identical, in that the latter is characterized by a greater degree of destruction of bone. Such is the present status of this question. It would be of little value to enter upon a detailed discussion of the pros and cons of the theories in regard to the unity or duality of rickets and osteomalacia. In my opinion the difference in the pathological lesions are of a quantitative rather than of a qualitative nature. The underlying pathological process is the same, although it must be admitted that there has not been a satisfactory explanation for the marked softening of the bone which forms so characteristic a phenomenon in osteomalacia. Until we have a better understanding of the relation of osteoporosis to the pathological lesions of rickets, judgment on this aspect must be held in abeyance.

A few lines may be added regarding a clinical condition termed *infantile osteomalacia* which was described at various times by Rehn, the well-known children's specialist. His diagnosis of osteomalacia was supported by v. Recklinghausen but controverted by Ziegler. The cases which Rehn described were those of female infants, mainly in the second year of life, who showed an extreme softening of the long bones, especially of the lower extremities, a softening which was attended by pseudoparalysis and an unusual degree of pain and tenderness. Cases of this description are depicted in some of the older text-books and atlases on rickets, for example that of Spillmann or Wohlauer—infants with greatly deformed and distorted extremities which resemble those of adults suffering from severe osteomalacia. It would seem that these are not merely instances of advanced rickets, but are combined with a nutritional deficiency which is perhaps associated with an endocrine disturbance. In some cases the marked tenderness may have been due to complicating infantile scurvy. The microscopic anatomy of these cases closely resembled the lesions which have been described in a previous chapter as typical of rickets—there is the characteristic overgrowth of cartilage at the epiphyses, as well

as the abnormal amount of osteoid tissue. No chemical study of the blood has been carried out.

Mention has been made of the fact that osteomalacia may be accompanied by lesions of the *parathyroid glands*. Among 6 cases of puerperal osteomalacia reported by Erdheim, hyperplasia or hypertrophy of the parathyroid glands was found in 5; in 1 instance this condition was noted microscopically. Schmorl, Strada and Schlagenhaufer, as well as Lichtwitz have described lesions of these glands in cases of osteomalacia. Strauch encountered some cases which had tumors of the parathyroid and Bull and Harbitz one with an adenoma or sarcoma of the parathyroid. Cases associated with tumors should not be included in the category of ordinary osteomalacia.

The relation of the development of osteomalacia to the function of the ovaries has been discussed in connection with pathogenesis. It should be mentioned in this connection that most authors have failed to find definite histological lesions in the ovaries. Ogata believed that the ovaries were enlarged, were longer and thicker in osteomalacia, and that the changes could be recognized even macroscopically. He made sections of the ovaries in several cases, in order to ascertain the number of follicles, and found them somewhat increased in number. More recently Fraser has described the development of an almost telangiectatic condition of the ovary. Whatever may prove to be the functional relationship of the ovaries to osteomalacia, this association is far too subtle to be explained by gross or even by microscopic anatomical changes.

The accounts of the spontaneous development of osteomalacia *among domestic and wild animals*, which have been maintained in captivity, are of little value in solving this problem. None of these studies is supported by sufficient pathological data to render it certain that the disease of the bones was true osteomalacia. Maxwell records an instance of a goat which developed bowing of the legs. Similar instances have been reported among cows, horses, sheep, etc., in the southern states of this country. An epidemic of osteomalacia was reported a few years ago by Reisinger among the cattle of lower Austria. White has published recently an interesting paper on osteomalacia among the birds and mammals, mostly monkeys, in the zoölogical park of Philadelphia. All of these reports are open to the same criticism, namely, that the histological data are insufficient to exclude bone disorders which, although similar, are essentially different.

THE METABOLISM OF OSTEOMALACIA.

As the metabolism of rickets has been fully considered in a previous chapter, it does not seem necessary to review in detail the

metabolism of osteomalacia. There are, however, several points in which the two disorders show distinct differences, and which lend interest to a consideration of the metabolism of osteomalacia. In the first place, the relationship of calcium and phosphorus to the two disorders is very different, as has been referred to several times. Furthermore, the marked frequency with which osteomalacia is associated with puberty and pregnancy brings into play factors which are not pertinent to rickets. The fact that osteomalacia is so often accompanied by clinical evidences of tetany also calls for special discussion from a metabolic point of view.

Normal bone is composed of about two-thirds inorganic and one-third organic matter. The bones of osteomalacia show a decided difference in this ratio. Many of the analyses date back a number of years, but all are in agreement that the inorganic salts are markedly decreased. Huppert's figures gave the inorganic constituents as forming about 25 per cent, and Durham's about 45 per cent of the bone; the organic matter was found to be proportionately increased. In a case of adolescent osteomalacia, McCrudden found 28.02 per cent of inorganic matter in dried bone as compared to 48.54 per cent in an analysis of normal bone. When we come to a consideration of the salts which constitute the inorganic material, we find that calcium is particularly deficient. In this case of McCrudden the calcium was little more than half the normal—15.44 per cent of calcium oxide in the dried bone compared to 28.85 in a normal case. *The total ash of the bones is diminished and there is a definite relative decrease of calcium.* This relative deficiency of calcium, if it can be accepted, is a matter of importance in considering the essential nature of osteomalacia. The phosphorus content is also low, but not as low as calcium; it is, approximately, two-thirds of the normal rather than one-half. For example, in McCrudden's case, 12.01 per cent of phosphorus pentoxide was found in the dried bone compared to 19.55 per cent in a similar normal bone. McCrudden states that "the ratio P_2O_5: CaO in the bone in osteomalacia is greater than the normal ratio."

The amount of magnesium was excessive, the normal figure being 0.14, whereas 0.57 per cent was obtained from the dried bone in osteomalacia. Huppert and others are in accord in regard to the increased magnesium. A disproportion of this kind in the amounts of the inorganic salts in the bone—the calcium being greatly diminished, the phosphorus but slightly diminished and the magnesium increased—constitutes strong evidence against the interpretation that osteomalacia is a simple halisteresis, a mere dissolution of bone such as takes place when it is subjected to the action of an acid. The sulphur content was found also to be greater than normal, as was to be expected in view of the fact that the organic matter, which is rich in sulphur, is increased. In McCrudden's case the

sulphur was four-fold the normal, a figure which would indicate a marked laying down of new tissue.

Studies of the *mineral exchange* in osteomalacia are very few and, as may be imagined, most of them were carried out many years ago. In reviewing them we encounter the same defects referred to in connection with metabolic investigations of rickets. The contradictory character of the results is such as to indicate clearly either that the disorders which were studied were not one and the same, or that different stages were under consideration. As stated in discussing rickets, healing has been found, both histologically and radiographically, to take place not only intermittently but even concurrently with the advance of lesions. Probably this holds true also for osteomalacia; some of the metabolic investigations were conducted while the disease was no longer advancing, or while healing and calcification were temporarily in progress. Some, on the other hand, were carried out at such an advanced stage that the tissues could not be expected to part with their scanty store of inorganic salts. Moreover, until recently, little regard was paid in these metabolic tests to the nature of the dietary, and of course none whatsoever to its adequacy in the fat-soluble and the antirachitic factors, both of which we now realize exert an important influence on calcium retention. Furthermore, the question of sunlight and of season was not considered by the early investigators. There are two investigations which stand out in relief both as to their chemical methods and the control of incidental factors—that of McCrudden carried out on an unmarried adolescent, and the still more recent study of Maxwell and Miles on a series of Chinese women suffering from puerperal osteomalacia.

The most constant metabolic phenomenon is a net loss of *calcium*. In a summary of 8 cases tabulated by McCrudden, a loss is shown in every instance. It should be mentioned, however, that reports are not lacking in which the calcium balance was positive, for example, some of the cases of Neumann, 1 of Huchison and Stapleton, 1 of the 4 studied by Maxwell and Miles. Of 12 cases compiled by Korenchevsky, the calcium balance was negative in 8, variable in 1 and positive in 4. Although these positive balances cannot be dismissed lightly, it would seem that in a disorder such as osteomalacia a loss of calcium must be taking place most of the time, and that a positive balance represents but a temporary phase and one not characteristic of the disorder. Attention should be called to the fact that in the course of osteomalacia the formation of urinary calculi, composed of calcium, has been reported by several writers. This is an indication of an excessive excretion of calcium by way of the urinary tract.

The phosphorus balance is generally positive. Just as it has been found that the bones showed a relative retention of phosphorus, so

the majority of metabolism tests indicate a retention rather than a loss. It should be mentioned, however, that the data in respect to phosphorus are much more variable than those relating to calcium.

McCrudden and his collaborators found that, corresponding to the increased content of *magnesium* in the bone, there was a net retention of magnesium. He believed that a replacement of calcium phosphate by magnesium phosphate takes place, that "new bone is being laid down but is poor in calcium phosphate and richer in organic matter and magnesium phosphate."

There is likewise a retention of sulphur and of nitrogen in osteomalacia. In general the parallelism is remarkably close between the analyses of the dead bone and the results of studies of intake and output during life.

TABLE 23.—CALCIUM AND INORGANIC PHOSPHORUS IN THE BLOOD OF WOMEN SUFFERING FROM OSTEOMALACIA.[1]

Patient No.	Age (yrs.).	Duration of disease (yrs.).	No. of pregnancies.	Relation of onset of disease to pregnancy.	Tetany.	Blood calcium (serum). Mg.	Blood phosphorus (plasma). Mg.
1 . .	23	5	0	None	No	5.2	2.5
2 . .	57	10	0	None	Yes	6.0	1.9
3 . .	30	⅔	2	During last lactation	Yes	7.4	1.8
4 . .	34	20	5	Began before first pregnancy at onset of menstruation	Yes	5.6	2.3
5 . .	32	12	2	After first delivery	No	5.8	3.0
6 . .	35	1	5	During last lactation	Yes	7.0	3.8
7 . .	25	7	3	During first lactation	No	5.8	3.4
8 . .	19	1	1	During lactation, pregnant 3 mos. on admission	Yes	7.0	2.4
9 . ..	37	9	2	None; both abortions	Yes	5.0	2.0
10 . .	24	6	3	During first lactation	Yes	5.4	3.2

[1] Combined table from Miles and Feng, Jour. Exp. Med., 1925, **41**, 137. Tetany refers solely to manifest tetany.

There have been numerous estimations of the calcium content of the blood in osteomalacia. The only investigation of this kind, however, which has been carried out with modern methods and which can be accepted is that published in 1925 by Miles and Feng. This study is of such interest and importance that we have summarized it in the accompanying table (Table 23). This summary includes estimations of the inorganic phosphorus of the blood and data in regard to tetany, etc. The salient fact to be deduced from this investigation is that, in general, *osteomalacia must be regarded as characterized by a deficiency of calcium in the blood.* The calcium is diminished in every case, falling to about 50 per cent of the nor-

mal in several instances. In 7 of the 10 cases, tetany is noted.[1] The percentage of inorganic phosphorus varies; in some cases it is diminished, but in the majority it is at about the normal level.

Will more extensive studies confirm these results, or will they show that osteomalacia may at times be associated with a normal calcium concentration and a diminution of inorganic phosphorus in the blood? If such proves to be the case, it will bring osteomalacia into harmony, from a pathogenetic point of view, with infantile rickets, which, as has been shown, may be characterized either by a low concentration of phosphorus or of calcium. Possibly the diminution of calcium observed in all of these cases was due to peculiarities in the dietary of the Chinese women, and that where the diet is markedly lacking in phosphorus we shall encounter a deficiency of inorganic phosphorus similar to that which characterizes infantile rickets. Such a result would greatly simplify the interpretation of the pathogenesis of osteomalacia and its relation to rickets. However, in view of the association of tetany with osteomalacia, whether occurring in China, Japan, India, Bosnia or Europe, the loss of calcium would seem to be an integral part of this disorder. The fact that no observer in these countries refers to infantile tetany or to convulsions in infants leads one to infer that the low calcium type of rickets is not exceptionally frequent. Such an omission hardly can be ascribed to oversight, as almost all writers on osteomalacia consider and comment upon the occurrence of rickets.

Analyses of the bones of fetuses of osteomalacic mothers have been reported recently by the investigators of the Peking Medical School. In 1923, Maxwell published the analyses of 3 dead fetuses which had been removed by Cæsarean section from women suffering from marked osteomalacia. His conclusions were as follows: "It will be noted at once that the proportions of the salts to one another are unaffected as regards calcium and phosphorus, but the difference in the ash per thousand is very marked and one may safely say that there is a definite calcium and phosphorus deficiency, as compared with the normal bone." The ash of the normal femora was, respectively, 139.60, 136.27, 145.68 and 106.79 parts per 1000, whereas that of the femora from osteomalacic mothers was 87.89 and 86.35. The data of an analysis of a premature infant have been omitted. No length measurements of these fetuses are given, so that we cannot be certain that they all were of the same age. A second series of analyses was published in 1925. This comprises chemical determinations of the bones of 3 full-term normal and 3 full-

[1] Miles and Feng remark: "While most of the patients had symptoms first during lactation, 2 of them had never been pregnant, in 1, the symptoms coming on after the menopause; while another had had two early abortions before the fetus could have caused a severe calcium drain; and in yet another, the disease began at the onset of the menstrual function. The menstrual flow in these patients was uniformly scanty and the cycle irregular."

term osteomalacic fetuses. These data are by no means as convincing as those in the first report; indeed, judged by themselves they would warrant no deduction. The authors, Maxwell and Miles, fully recognizing the unconvincing nature of the figures which they present, suggest that the irregularities may be due to the fact that the osteomalacia was not active in all of the cases.

THE SYMPTOMS OF OSTEOMALACIA.

The onset is generally insidious, the first symptoms consisting of indefinite pain in the lower part of the back or in the groins. So characteristic is this symptom that in China the disease is popularly known as the "back and thigh pains." The pain is described as of an aching character, varying greatly from day to day, but usually intensified during the winter months. In some cases the onset is more acute and, according to several observers, is ushered in with fever of varying degree; it is such cases which have suggested an infective origin.[1] *The distinctive symptom of osteomalacia is pain.* This is all the more striking when we consider that pain is absent in infantile rickets; in fact, the absence of pain or tenderness differentiates rickets from infantile scurvy. Pain seems also to be decidedly less common in late rickets than in osteomalacia. It is difficult to explain this difference; but osteomalacia has a tendency to involve the nervous system as indicated by the frequent occurrence of tetany. The pain tends to become more severe as pregnancy advances, in many cases entirely incapacitating the woman. After delivery there is often a definite remission. Maxwell gives a typical history in the following words: "First pregnancy, normal. Second pregnancy, pain during last few months, normal labor. Third pregnancy, pain beginning early in pregnancy, say about the third month. Labor difficult, needing forceps or even craniotomy. Fourth pregnancy, pain as already described but more severe; a difficult craniotomy or a Cæsarean section needed. Birth of a living child, *per vias naturales*, not possible. But the disease may appear in the first pregnancy and progress so fast that the Cæsarean section may be necessary at the time of the first labor; . . . As a rule, the disease flares up after lactation is complete, or even before this time, and may recur again and again; but some of the victims seem to have symptoms for many years, and in a minority the disease begins and steadily progresses, making the patients bedridden invalids, until they die of asthenia or some intercurrent affection."

[1] The observation that numerous members of the same family may be attacked by osteomalacia has also led some to believe that it is infectious in nature. Posselt describes 4 cases developing among sisters, and Oppenheim reports 24 cases of a family nature, of which 21 came from North Tyrol.

In addition to sensory symptoms there are definite motor disturbances which appear in the early stages of the disorder. One of the common complaints is difficulty in rising and in walking. The mode of rising from a squatting posture is often characteristic and is very similar to that which is so well-known and has been so frequently illustrated in connection with the hereditary muscular dystrophies—the woman climbs up laboriously upon her knees and thighs. The difficulty in walking tends to increase as pregnancy advances, and

FIG. 46.—Severe osteomalacia. (Courtesy of Dr. R. T. Frank.)

frequently results in a total inability to walk. The picture which Krajenska draws of the Mohammedan women in Bosnia is most pitiful. Muscular weakness becomes so great and the pain on movement so intense, that in the later stages the women spend their days and nights curled up on the floor or in bed unable or unwilling to make the slightest movement (Fig. 46).

Such is the picture of the extreme case. As a rule the weakness and discomfort lead only to a marked disturbance in gait which is

stated to be typical and "of great diagnostic importance—once seen it is not easily forgotten. The patient moves slowly and cautiously, as if to avoid pain; the feet are kept wide apart and raised but slightly from the ground. This leads to the characteristic waddling. This picture is rendered all the more characteristic by the undue prominence of the buttocks due to the marked lordosis."

As in rickets the part most affected is *the skeleton*. Although the bones of the extremities are by no means spared, those of the trunk are mainly altered—the sternum, the vertebral column, the ribs and the pelvis. The signs in the pelvis are most marked, most characteristic, and clinically most important. The extent of the deformity of the pelvis depends naturally on the degree of softening. In the early stages the pelvis is flattened due to the forcing downward and forward of the promontory of the sacrum leading to a diminution of the normal antero-posterior diameter.

The sacrum is thrown back somewhat, its inner concavity is increased, and the coccyx is generally bent forward.[1] Scott states that the typical Y-shaped pelvis observed in Europe does not develop owing to the fact that the Indian women generally maintain a sitting posture, but that the pelvis becomes more irregular and crumpled. The typical beaking of the pubes is nearly always present. The outlet of the pelvis is greatly narrowed in its anterior portion, and in advanced cases the pubic arch is obliterated. The ischial tuberosities are pressed together, thus tending to narrow the outlet. It is evident that bony deformities of this character and degree must lead to serious difficulties in child-birth, both for the mother and child. As stated, the maternal mortality in China in a district where osteomalacia is rife reaches the astounding figure of 2 to 3 per cent. In a general way it can be stated that where operative intervention—Cæsarean section, craniotomy, etc.—has to be resorted to in a large percentage of cases, osteomalacia is present in high degree, and conversely, that where child-birth takes place normally, neither osteomalacia nor rickets can be excessively frequent.[2]

Although the long bones are not affected to the same degree as in rickets, they are rarely spared. There are the usual curvatures, the bow-legs or knock-knees, the bones of the legs being the seat of lesions far more often and in greater degree than those of the arms. Fractures are common and, as in infantile rickets, their presence may

[1] Ogata, who has described an epidemic of osteomalacia in Japan, stated that he has never found the typical flat pelvis in children under six or seven years of age. He ascribes this to the fact that whereas in Europe the children are kept on their backs previous to walking, in Japan, especially in the district which was investigated, they sit in straw baskets or are carried on the back in a sitting posture.

[2] Maxwell states that chloroform is very dangerous in these cases and that ether should be used, preceded by an injection of atropine but not morphine. Mellanby drew attention to the fact that ether narcosis was liable to lead to the death of puppies in which experimental rickets has been induced. Rats suffering from experimental rickets die readily under ether narcosis.

remain unsuspected until revealed by a casual radiograph. Enlargement of the epiphyses occurs, but is not a notable sign, as would be expected considering that osteomalacia is a disease of adult life, a period when the epiphyses are generally united. Beading of the ribs is more common than enlargement of the epiphyses of the long bones, and often is associated with tenderness. Coxa vara may occur. It is of interest that all authors are in agreement that caries of the teeth is not one of the signs of osteomalacia. That such is the case is a cogent argument in favor of the view that teeth which are fully developed and erupted are not readily depleted of their inorganic salts, for if any pathological condition should bring this about, it would be osteomalacia. Although the teeth themselves do not suffer, they frequently loosen and fall out.

It is an old observation, noted by Dance about one hundred years ago, that *tetany* often accompanies osteomalacia. About twenty years ago Weber, as well as Hecker, reported experiences in Germany, confirming the close association of these two clinical conditions. Trousseau met with osteomalacia so commonly among nursing women in Paris that he proposed the name "rheumatic contracture of lactating women" for this disorder. In passing, it may be noted, as an indication of how the geographical distribution of diseases shifts from period to period, that both tetany and osteomalacia are now uncommonly rare in Paris. In calling attention to the high incidence of osteomalacia in India, Scott remarked on the frequency of tetany. Huchison and Stapleton report that one-fifth of their cases of late rickets showed signs of tetany, and one-third of the cases of osteomalacia. A paper published by Stapleton in the following year states that 30 among 63 patients had definite tetany or attacks of cramps in the hands and sometimes in the feet. The investigations from China are in general agreement with these reports from India. Maxwell goes so far as to state that practically all the patients had tetany at one time or another. He found that many complained of some numbness of the extremities preceding the tetany, in others the typical signs followed prolonged spasms. Miles, whose cases are drawn from the same district in China, observed tetany in 7 out of 10 instances. Januszewska noted tetany in Bosnia in 338 of the 3510 patients who suffered from osteomalacia.

The reason why so large a proportion of cases of osteomalacia have *tetany* lies in the fact that osteomalacia generally is accompanied by a diminished concentration of calcium in the blood. (The various types of tetany, as well as its signs and symptoms, will be discussed in the subsequent chapter.) Whatever may be the interpretation as to the significance of this lowered calcium, there is a rare unanimity of opinion among both clinicians and laboratory workers, as to its constant association with tetany. Such

being the case, the great frequency of tetany in osteomalacia acquires an important nosological significance, indicating that this disorder is the counterpart of the type of rickets which is characterized by a low percentage of calcium, rather than by a low percentage of phosphorus. In this respect, it is just the opposite of ordinary infantile rickets, which almost always is associated with a low concentration of inorganic phosphorus in the blood, and in which the occurrence of tetany and lowered calcium is exceptional. It is impossible at present to interpret satisfactorily this distinction between infantile rickets and osteomalacia; various hypotheses might be suggested. The most plausible seems to be the action of the gonads or other glands of internal secretion.

The position of Vienna in regard to tetany and osteomalacia requires particular mention. As stated, many observers have commented upon the fact that osteomalacia occurs with exceptional frequency in Vienna. It may be added that the same holds true in regard to the incidence of tetany. The great authority on this disorder, Frankl-Hochwart, collected a series of 576 cases observed in Vienna. The tetany of adults has a characteristic seasonal incidence; like osteomalacia and "hunger osteomalacia" it occurs most often in March, the cases becoming steadily fewer until they reach the lowest ebb in mid-summer. It will be remembered that this is essentially the curve-incidence of rickets, and it may be added, it is identical with the seasonal distribution of infantile tetany. But, reverting to the experience of Frankl-Hochwart, we find that "almost only men, and relatively seldom women" developed tetany, a characteristic which he states held true not only for the clinic at Vienna, but elsewhere. Shoemakers and tailors developed the disorder most often, so that it was frequently dubbed "shoemaker's cramp." In view of the fact that osteomalacia, accompanied or unaccompanied by tetany, has been found everywhere and by everyone to involve almost exclusively women, it is difficult to interpret this susceptibility of males to tetany. Evidently the fundamental factor in osteomalacia and tetany cannot be a simple lack of calcium. That most of the cases of osteomalacia are associated with pregnancy no doubt accounts for the marked difference in incidence between males and females.

A peculiar *psychic state* frequently develops in osteomalacia as the result of the extreme tenderness and the fear of being disturbed. The gentlest touch brings about muscular contraction and causes the patients to scream and beg to be left in peace. This overwrought condition was termed by Trousseau and Lasègue "susceptibilité nerveuse."

There are practically no symptoms referable to the internal organs. Although the patients are usually thin, their digestion seems to be unaffected. Scott states this to be true likewise of the respiratory

system, except in cases in which deformity of the thorax leads to bronchitis and cough. On the other hand, Masueger writes that although osteomalacia involves the intestinal tract rarely, it involves the respiratory tract frequently. If such be the case, it constitutes another clinical link between osteomalacia and infantile rickets. Scott states that "menstruation was normal and regular in all the cases" which she examined. It has been stated that fertility is above the average, but this phenomenon may be merely apparent, due to the fact that those women who have most children are rendered more susceptible to osteomalacia.

The radiographic changes require but little comment, as they resemble those noted in rickets, especially in late rickets. The main difference is that in many of the patients the epiphyses have already united, so that we miss the widened epiphyseal area which is so characteristic of rickets. There is the same thinning of the walls of the diaphysis, the coarsened pattern of the cancellous tissue at the end of the shaft, and the typical cupping. In early cases the diagnosis is difficult to establish by means of the Roentgen rays. There may be marked osteoporosis and fracture. Looser emphasizes the value of noting the changes in the bones of the hand. He also draws attention to the "light areas" (Aufhellungs-zone) to be noted traversing the shafts of the long bones, corresponding to the formation of calluses which have developed at the sites of incomplete fractures. Maxwell describes a mottled appearance, stating that "there are distinct resemblances between this mottling, and what is seen in "Paget's disease" (osteitis deformans).

THE DIAGNOSIS OF OSTEOMALACIA.

In a district where osteomalacia is known to be endemic, the diagnosis does not present any difficulty. A sporadic case, however, if not associated with pregnancy, may readily lead to error. The commonest mistake is to consider the condition chronic rheumatism. There is little doubt that the great esteem with which at one time cod-liver oil was regarded for the treatment of rheumatism was due to a confusion between these two disorders. It seems unnecessary to go into detail regarding the differential diagnosis between osteomalacia and chronic rheumatism—the lack of involvement of the joints, the deformities of the vertebral column, of the pelvis and the lower extremities, the roentgenographic picture, the lowered calcium concentration in the serum should enable a differentiation to be made readily. Osteomalacia has been diagnosed as gout. Another error is to regard it as a neuritis, especially as sciatica. A careful localization of the site of the pain, whether along the nerve trunk or in the bones, should prevent the occurrence of this mistake. A lesion of the cord has been diagnosed—myelitis, tabes dorsalis, or

other syphilitic affection. The general picture, more especially the exaggerated degree of sensitiveness and the psychical condition associated with this state, has led to the diagnosis of hysteria. Finally osteomyelitis should be mentioned. In India this pathological condition is mistaken for osteomalacia; on the other hand, in Europe where osteomalacia occurs sporadically and rarely it is apt to be regarded as osteomyelitis. In general it may be stated that if the possibility of osteomalacia is borne in mind, a careful physical examination, fortified by laboratory tests of the blood, should render the diagnosis clear. There is no doubt, however, that what applies to nutritional disorders in general, holds true for osteomalacia, namely, that the mild cases are frequently overlooked or regarded and treated as an indefinite form of one of the common ailments.

THE RELATION OF RICKETS TO OSTEOMALACIA.

This subject has been considered from an etiological, pathological and chemical point of view, but should be regarded also from the clinical standpoint. One would imagine that valuable information could be gleaned from a study of the incidence of rickets in districts where osteomalacia is endemic. As a matter of fact, this field has not proved fruitful. An investigation of the data emanating from China, India and Bosnia, where osteomalacia is still very prevalent in certain large districts, fails to add much of significience to the solution of this important aspect of the rickets problem. In 1880 Huntly, "with Cheadle's dictum regarding diet fresh in his mind," published the first paper on rickets *in India* and reported that his search for rickets had been fruitless. In view of the defective dietary of the natives, he drew the interesting deduction that diet could not be the main etiological factor of rickets, or at any rate that it was counterbalanced by the abundance of sunlight with which the people were surrounded. Scott, writing some years later, stated that she "saw only one case of undoubted rickets." On the other hand, Huchison and Shah carrying out a house to house inquiry for rickets in 1920 found a large number of severe cases. They attributed the wide-spread belief that rickets is an uncommon disorder in India to the fact that the mothers of the well-to-do and the rich—in which social strata rickets is most prevalent—do not bring their children to the hospital. Among some 1000 children of well-to-do parentage, whose mothers observed purdah, they found about 25 per cent with definite signs of rickets, and among some 2300 children of the lower-caste Hindus about 5 per cent. The discrepancy between this report and the earlier reports of Huntly and of Scott shows the caution which must be exercised in accepting data in regard to geographical distribution of disease, especially statements to the effect that a disease is rare or

non-existent in a country. Probably Huntly was correct in stating that he did not encounter any cases of rickets, but the failure was due to his limiting his examinations to the children of the poor, among whom rickets is notably infrequent in India.

TABLE 24[1].—INCIDENCE OF RICKETS IN INDIAN (NASIK) FAMILIES.

All Mohammedans } Well-to-do Hindus }	purdah	399	138	34.0
Poor Hindus		260	17	6.4
All well-to-do		326	120	36.7
All poor		333	35	9.5

There is only one record of an investigation of both osteomalacia and rickets in the same district. In their study in the city of Bombay, Huchison and Patel found about 5 per cent of osteomalacia among the well-to-do Mohammedans, and about 1 per cent among the Hindus. In this paper they state "severe rickets with bony deformities is a comparatively rare condition in Bombay." Soon after making this survey Huchison, in conjunction with Shah, conducted an investigation of rickets in Nasik, a district about 100 miles distant from Bombay. The data of this study are reproduced in the accompanying table (Table 24). We note the same high incidence of rickets among Mohammedans compared to Hindus, and among the well-to-do compared to the poor as was evidenced in regard to osteomalacia, showing that caste and social conditions exert their effect on the infant as well as on the adult. The percentage of rickets recorded probably errs on the side of being too low. It must be remembered "that in all cases breast-feeding is practically universal. It is usually supplemented with other food about the seventh or eighth month, with cow's milk among the well-to-do, and rice among the poorer classes." A peculiar custom of the people is that "a newly-born child is not taken out of the house as a rule for the first six months of life. We see, therefore, that the infant has the advantage of breast-feeding and the disadvantage of a lack of sunlight." The inherent difficulty in judging of the occurrence of rickets in the children of India, where radiographic examination of the bones or chemical determinations of the blood cannot be carried out, is further emphasized by the statement of Huchison and Shah that beading of the ribs was found in 68.7 per cent of the children examined, but that they could make no use of the costal rosary as a diagnostic sign because it seemed evident that "the prevailing complaint among the poorer classes is scorbutic in character." In view of the occurrence of marked beading in these atrophic infants, of the prevalence of swollen and bleeding gums, and of the low consumption of vegetables among all classes of the

[1] Huchison, H. S., and Shah, S. J., The Etiology of Rickets, Early and Late, Quart. Jour. Med., 1922, **15**, 167.

population, this difficulty can be realized. However, if we are deprived of this valuable clinical sign, our difficulties in judging of rickets become greatly enhanced. The most common indication of rickets was enlargement of the epiphyses. The so-called "Chvostek sign" or "facial phenomenon," although found very frequently in adults and in 50 per cent of the children ten years of age and 25 per cent of those between the ages of six and seven years, "curiously enough was not found in children under four years of age." This observation is of interest in view of the fact that this sign generally accompanies the tetany of osteomalacia, and is associated with a diminished percentage of calcium in the bones and in the blood. Does this absence of the "facial phenomenon" indicate that the rickets was of the low phosphorus variety which is the common type throughout Europe and America? It would be most interesting to obtain chemical data to elucidate this point, for it would inform us as to whether we can have simultaneously and side by side, among the same group of people, osteomalacia associated with a diminution of calcium, and infantile rickets associated with a diminution of inorganic phosphorus.

Viewing these clinical reports from India as a whole, it would seem that there is not the close interdependence between osteomalacia in the mother and rickets in the offspring which we should expect if the prenatal factor is of prime importance in the etiology of rickets. Were such the case, these districts in India should be preëminent for the high incidence and marked severity of infantile rickets.[1]

The reports from *China* supply little of clinical value, either for or against the rôle of osteomalacia in the incidence of infantile rickets. Mention has been made of the chemical analyses of the bones of fetuses of osteomalacic mothers. Roentgenographic studies have also been made of such fetuses. Maxwell writes: "Three dead fetuses removed by Cæsarean section from cases of marked osteomalacia have been examined and also 4 fetuses apparently normal in every way, as controls; 2 of the 3 from cases of osteomalacia were at full-term, the third at about seven and a half months. Roentgenograms show that the proper centers of ossification are present and the appearance of the bones is that of a normal fetus." "At the same time a fetus removed by Cæsarean section from a very marked case of osteomalacia and still living showed at the age of one month certain changes in the ends of the femora." This consisted of flattening of the epiphyseal ends of the bones. In general he believes that these bones are more transparent than normal. In his 1925

[1] Huchison and Shah state that "carious teeth are very uncommon among the children and that in no case did I find the mouthful of carious teeth so often seen at home." "The teeth in the most marked rachitic cases were nearly always in excellent condition." This observation constitutes a striking argument against the frequent statement that caries of the teeth in children is brought about by a deficiency during intra-uterine life of the same dietetic factors which induce rickets.

report with Miles, he states "2 out of 3 of the fetuses, however, from mothers with active osteomalacia showed curious changes about the ends of some of the bones, especially the ulna, the main change being an apparent cupping of the end of the bone, which at once suggested the possibility of this cupping being rickety in nature." The illustrations which accompany the text are not convincing and suggest changes similar to those which were reported by Hess and Weinstock in the course of a routine examination of the epiphyses of some 500 new-born infants. It should be added, however, that the failure to demonstrate rickets radiologically cannot be regarded as tantamount to an absence of rickets, for the typical rachitic changes may not become evident in the epiphyses of the fetus, and the sole indication may be a marked degree of osteoporosis.[1]

In his second report, Ogata gives figures to show that rickets was rife in children under five years of age in the district of *Japan* where he found osteomalacia to be endemic. He does not state its incidence, but the illustrations of infantile rickets represent the most severe type of the disorder, the type which has been termed "osteomalacic rickets." In my opinion the photographs of these horribly deformed children constitute presumptive evidence that osteomalacia in the mother intensifies rickets in the offspring. On the other hand, data of this kind are controverted by the experience of an observer such as Januszewska, who in the course of ten years' practice in Bosnia saw 3510 cases of osteomalacia among 20,232 patients, and specifically states: "Infantile rickets does not occur more or less frequently here than elsewhere, and to the same extent among the children of osteomalacic as among normal mothers." It is evident that until further data are available, judgment must be suspended as to the degree and extent of the influence exercised by osteomalacia on the development of rickets in the infant.

"WAR OSTEOPATHY" OR "HUNGER OSTEOMALACIA."

As mentioned in considering late rickets, a nutritional disorder which was generally termed "war osteopathy" or "hunger osteomalacia" made its appearance among the peoples of "Central Europe" shortly after the cessation of the World War. It was of common occurrence in Austria, especially in Vienna, as well as in Germany and in Poland. This disorder was characterized by pains, especially in the back and to a less degree in the groins and legs, by a somewhat characteristic waddling gait, by difficulty in climbing stairs and a

[1] In 1927 Dr. F. J. Wampler, who has had a large experience in China with osteomalacia wrote me: "The offspring of osteomalacic women appear to be remarkably free from rickets" and that "rickets is not marked in the section of China where osteomalacia is prominent. There is some rickets but always very mild and the children of these women seem to be no more subject to it than the children of healthy mothers."

slight degree of tenderness of the bones, especially of the vertebrae, which made it simulate spondylitis. From this cursory outline it is evident that "war osteopathy" resembled the mild form of osteomalacia. In sex and age incidence it was most peculiar (Fig. 47). In Vienna adolescent males were particularly attacked—those between the ages of fourteen and twenty years; it is stated that two to four times as many males of this age-period were affected as females. Strange to state, however, the female sex largely preponderated among the adults who developed this disorder. Beninde, who studied the course of this endemic as it appeared in various parts of Germany, reports a similar age and sex distribution. He states that children aged six to fourteen years, were absolutely spared, but

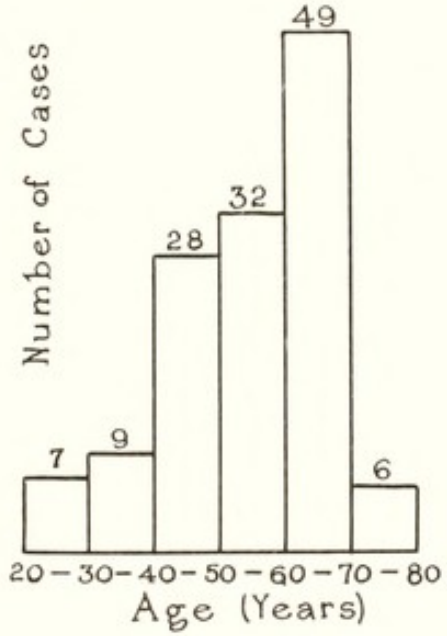

FIG. 47.—Age-incidence of 131 cases of "hunger osteomalacia" in Vienna. (Hume and Nierenstein, Report Med. Res. Council, London, 1923.)

that there was a marked susceptibility of adolescents, mainly boys and young men aged fourteen to nineteen years, almost no cases occurring between the ages of twenty and thirty-five, whereas there was *a high incidence during the period from forty to sixty years, confined almost entirely to women.* Although pregnancy and the puerperium tended to increase and intensify the disorder, the incidence was not strikingly marked among women in this condition, in contradistinction to what has been noted so often in regard to osteomalacia. This distinction may have been due to the fact that pregnant and lactating women were allowed an extra quota of rations. Among 131 cases of hunger osteomalacia seen between February and July, 1920, and summarized in the report of the Medical Research Council's "Studies of Rickets in

Vienna 1919-1922," 109 occurred between the ages of forty and seventy years. *Tetany was frequently associated with this disorder.*

Such in outline is a description of the nutritional state which resulted from the long period of malnutrition incident to the war. Some are of the opinion that this disorder should be considered ordinary osteomalacia, and that the appellations "war osteopathy" and "hunger osteomalacia" are misnomers. Unfortunately, pathological reports of these cases are few and furnish insufficient evidence on which to form a judgment. Moreover, the same moot question arises again, more urgently in this connection than in any other, as to the relation of osteoporosis to osteomalacia and rickets. Special importance should be attached to the necropsy reports of Partsch, as they emanated from the laboratory of Schmorl who controlled the microscopic examinations. In the course of two months, among a total of 212 necropsies, 15 instances of this bone disorder were noted at the pathological institute in Dresden. Eleven were women and 4 men, the only case under sixty years of age being a male. They all were marasmic, none had deformities of the extremities or enlarged epiphyses, and in none was the skull involved. The significance of this report lies in the fact that Partsch and Schmorl regard the histological lesions as those of true osteomalacia, and not as a new nutritional disorder of the osseous system. Indeed, Partsch states that cases of this kind had been observed for years at this pathological laboratory; that in 1904 there were 6 among 332 necropsies, in 1905, 7 among 345, and that the only point worthy of note was the remarkable increase in the occurrence of osteomalacia during the post-war period. The distinctive histological feature was the extreme degree of osteoporosis.

In rickets the ratio of calcium to phosphorus is normal in the ash of the bones. In osteomalacia, as noted, the calcium is claimed by some to be relatively decreased. The only analyses of the bones in "hunger osteomalacia" were carried out in the investigation of Loll of 4 marked cases of this disorder, in which he analyzed the ribs, pelves and tibiæ. In addition to a general decrease in the total ash, which was to be expected, he found a relative increase of calcium and a relative decrease of phosphorus. If confirmed, such relationship would distinguish this pathological condition from rickets and osteomalacia.

It is evident that there is a very close resemblance between "war osteopathy" or "hunger osteomalacia" and the classic osteomalacia, and it would seem of advantage to class them as one and the same disorder. In general, clinical phenomena and histological appearances will differ somewhat according to the nature of the nutritional and hygienic deficiencies. The diet in the various countries of "Central Europe" during this period was defective in

many particulars and in this respect varied in different localities. In Germany the dietary was almost wholly lacking in meat, eggs and milk, but was unusually ample in green vegetables; in fact it consisted largely of root vegetables and bread. The lack of food of adequate calorific value no doubt also played a part. These explanations are, however, not entirely satisfactory. All observers agree that none of the Indian famines has been followed by epidemics of osteomalacia, although the severity of the privation has been much greater than that which existed in Vienna after the war. The important factor seems to be the duration, rather than the intensity, of the nutritional castastrophe.

THE TREATMENT OF OSTEOMALACIA.

The *therapeutic agents* which are specific for infantile rickets have been found to be specific also for osteomalacia, namely, cod-liver oil, irradiated ergosterol and ultra-violet irradiation. In Schuette's original communication on cod-liver oil, published in 1824 and entitled "Observations on the Value of Bergen Cod-liver Oil," the very first case which is cited is entitled "Rheumatism with Paralysis of the Lower Extremities," and evidently is a case of osteomalacia or "malacosteon," as it was termed at that time, and not chronic rheumatism. The account, translated from the German, is as follows:

The wife of the iron manufacturer, Peter Wiebel . . . suffered during the years of 1799 and 1800 from chronic rheumatism, and as a result of pain in the hips, lost the use of her lower extremities. All known medications against this disorder were employed by the physicians in order to restore the function of her limbs, but without any perceptible effect. Her husband, who in the course of his business had to travel a great deal, brought from abroad cod-liver oil which was only known to the tanners, and which he had been assured was the very best medicine for gout and rheumatism. It was accordingly tried in this case, and after being used for two weeks, the woman could walk once more, and after four weeks she was completely cured, much to her joy and to that of her friends. Every morning and evening she took 1 tablespoonful of the oil, and in order to digest it better took immediately thereafter the same amount of bitter brandy or anise. This patient was the first in this vicinity to use cod-liver oil from Bergen as a curative agent.

The good effect of *cod-liver oil* has been noted not only clinically, but has been verified in metabolism experiments on patients in China. Maxwell found a marked benefit in the calcium balance, as well as in the calcium content of the blood, following its use. In these cases there followed, as usual, an increased excretion of calcium in the urine, accompanied by a decreased excretion in the feces. The greatest effect was obtained with cod-liver oil given in combina-

tion with calcium phosphate. In one instance, where 3 grams of calcium phosphate were given without cod-liver oil, the condition grew worse rather than better. It is to be noted that in the course of these metabolism experiments, although the calcium balance was improved, the increase in retention of phosphorus was much less. Maxwell observes that the symptoms of tetany, accompanying the disorder, also rapidly recede and that the pain becomes markedly lessened in intensity. He adds, however, that "the recovery rate is very variable in its rapidity" and that "one sometimes seems to succeed up to a certain point and then one's efforts apparently fail to press the cure to a full recovery." Possibly this failure was due to an insufficient dosage of oil. The dose should be, if possible, 2 to 4 ounces (60 to 120 gm.) daily.

As in rickets, cod-liver oil has been given in combination with elementary phosphorus, and the improvement or cure has been ascribed to the phosphorus rather than to the cod-liver oil in which it was dissolved. There are no results which would lead us to infer that phosphorus is a specific therapeutic agent for osteomalacia, although it may improve the accompanying osteoporosis. Looser reports 3 cases in which he believes that phosphorus was of value, but 1 of these had been castrated and another partially castrated.

Recently Hottinger, Starlinger, as well as others, have reported favorable results from the use of preparations of *irradiated ergosterol*. It would seem that this form of medication should be specially suited to osteomalacia, which may be regarded as a severe type of rickets, and as such should be amenable to activated ergosterol, although refractory to cod-liver oil. It would be well to give comparatively large doses, fifteen or twenty drops of the standard preparation, controlled when possible by chemical estimations of the calcium and inorganic phosphorus content of the blood. Irradiated ergosterol is a specific for osteomalacia. It may fail in the occasional case met with in the temperate zones, which, there is some reason to believe, is often quite a different metabolic disorder.

Heliotherapy should be made use of, and would seem to be especially applicable in countries where the diet cannot be improved nor specific medication given, owing to the social condition of the people. The details of carrying out heliotherapy are similar to those employed in the prevention or cure of infantile rickets and will be described in the chapter on the Treatment of Rickets. There is no record of the systematic employment of sunlight or of artificial irradiation in cases of osteomalacia. Wampler stresses the value of exercise in this disorder which is known in some parts of China as "lazy woman's disease."

Wherever osteomalacia has occurred, there have been one or more defects in the diet, indicating that an improvement of the dietary should form a part of the treatment. It should be rendered ade-

quate in quantity, in its content of calcium and phosphorus, and should, if possible, include eggs and milk. Although a diet of this kind may be prescribed and carried out in isolated cases, it is evident that in a country such as China, where poverty prevails, we cannot at the present time hope to combat osteomalacia by dietary measures. The best that can be done in that country, as well as in India, is to educate the people to appreciate the value of sunlight and of exercise and to recognize that osteomalacia can be prevented if the women are allowed to lead a freer life. In India such a change involves abandoning the purdah system by the Mohammedans and higher caste Hindus, a breach of custom which it will take years to accomplish. Until such a time, it might be practicable to dispense irradiated ergosterol freely at a low price, just as quinine is dispensed in Italy in malarial districts.

Castration, as a routine measure, does not seem to be advisable. However, when the pelvis is contracted so markedly as to constitute a serious obstruction to labor, endangering the life of mother and child, it would seem advisable to tie off the Fallopian tubes, in order to prevent the possibility of further pregnancies.

CHAPTER XIV.

INFANTILE TETANY (SPASMOPHILIA).

Convulsions are such a striking phenomenon that we should hardly expect them to have been overlooked by the earlier physicians. Indeed we find carpopedal spasm, a sign of manifest tetany, described as early as 1699 by Etmuller, Professor of Physics at Leipzig, under the title "Spasmus Extremorum or Morbus Hungarius;" at the same time he referred to convulsions caused by "the breeding of teeth, especially the sharp eye teeth." A century passed before further reference to infantile tetany was made in the literature. In Hamilton's book on diseases of infancy and childhood, published in Edinburgh in 1813, we find a chapter devoted to "Convulsions." Clarke, in 1815, in his "Commentaries of Some of the Most Important Diseases in Children," gives us for the first time a clear account of this disturbance. In connection with symptomatology, we shall take occasion to quote from his vivid description. The name "tetany" was coined in 1852 by Corvisart, the distinguished French clinician. Associated with a fuller understanding of this clinical condition are the names of Trousseau, Rilliet and Barthez in France. Recent advances are due largely to the studies of Viennese investigators, to Frankl-Hochwart in the field of adult tetany, to Escherich and to Kassowitz in the elucidation of the clinical aspects of infantile tetany, and to Erdheim and his assistants in the realm of experimental pathology. Escherich made a vain attempt to introduce the term "rachitic tetany," but finally accepted the more popular appellation of "infantile tetany."

In considering tetany we shall confine ourselves more especially to infantile tetany, the so-called idiopathic tetany of infants, as our interest is primarily in its association with rickets, essentially a disorder of infancy. This form of tetany or spasmophilia may be defined as a condition of disordered nutrition which induces hyperirritability of the nervous system, that is manifested by galvanic and mechanical hyperexcitability and a tendency to clonic and tonic spasms and general convulsions. From a clinical point of view, it has been well subdivided into a latent and a manifest form. The former presents no apparent symptoms but must be elicited by artificial excitation of the peripheral nerves, whereas the latter gives rise to tonic states, for example the typical carpopedal spasm, as well as to general clonic convulsions.

THE SYMPTOMATOLOGY OF TETANY.

Latent Tetany.—The most significant advance of recent years in connection with clinical tetany is the realization that this disorder occurs frequently, in fact generally, in a latent form. This is true of other nutritional disorders—for example, infantile rickets, scurvy and beriberi—all of which prevail in a latent state. In regard to tetany we are exceptionally fortunate in being able to recognize this early stage by means of a delicate and reliable test. It is a phase which is characterized by pathological hyperirritability of the nerves, those of the periphery as well as of the central nervous system. This hypersensitive state was first appreciated clinically by employing the galvanic current in order to distinguish the degree of irritability of the peripheral nerves. This method had been employed in the physiological laboratory by Pflueger, and was introduced in 1874 into the clinic for the diagnosis of adult tetany. It gives rise to the reaction which is commonly known as *Erb's phenomenon*. In 1890, Escherich employed this test in a study of infantile tetany, but it was not until ten years later that it was placed on a sound clinical basis by the work of Thiemich and Mann. Not only is the galvanic reaction the most reliable and delicate sign of infantile tetany but it has contributed more than all else to an appreciation and recognition of this clinical condition, and constitutes today the final criterion in regard to the inclusion or exclusion of nervous disorders which resemble tetany in their clinical behavior.

According to Thiemich and Mann, the average intensity of galvanic current required by the median nerve to produce a visible muscular response in normal children and in those suffering from latent or manifest tetany is as follows:

TABLE 25.

	Cath. C.	An. C.	An. O.	Cath. O.
Normal children:				
Under eight weeks	2.61	2.92	5.12	9.28
Over eight weeks	1.41	2.24	3.63	8.22
Children with tetany:				
Latent	0.70	1.15	0.95	2.23
Manifest	0.63	1.11	0.55	1.94
Recovered	1.83	1.72	>2.30	>7.90

From this table it is evident that infants under eight weeks of age are less sensitive to the galvanic current than are older children. In point of fact, the normal figures are somewhat higher than those given in this table, as Thiemich found later that some children which he had regarded as normal suffered from latent tetany.

In carrying out this test, electrodes of the standard size should be employed (50 cm.^{2} for the indifferent and 3 cm.^{2} for the Stintzing electrode), and the tests should be repeated if the results approxi-

mate the pathological. A certain amount of practice is necessary in order to interpret the reactions. In the hands of the experienced, Erb's phenomenon is the earliest indicator of infantile tetany, and unequalled by any diagnostic test associated with disorders of nutrition. For clinical purposes, the most serviceable of the reactions is the exaggerated cathodal opening response—a contraction with less than 5 milliampères. However, if more than 5 milliampères are required for a visible reaction, the conclusion is not warranted that tetany is not present; especially is this true if the test has been carried out but once. The anodal opening reaction, sponsored first by Pirquet, is more delicate but likewise more difficult to interpret. Occasionally it is elicited with less than 5 milliampères in infants which apparently are normal. The reversal of anodal reactivity, in other words, a contraction on anodal opening with a current less than that required for anodal closing (AOC < ACC) is also of diagnostic significance. The cathodal closing reaction, which requires the least electrical current, has but little clinical importance, although it should be remembered that all increased reactions indicate a hyperexcitability of the peripheral nerves. Tetanus resulting from cathodal closure, which renders it impossible to bring about an opening contraction with less than 5 milliampères, is often an early and, as pointed out by Escherich, a characteristic sign. Such, in summary form, is the established opinion in regard to the clinical significance of the various galvanic reactions which comprise the Erb phenomenon.

There are certain features which should be noted in connection with this valuable test. In the first place, it is somewhat variable, from week to week, and even from day to day. This denotes merely that latent tetany is characterized by an irregular course. These variations may come about from various causes—from differences in diet, in the psychic state of the infant, in meteorological conditions, etc. Indeed, one of the most striking clinical phenomena in connection with tetany is its variability, a characteristic which it shares with rickets and numerous other nutritional disturbances. The fact that we have at our command, in the electrical reaction, an indicator of such sensitivity, merely allows us to appreciate more readily the frequent and rapid fluctuations in the clinical progress of tetany. What holds good for the clinical course must be true likewise of the metabolic course, a fact which serves to emphasize the inherent difficulties of studying the metabolism in disorders of this kind. Occasionally, as many clinicians have noted, the test is misleading. An infant may be evidently spasmophilic, nervous and hypertonic, but give normal electrical reactions—a day or two later it may show manifest signs of tetany associated with the typical electrical reactions. Furthermore, immediately following a convulsion hyperexcitability may be temporarily absent. Conversely,

after the current has been applied for a long time, irritability may be found artificially enhanced. Finally, it should be emphasized that the reaction does not bear a quantitative relationship to the severity of the symptoms, as it is most marked at times when clinical signs are but slightly evident. Nor does the phenomenon always run parallel to the concentration of calcium in the blood.

Recently French physiologists, Bourguignon and others, have criticized the Erb phenomenon as representing an artificial and non-physiological reaction. In their opinion the important factor is not the intensity of the current which is required to bring about nerve response, but the interval which elapses between the application of the electrode and nervous response. This interval, under conditions where a minimum intensity is applied, they term "*chronaxie.*" At the present time the application of this method is so difficult and its reactions so delicate that it is not suitable for the clinic. It is quite possible that the technique of chronaxie may be so modified as to give it clinical value.

The clinical symptom of latent tetany second in importance is the *Chvostek sign or the facial phenomenon*, by which is understood hyperirritability of the facial nerve to a mechanical stimulus. This sign is elicited by tapping the trunk of the facial nerve with the finger or percussion hammer, just anterior to the external auditory meatus, or just below the zygomatic process. Where latent tetany exists, this procedure leads to a greater or less contraction of the muscles supplied by the nerve. The twitching may involve the entire side of the face, or merely the muscles of the alæ nasi or of the mouth or of the eye on the corresponding side. This reaction should not be confused with "the lip or mouth phenomenon," a pouting of the mouth which can be brought about by tapping the lip, which must be regarded as a reflex and not as the result of a direct stimulation of the nerve trunk. The lip phenomenon often involves both sides of the mouth, can be elicited almost solely during sleep, and is purposive and coördinated, as pointed out by Thomson. When present in marked degree, the Chvostek sign is striking, but when mild it is often difficult to interpret. Frequently, muscular contraction may be brought about merely by a superficial scratching of the skin overlying the course of the facial nerve. This phenomenon was regarded by some as a reflex and not as the result of a direct irritation of the facial nerve. However, Escherich demonstrated that such is not the case, as it can be elicited even after the overlying skin has been completely anesthetized.

The facial phenomenon has not the clinical significance of electrical hyperirritability, for the relationship of the former to tetany, both during early infancy and during childhood, is not clearly understood. Escherich found that about one-half of all infants showed signs of latent tetany. The majority of these evinced only

galvanic hyperirritability, the facial phenomenon being elicited in only 50 per cent of those who showed cathodal hyperirritability, and in only 4 per cent of those who showed anodal hyperirritability. This statement, which agrees with more recent investigations, indicates not only the relative importance of the two methods of demonstrating hyperirritability of the peripheral nerves, but the remarkable frequency of this disorder. *The incidence of tetany, including its latent form, is comparable to that of infantile rickets and greater than that of any other constitutional disorder at this period of life.* Finkelstein found signs of tetany in about 55 per cent of all bottle-fed and in about 8 per cent of all breast-fed infants, three to nine months of age. The facial phenomenon has little clinical significance in infants under two to three months of age, owing to the high reflex irritability during this early age period. This is true, to a still greater extent, in regard to premature infants whose nerves are peculiarly irritable. Its incidence is greatest between the fourth and sixth months and decreases during the second half of the first year of life. It is not exceptional, however, to note the facial phenomenon during the second year and even later in childhood. Frequently it can be elicited in older children, but there is a difference of opinion as to whether hyperexcitability at this period of life should be regarded as an indication of latent tetany or be ascribed to some other abnormal condition.

Lust found that the peroneal nerve could be employed to show the existence of hyperirritability to a mechanical stimulus. In order to elicit this sign, one should support the leg of the child in the left hand and tap the peroneal nerve with the percussion hammer at or somewhat below the head of the fibula. A positive reaction is indicated by a dorsal flexion of the foot associated with slight abduction. This sign, according to its author, possesses no significance after the first year of life. It has no advantage over the facial phenomenon, except for the fact that it can be elicited even while the infant is crying.

The third sign among the so-called "triad" of latent tetany is the *Trousseau phenomenon*, which is elicited by applying pressure, for example a tourniquet, to the inner aspect of the arm along the course of the large nerves and bloodvessels. This test is regarded as positive when such pressure occasions a typical contracture—the obstetric position—of the fingers and the hand. The value of this sign for the diagnosis of latent tetany cannot be compared either to galvanic or to mechanical hyperirritability. In my experience it has proved to be very unreliable. There has been some question as to whether this reaction should be interpreted as a response to mechanical irritation, or as a simple reflex phenomenon. Frankl-Hochwart and Escherich regarded it as a reflex, the former claiming that he had observed a bilateral Trousseau phenomenon

on pressure of one arm. A similar phenomenon has been described in connection with pressure of the leg, but possesses no special clinical significance.

One of the most valuable and constant signs of tetany is the *lowered concentration of calcium in the blood.* This is true of the tetany of adults as well as of infants. It is a sign that almost never fails, and is almost pathognomonic. However, in nephritis we may find equally low percentages of calcium in the serum without any evidence of tetany. De Waard, and Kramer and Tisdall devised a simple technique for its quantitative determination in small amounts of serum. Whereas in the normal infant, calcium is remarkably constant, ranging between 9 and 11 mg. per 100 cc., and rarely reaching these extremes, in cases of tetany it is regularly low. In the latent case it falls to about 7 to 8 mg. and when the signs become manifest, may have dropped to 5 or 6 mg. per 100 cc. of serum. It rarely gets lower than 5 mg., and almost never below 4 mg. The inorganic phosphorus may remain unchanged, but has a tendency to rise, sometimes reaching a concentration of 7 to 9 mg.; even when it is not absolutely high, its ratio to calcium is increased, exceeding the normal ratio of 1 to 2. Although there is some relationship between the severity of symptoms and the degree of diminution of calcium, this relationship is by no means constant. The same holds true in general as to the mutual relationship between rickets and the level of inorganic phosphorus in the blood. At times we are surprised to find a case of latent tetany with a concentration of calcium of 6 or 7 mg., or, on the other hand, a case of manifest tetany with a concentration as high as 8 mg. This lack of complete harmony between the clinical manifestations and the calcium in the blood indicates that some factor other than calcium concentration must be at work. Probably the calcium in the serum is not a reliable index of the level of calcium in the tissues. It has been suggested frequently that the important factor is not the total calcium of the serum, but the amount ionized. This point of view has been accepted by many, but it should be remembered that it is not yet possible to estimate accurately the amount of free calcium; the amounts reported have been obtained by computation. It has been found by Meysenbug and McCann, as well as by others, that there is no variation from the normal in the ratio of the dialyzable to the non-dialyzable fraction. But it should not be forgotten that a normal ratio of dialyzable to non-dialyzable calcium, associated with a lowered total amount of calcium, indicates a lessened concentration of dialyzable calcium.

Although it has become increasingly evident during the past few years that the diminution of calcium in the blood may not be the primary cause of tetany, but is the result of some mechanism which is more fundamental, this phenomenon must be regarded as one of

the most trustworthy clinical signs of tetany and as pathognomonic of this disorder (Fig. 48).

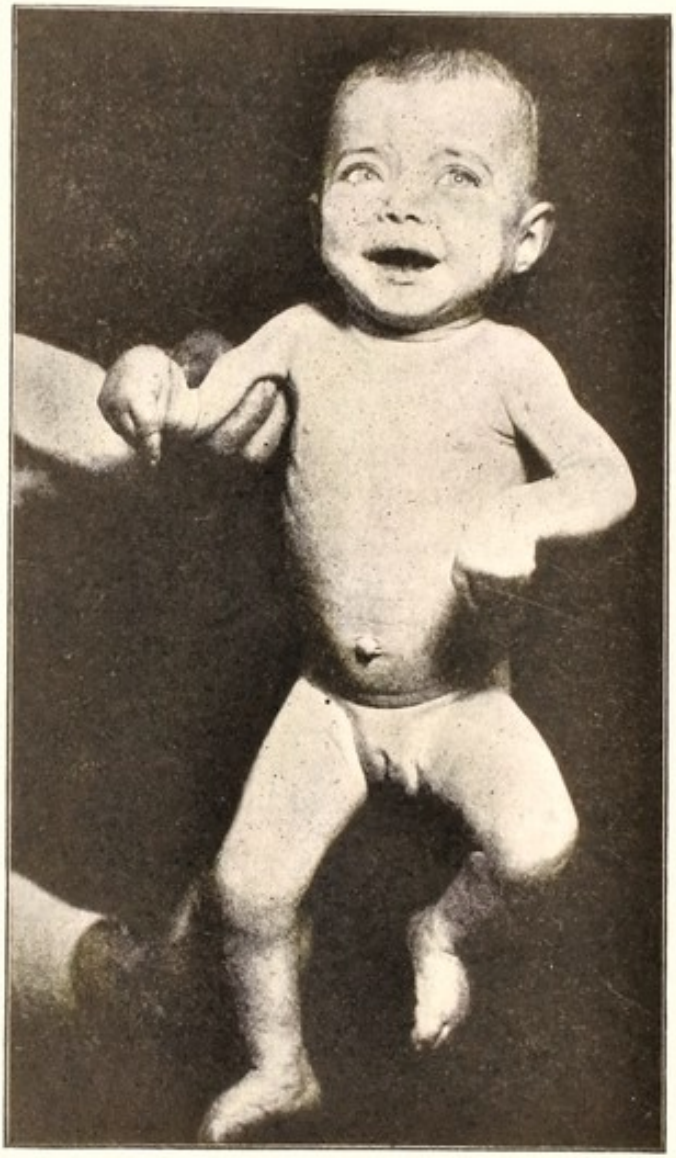

FIG. 48.—Persistent tetany, marked carpopedal spasm. (Ibrahim, Feer's Lehrb. d. Kinderh., G. Fischer, Jena, 1911.)

Manifest Tetany.—The signs of manifest tetany are mainly carpopedal spasm, laryngospasm, commonly known as laryngismus stridulus or spasm of the glottis, and infantile convulsions or eclampsia. These symptoms are almost always preceded by a shorter or longer period of the latent form of the disorder. One of the commonest clinical forms is the *carpopedal spasm*, vividly described by Clarke over one hundred years ago. In a chapter on "a peculiar species of convulsions in infant children accompanied by spasmodic expiration" Clarke writes in 1815: "Accompanying these symptoms, a bending of the toes downward, clenching of the fist, an insertion of the thumbs into the palms of the hands and bending the fingers upon

them is sometimes found, not only during the paroxysm, but at other times. Clenching the fist with the thumb inserted into the palm of the hands often exists for a long time in children that are being observed, yet it is always to be considered an unfavorable symptom and frequently is the forerunner of convulsive disorders, being itself a spasmodic affection." Truly a remarkable description! The position of the hands and fingers is commonly termed the "obstetric position;" and the position of the upper extremities, with elbows bent and arms pressed tightly against the thorax and wrists markedly flexed, has been compared by the Germans to that of the forelegs of a dog in the sitting or begging posture. The legs are bent at the hips, the knees are also flexed and the feet are in a position of equino varus, the toes being bent downward. When the spasm or contractures of the extremities persist for a long time, edema may gradually develop on the posterior surfaces of the hands or the feet. These swellings are firm and do not pit readily on pressure. The child generally appears comfortable and there is little pain unless an attempt is made to flex the joints.

The face has often a characteristic expression which has led to the term "*tetany facies;*" it appears rigid and stiff, and the corners of the mouth are drawn downward and the forehead is somewhat furrowed. The muscles of the eyes may be involved, leading to strabismus or to inequality of the pupils. The entire body may be held somewhat rigid and there may even be definite opisthotonus which has been mistaken for a sign of meningitis, especially when associated with strabismus. Trismus or nystagmus may also occur. These various evidences of muscular spasm vary greatly, not only in distribution and in intensity, but in duration. Sometimes they are present for a few hours, and relax without seeming cause, at other times the contractures persist continuously for days or weeks. Again they may disappear without further complication, or be followed by convulsions.

The most frequent sign of manifest tetany is *laryngospasm* (laryngismus stridulus, spasm of the glottis), which is typical of tetany, although some have described it in association with organic brain disease and epilepsy. The loud, crowing inspiration due to a spastic narrowing of the glottis is a symptom which long has been known to physicians. The spasm may be mild and occur only occasionally. On the other hand, one attack may follow the other in rapid succession and be accompanied by great difficulty in breathing, by cyanosis, exophthalmus and even unconsciousness, and alarm not only the parents but the physician. Such attacks may be brought about by fright or irritation, by a draught of cold air or a sudden awakening from sleep. If the diaphragm becomes involved, a form of suspended respiration termed "*inspiratory apnea*" may develop, associated with marked cyanosis and followed by a convulsive

seizure. Usually, however, just when the spasm of the glottis begins to grow alarming and seems to call for energetic and active measures, air is heard softly entering the larynx, the cyanosis becomes less intense, and the baby makes a feeble attempt to open its eyes. How slight a reflex irritation is needed to precipitate such a serious disturbance of respiration is shown by the accompanying pneumographs of Masslow (Fig. 49). These reproduce the reactions following the slight irritation of the skin by the algesimeter. It will be noted that whereas the normal infant does not react to this stimulus, the spasmophilic infant may react violently by a

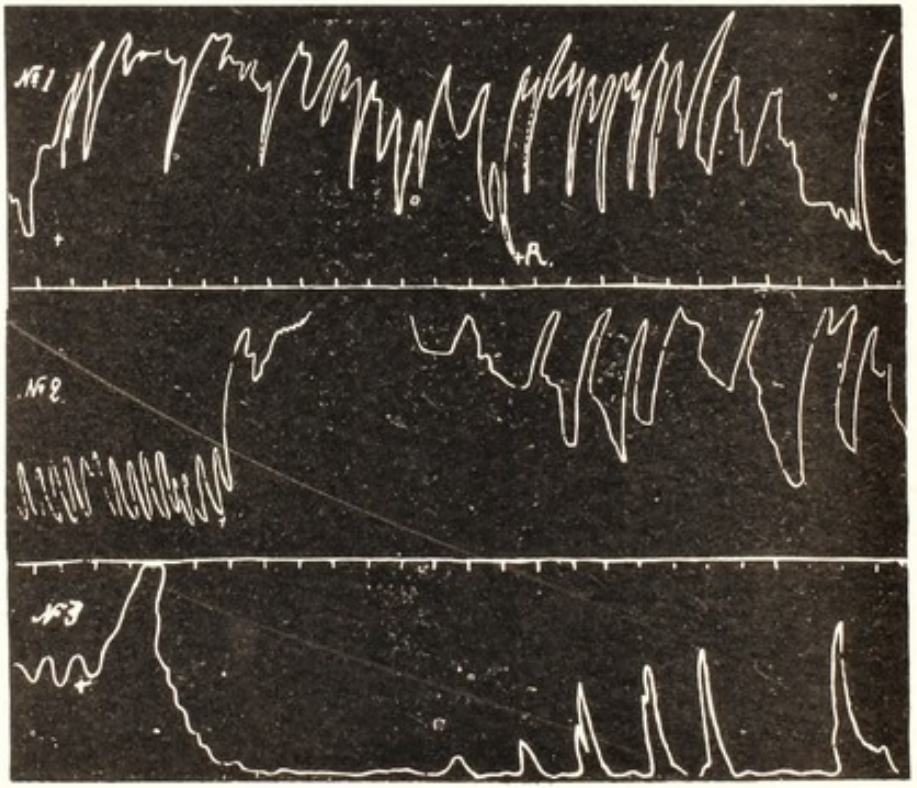

FIG. 49.—Pneumographs following slight irritation of skin by an algesimeter. (1) Normal infant, no reaction; (2) spasmophilic infant, inspiratory apnea; (3) expiratory apnea (eight seconds). (M. Masslow, Monatsch. f. Kinderh., 1916, **13**, 99.)

sudden cessation of respiration either in inspiration, the more common reaction, or in expiration; in the latter phase respiration was suspended for eight seconds.

Some years ago Kassowitz described a closely allied type of respiratory failure which he termed "expiratory apnea." This failure comes about without warning, not being preceded by laryngismus stridulus, which generally accompanies the common form. It has been reported even in cases where Erb's phenomenon was stated to have been lacking. The symptoms are very much the same as those just described, except for the fact that under these

conditions the fatality is associated with expiratory rather than with inspiratory apnea. Expiratory apnea is by far the rarer form.

Allied to this condition from a pathogenetic standpoint is the symptom-complex which Ibrahim has attributed to *cardiac tetany*. This is characterized by the sudden death of an infant suffering from tetany, at times even of mild intensity. This catastrophe may occur so quickly as to escape the notice of the mother or nurse who has been out of the room for but a few minutes. The infant becomes pale, apneic and a few seconds later is dead. In an institution which cares for a large number of infants this is a not infrequent episode, in spite of conscientious nursing and the attendance of a resident physician. In a case of this kind which occurred recently, the heart was found in systole, of the consistency of wood, and the pyloric area markedly contracted. Ibrahim believes that it follows stimulation of the vagus which, as is well known, brings about diastole in the cardiac rhythm. He found the hearts in the phase of diastole in 2 of 3 infants which died under these circumstances. Finkelstein reports a case of tetany in which, following lavage of the stomach, a pulse-rate of 200 and respirations of 100 developed, which lasted for several hours. In connection with infantile scurvy I have described a similar tachycardia, which seemed to be due to a disturbance of vagus innervation. Morgenstern's electrocardiograms of the heart in tetany seem to support this interpretation. Some have attributed these sudden deaths to a status thymolymphaticus, a condition which is but little understood.

The vegetative nerves may be involved, especially those supplying involuntary muscle. One of the conditions which fits into this category is the *broncho-tetany* described by Lederer, who noted it in 10 per cent of his cases. It is a difficult condition to diagnose except with the aid of the electric current (Erb's sign) and the Roentgen rays. The main symptoms are marked expiratory dyspnea with great rapidity of respirations, signs which develop in dogs following parathyroidectomy. The lungs show areas of dullness, associated with loud bronchial breathing, sometimes accompanied by fine râles and scattered areas of compensatory emphysema. The radiographic picture also is not typical. It is supposed to be possible to differentiate the atelectatic areas of consolidation from ordinary areas of consolidation by their lack of sharp definition. Goettsche has recently made use of serial radiographs for this purpose. Not infrequently broncho-tetany is associated with high fever or even hyperpyrexia. The prognosis is bad. At postmortem, atelectatic areas are found with edema in the neighboring bronchi and vicarious emphysema in the rest of the lung.

The most striking symptom of tetany is *convulsions*, which may be preceded by laryngospasm or carpopedal spasm, or make their appearance out of an apparently clear sky. Some forty years

ago, Cheadle, the well-known English children's specialist, wrote: "Laryngismus, tetany and general convulsions are the positive, comparative and superlative of the convulsive state in children"—a statement which is correct if we exclude latent tetany. No doubt if we had the opportunity of testing the galvanic reaction previous to convulsions we should almost always find that hyperirritability preceded the attack. The convulsions usually are general in nature, involving both sides of the body and are often preceded by a slight twitching of the face, especially of the mouth, a danger signal which in itself should lead to the application of preventive measures. There may be but a single convulsion, or but two or three, which is usually the case. However, a "status eclampticus" may develop, with convulsions succeeding one another in rapid succession, sometimes accompanied by high fever. The outcome in the great majority of the cases is favorable, but at times death ensues. Convulsions due to tetany are rare in very young infants. Recently Powers described an instance in a baby, aged five months, manifested by a convulsive state which recurred several times; the calcium in the serum was less than 6 mg. per 100 cc. In convulsions complicating the infectious diseases, such as pneumonia, the calcium will generally be found to be at about the normal level.

Mention should be made of the involvement of various involuntary muscles of the body. Ibrahim has laid stress on tetany of the rectum and of the sphincter ani. Spasm of the sphincter of the urinary bladder causing retention of urine also has been described. It is interesting to note in this connection that in 1841 Marshall Hall, the well-known English neurologist, in describing the crowing inspiration of infants associated with carpopedal spasm mentioned "spasm of the sphincters of the bladder and intestine, dysuria, strangury and diminished secretion of the flow of bile or "bileless feces." Some have attributed the gastro-intestinal symptoms, which are not infrequently associated with tetany, to an involvement of the nerves of the small and large intestines.

In a rachitic infant tetany may be brought about by large doses of atropine. An instance of this kind occurred in my institution a few years ago. In this case the latent tetany was increased to manifest tetany, by several attacks of vomiting and was associated with a calcium concentration in the serum of only 4 mg.

Tetany is a common complication of the nutritional disorder termed cœliac disease (Herter's intestinal infantilism). In this association it is manifested by the typical carpopedal spasm, edema of the hands and feet and hyperirritability of the nerves. I have never known of a case which developed convulsions. This clinical condition results in part from a deficiency in the calcium intake, for one of the salient features of the dietary is the reduction or total exclusion of cow's milk. There is also, undoubtedly, defective

absorption of calcium, as is the case in sprue, which likewise is often associated with tetany. This clinical condition has already been considered in relation to the so-called "cœliac rickets," which by some has been segregated as a distinct form of late or juvenile rickets.

There are a number of so-called "trophic disturbances" associated with infantile as well as with adult tetany. The most interesting of these is *cataract*. Nutritional disturbances of other ectodermal tissues have been reported, for example, of the enamel of the teeth, the skin, the hair and the nails. Cataract occurs generally in later childhood, but its inception possibly dates from infancy. This symptom is particularly suggestive on account of its relation to the parathyroid glands, a subject which will be discussed below. As is well known, Erdheim and others have described the development of cataract in rats which have been deprived of their parathyroids. It would seem that this alteration of the lens is directly due to a disturbance of the salt metabolism.[1] The lesions of the enamel of the teeth likewise have their counterpart in experimental tetany. Erdheim described defects in the enamel of the incisor teeth of rats after they had been deprived of their parathyroid glands, an observa- which has been confirmed by many investigators. Fleischmann, who devoted much attention to this subject, regarded hyperplasia of the enamel as a sign of tetany in man, describing horizontal lesions of the enamel as characteristic of this disorder. Hesse-Phleps reported that among 77 young adults suffering from cataract, 80 to 90 per cent were attributable definitely to tetany; 43 showed signs of hyperplasia of the enamel.

As in the case of rickets, there are no distinctive cellular changes in the blood. Anemia seems to be somewhat more common than in rickets. The urine is generally normal, except for a trace of albumin, as described by Escherich. Czerny has laid stress on the frequent occurrence of acetone and diacetic acid, a sign which more recently has been emphasized by Liefmann. This is a metabolic change which should be borne in mind and made the basis of further study.

The infants attacked by tetany do not belong to one particular type. On the whole they are nervous, restless, hypertonic and too alert for their age. They cry without seeming cause, do not sleep well by day or by night, they have a capricious appetite and are disturbed by slight noises or by jolting of the crib. They may be well nourished, but pasty and fat, or on the other hand thin and poorly nourished. Finkelstein has well described these two types of infants who are predisposed to tetany. "At one end of the series

[1] Burge has shown by *in vitro* experiments that slight alterations in the ions of the medium may lead to a precipitation of the lens protein. Analyses of senile cataractous human lenses show a definite increase of calcium and magnesium. These changes may be secondary.

one finds well nourished, often fat children, with satisfactory and even abnormally great gains in weight, and with no gastro-intestinal symptoms whatsoever. In the midst of apparent health, suddenly manifest signs, laryngospasm, eclampsia, burst forth, whereas spasms of the extremities do not occur. At the other end are the thin, poorly-nourished children who suffer from prolonged digestive disturbances, who in spite of a very low diet, gradually develop the symptoms of hyperexcitability, characterized by a tendency to spasm of the extremities rather than to laryngospasm and general convulsions." These groups, the one well nourished and the other atrophic, correspond to similar clinical types which have been noted in relation to rickets.

The clinical course of tetany is distinguished by marked irregularity. If the electrical irritability is followed systematically for a long period, it will be found that latent tetany may exist for a short or a long time, that it may persist in this undeveloped form or change by insensible gradations into manifest tetany; on the other hand, the disorder may be ushered in from the outset with the most exaggerated sign of manifest tetany, namely, convulsions. The same irregularity is true in regard to the cessation of tetany, which tends to abate toward the end of the first year of life. However it may be rekindled by an infectious disease or other intercurrent factor and signs of the latent or the manifest disorder may recur during the second year of life. Indications may be found from time to time even during the early years of childhood which suggest a constitutional instability of the nervous system.

THE PATHOLOGY OF TETANY.

Very few lesions have been described in connection with infantile tetany, and in regard to these few a difference of opinion exists. Rudinger found changes in the anterior horn ganglion cells of the spinal cord, lesions which have been described in connection with cases of adult tetany. Blum, in his recent monograph on the parathyroid glands, portrays similar changes in the ganglion cells of dogs following parathyroidectomy. According to numerous observers, the brain and spinal cord of infants who have died of tetany are exceptionally rich in blood and in tissue juices. In this connection, it should be remembered that the pressure of the spinal fluid may be abnormally high during life. Escherich describes a moderate degree of internal hydrocephalus in 6 of the 23 cases which came to necropsy, but we should bear in mind that hydrocephalus is a frequent accompaniment of rickets.

About twenty years ago Yanase, a pupil of Erdheim, carefully investigated *the parathyroid glands* of normal infants and of those which had shown signs of latent or of manifest tetany during life.

He was led to this investigation by a series of experimental investigations, particularly those of MacCallum and Voegtlin, which clearly showed a functional connection between the removal of these glands and the development of tetany. He came to the conclusion that congestion and hemorrhage of these glands were found far more frequently in infants which had manifested signs of tetany during life than among those in which such signs had been absent. Yanase reported the histological data of 50 cases which had been tested by the galvanic current previous to death. His conclusion that hemorrhages into the parathyroid glands were the direct cause of tetany was accepted by Escherich and led to a series of similar investigations which have been continued to the present time. Pathologists have failed to substantiate Yanase's data, finding hemorrhages frequently in the parathyroid glands of normal infants. The latest study of this question, carried out by means of serial sections of the glands, is that of Danisch, who found hemorrhages in about one-third of the parathyroids of infants and could establish no parallelism between such hemorrhages and the symptoms of tetany. He describes an interesting case in an infant, aged three months, in which there was marked parenchymatous destruction of the gland leading to what he terms "hypoparathyroid tetany," an interpretation suggested some years ago by Erdheim in cases showing old hemorrhages. It would seem that, in general, tetany comes about without the occurrence of hemorrhages into the parathyroids and that its association with these glands should be regarded as functional rather than anatomical.

THE ETIOLOGY OF TETANY.

Congenital factors play an important rôle in the etiology of tetany, as in other constitutional disorders. But it is also true that the underlying predisposition is always coupled with important postnatal factors. Numerous clinicians have noted the frequent conjunction of the facial phenomenon in parents and their offspring; mothers manifest this phenomenon far more often in association with their children than do fathers. An interesting case in point is cited by Finkelstein:

In a breast-fed child which he had observed from birth, mild laryngospasm and the facial phenomenon with cathodal hyperexcitability made their appearance at five months of age; at six months, three days after giving cow's milk, a series of general convulsions developed and the cathodal opening contraction fell from 3 to 1 milliampères. The mother had a definite facial phenomenon and a cathodal opening contraction between 4 and 5 milliampères, and stated that she had suffered from convulsions from the first to

the third year of her life. In corroboration of this history, she had a cataract which developed during early childhood.

Finkelstein draws the distinction that where tetany rests on a constitutional basis, convulsions develop, whereas where it is based on an exogenous cause, laryngospasm develops.

Age is an important predisposing factor. Tetany is most prevalent during the second quarter of the first year of life, occurring rarely before the infant is two months of age and infrequently after it has reached the age of one year. This age incidence, it will be noted, closely resembles that of rickets. Probably the same will be found to hold true for tetany as for rickets, namely, that the

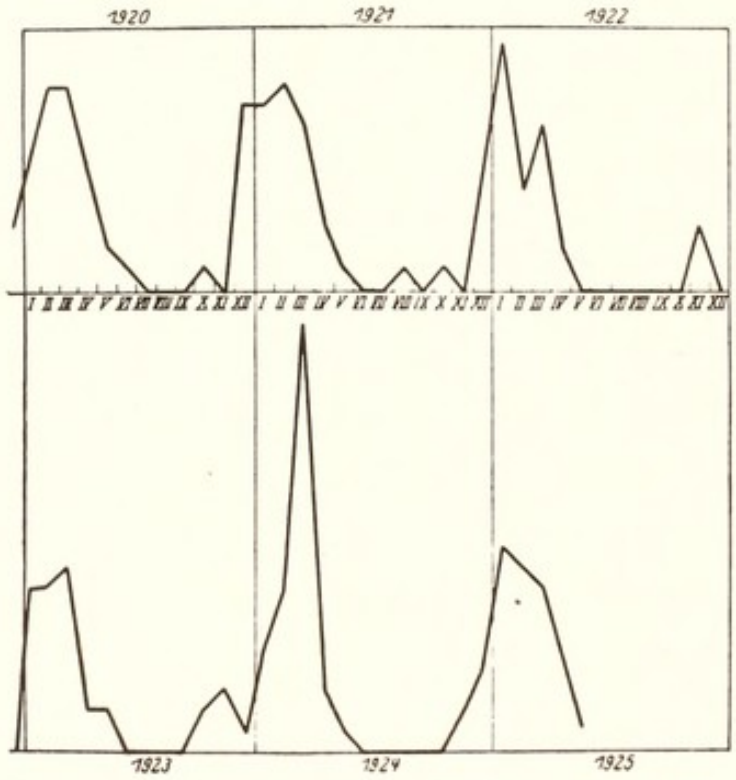

FIG. 50.—Seasonal curve of incidence of laryngospasm. (Japha, Archiv f. Kinderh., 1905, vol. **42**.)

onset often dates back to the first few months of life. Authentic tetany of the new-born has not been described. It is quite possible that under extreme conditions, for example, where the mother has suffered from tetany during later pregnancy, her offspring may be found to show signs of this disorder. Such has been the experience in relation to other nutritional disturbances, for example, beriberi, a disorder which likewise affects the nervous system.

As Bakwin recently has shown, male infants are more susceptible to tetany than female infants; in a series of 136 cases over two-thirds were males. A similar susceptibility in regard to *sex* has been noted by Frankl-Hochwart in adult tetany. However, the tetany complicating osteomalacia occurs almost solely in females.

Season, which plays such a prominent rôle in the etiology of rickets, is even more pronounced a predisposing factor in tetany. This peculiarity has been noted for many years and was stressed by Kassowitz in relation to infantile tetany, as well as by Frankl-Hochwart in adult tetany. As in rickets, the peak of incidence is in the early spring, especially toward the end of March. In his monograph on adult tetany, Frankl-Hochwart records 64 cases, 47 of which occurred during the first four months of the year. Japha brought out this phenomenon strikingly in a report of the seasonal incidence of infantile tetany in an out-patient clinic in Berlin during a period of twenty years (Fig. 50). Throughout the summer practically no cases developed—an observation which holds true for rickets. Exceptionally, latent tetany may be noted during the summer, the number increasing during September and October and becoming more numerous as winter progresses. Not long ago Moro plotted a curve of incidence of infantile tetany in Heidelberg for the years 1920–1925, and showed that in addition to the March peak, there may be a rise in January. Furthermore there are "tetany years," just as there are "rickets years."[1] This phenomenon is especially noteworthy when it occurs in an institution where for a long period of years infants have been maintained under apparently the same hygienic and dietetic conditions. Meteorological conditions must be regarded as the exciting cause of the sudden metamorphosis of latent tetany into one of the forms of manifest tetany. It is suggested by Moro that the active signs are brought about by such meteorological conditions as are associated with "the warm, sunny days of early spring." In this connection the observation of Huldschinsky and others may be recalled, to the effect that following artificial ultra-violet irradiation, rachitic infants sometimes react by a sudden change from latent to manifest tetany. In describing the seasonal tide of blood phosphate, Hess and Lundagen (1922) observed that "the seasonal increase of phosphate beginning in April and ascending still higher in May, tends in some cases to the development of tetany late in the spring." It may be mentioned that following irradiation, galvanic irritability may increase and that the calcium concentration of the blood may decrease.

Premature infants and twins are particularly prone to tetany. The analogy to rickets is rendered still closer by the fact that negro babies are also markedly susceptible. This may be but the expression of a common etiological factor. There can be no doubt,

[1] There are also "tetany-lean years." This spring (1929) has been remarkable for the low incidence of infantile tetany throughout the city of New York. This has held true for both white and negro babies. This lack of tetany is all the more striking as rickets has not been notably mild or infrequent. The winter has been rather mild and the spring rainy.

however, that the atrophic and poorly-nourished infant tends to develop tetany more often than rickets. In these cases rickets possibly exists in a latent form. The high incidence of tetany in premature infants and in twins was brought out some years ago by the study of Rosenstern. He ascertained the occurrence of the Erb phenomenon in a group of 78 poorly-nourished infants, weighing less than 2500 gm.; a few of these were classed merely as atrophic. The infants were tested in a routine way for a period of six months, from July to December. Seventy-six, in other words almost all of these babies, showed an increase in the cathodal opening reaction, many of them giving evidence of hyperexcitability at an early age. The majority evinced this diagnostic sign even in the period during which they were fed woman's milk. It is worthy of note that the incidence of rickets, which runs so nearly parallel to that of tetany, would not have been so great at this season of the year, even if elicited by the most refined methods.

In regard to etiology, the same holds true for tetany as for rickets; physicians have been divided into two schools, the one stressing almost exclusively diet and nutritional inadequacies, the other faulty hygiene. It is now evident that both schools are correct, that diet as well as hygiene plays an important rôle in etiology. Gregor emphasized *the marked difference in effect between woman's and cow's milk*, a point to which Escherich likewise drew attention. This aspect which is important from a pathogenetic, as well as from an etiological standpoint, has been studied in detail by Finkelstein and his pupils. He states that, whereas over 55 per cent of bottle-fed babies in his clinic showed cathodal hyperexcitability, approximately only 8 per cent of the breast-fed babies showed this phenomenon. Indeed, it has been the general experience of clinicians that signs of latent or even manifest tetany may develop within a few days of the time when cow's milk is first given. This is apt to happen especially if the initial milk mixture is rich, or if milk is given in too large quantity. Some have thought that the nerve irritability is due to the fat, and others to the protein, but Finkelstein is probably correct in attributing its harmful effect rather to its salt constituents. He has shown that galvanic irritability is heightened when whey is given and ascribes this reaction largely to its high content of potassium and sodium phosphates. It has been shown in the clinic by Jeppsson, Rohmer, Woringer and other investigators that additions of phosphate to the diet bring about nerve hyperirritability only in those infants who are suffering from latent or manifest tetany. Its action is indirect—a reduction of the level of calcium in the blood. The irregularity in galvanic reaction in tetany, which some have noted on giving cow's milk may be attributable to variations in absorption. The ions in milk, for example, calcium and magnesium, which tend to reduce nerve irritability are absorbed in

greater or lesser amount, according to the hydrogen-ion concentration and other fortuitous conditions within the intestinal canal.

It has long been recognized that there is an intimate *relationship between infantile tetany and infantile rickets.* Indeed, Kassowitz regarded tetany merely as a nervous manifestation of rickets, and Shipley, Park and their colleagues refer to it as the low calcium form of this disorder. Although tetany may occur occasionally in an infant free from rickets, from a clinical point of view it may be considered that practically all infants with signs of tetany have rickets to some degree. A thorough investigation of this question has never been carried out, making use of all the newer diagnostic criteria of both disorders. It would be interesting and worth while to ascertain the clinical parallelism between these two conditions in a series of infants in which galvanic irritability, the calcium and phosphorus content of the blood, radiographic pictures of the epiphyses—as well as the more evident clinical manifestations—had been followed throughout a winter and spring. It would be still more valuable if in a large number of cases these clinical signs could be controlled by a histological examination of the bones. Although, as stated, tetany rarely occurs independently of rickets, the contrary does not hold true, for many cases of rickets, especially in the late fall or early winter, show none of the stigmata of tetany. As tetany develops somewhat later than rickets, it has been regarded as a complication of the rachitic condition. The fact, however, that tetany associated with diminished calcium, occurs in adults quite apart from any trace of rickets argues against this point of view. A peculiar phenomenon in connection with this relationship is the lack of parallelism between the severity of the rickets and the tendency to develop tetany. In its severest form we often find either a complete absence of tetany or merely latent signs. This peculiarity is corroborated by the observations of Iwamura on the occurrence of spasmophilia in Toyamaken, Japan, the very district which Ogata surveyed for osteomalacia, and which, in the previous chapter, we have described as a center not only of osteomalacia but of severe rickets as well. Among 174 infants that were examined by him 122 were breast-fed, and 36 were found to have rickets. Forty-three were tested for galvanic irritability, but only 2 showed signs of spasmophilia, 1 having laryngospasm and the other latent tetany. This difference between rickets and tetany seems too significant to be attributed merely to faulty observation. Finkelstein states that the great increase of severe rickets in the course of the war and the post-war period did not correspond to a similar increase in spasmophilia; indeed manifest tetany and severe laryngospasm were exceptionally infrequent. The points of similarity, however, between rickets and tetany are striking. The age incidence is similar; premature infants are exceptionally predisposed to both; a marked increase in gain of

weight is a predisposing factor; a heightened susceptibility of infants fed on cow's milk is common to both conditions; furthermore, cod-liver oil, its extract, and activated ergosterol prevent or cure rickets as well as tetany, and the same holds true for ultra-violet irradiation.

Animal experiments have not as yet been of great aid in solving the knotty problem of the relationship of tetany to rickets. This gap may be ascribed to several causes. In the first place, thyro-parathyroidectomy has been the common method of inducing tetany. When we bear in mind that this is a disorder which children develop slowly and gradually as the result of functional disturbance, it is clear that the analogy to parathyroprivic tetany is strained. Furthermore, the tetany which is brought about by operative means does not evolve on the foundation of rickets, differing in this important respect from infantile tetany. A condition resembling tetany can be induced in the rat by feeding a ration very low in calcium. The animals become highly irritable, have a diminished percentage of calcium in the blood and, according to Shohl and Bing, develop galvanic hyperirritability. This method has the advantage that the tetanic condition comes about gradually, but differs from the tetany of infants in that the lesions which rats develop as the result of a low-calcium ration are by no means typical of rickets; they show an excess of osteoporosis with but a slight increase of osteoid tissue and no overgrowth of the proliferating cartilage.[1]

In laboratory studies of the relationship between rickets and tetany it is essential that at the outset rickets should be induced in the animals and that tetany should be superimposed, for this sequence constitutes the significant feature in the clinical relationship between these disorders. For example, it happens not infrequently in the spring that a case of moderate rickets, manifesting the typical signs by clinical examination and by radiograph, with serum-calcium normal in percentage but inorganic phosphate definitely reduced, changes completely within less than a fortnight; the calcium is found to have become reduced, the inorganic phosphorus to have risen and the infant to have developed signs of manifest tetany. Such a case is the following:

An infant, aged eleven months, was found in March to have the typical signs of rickets, associated with a concentration of calcium in the blood of 12.5 mg. and of inorganic phosphorus of 3.5 mg. In April conditions were approximately the same. In May the entire

[1] Cavins has been able to bring about tetany—serum as low as 5.4 mg., followed by convulsions—by means of fasting rats which had rickets. This is an interesting phenomenon but, of course, not comparable to what takes place in the clinic. The so-called parturient paresis (milk fever), which occurs in heavily milking cows soon after calving, is probably a form of tetany. Several investigators (Little and Wright, Sjollema) have found the symptoms to be associated with low concentrations of calcium in the serum, a phenomenon which I can confirm.

picture had changed. The infant had manifest tetany, the calcium had fallen to 7.5 mg., whereas the inorganic phosphorus had risen to 4 mg. Throughout this period the infant had been in the same ward and had received the same dietary.

This is the phenomenon which must be elucidated. Greenwald has suggested that it results from too rapid healing of the rachitic process, with a consequent withdrawal of calcium from the blood and deposition in the bone.

It is of little value to theorize in regard to the unique relationship between rickets and tetany. It is a question which is being actively studied at present both in the laboratory and in the clinic, and there is every prospect that the next few years will bring us information of value on this interesting aspect. Cases must be carefully observed in the clinic as they progress from the rachitic to the tetanic state. Not only must the clinical signs be closely followed, the galvanic reaction, etc., but the changes in the calcium, phosphorus and the physical state of the blood must be ascertained step by step in the course of the metamorphosis. At the same time the intensity of sunlight and of other meteorological conditions should be carefully recorded in an effort to bring them into correlation with the remarkable change in metabolism and in the clinical picture.

THE PATHOGENESIS OF TETANY.

Attention has been focussed mainly on the inorganic salts in connection with the study of the pathogenesis of tetany. This viewpoint is the result largely of the fundamental work of Loeb who showed in a series of papers, which appeared from 1899 to 1908, the interrelationship of the various ions to muscle and other tissues. Using a nerve-muscle preparation as his gauge, he demonstrated the effect which ions, such as calcium, phosphorus, sodium, potassium and magnesium, exerted independently and in combination on irritability. From our point of view the most important conclusion which Loeb deduced was the antagonistic action of the Na^+ and the Ca^{++} ions, the former increasing and the latter decreasing irritability. This conception was later extended to embrace the monovalent sodium and potassium ions which were shown to be physiologically antagonistic to the divalent alkaline earths, calcium and magnesium. At about the same time Mathews showed that a similar relationship holds good for the nerves, and that the physiological actions of ions depend on their electrical state. This relationship may be expressed by the formula $\frac{Na + K}{Ca + Mg}$, the quotient of which is the deciding factor in regard to nerve and muscle irritability. It should be borne in mind in connection with infantile tetany that this reaction was

shown to hold true for heart as well as skeletal muscle. These studies, although carried out in America, aroused greater interest in Europe and directed the attention of physiologists and clinicians to the nature of nervous disorders such as tetany, in which contraction of muscle plays the outstanding rôle. About the same time (1901) Sabbatani and his pupils showed that when an isotonic solution of a calcium salt was applied to the motor areas of the surface of the cerebrum, irritability to electrical stimulation was markedly diminished, as it was following intravenous injections of calcium. On the other hand, salts which precipitate calcium, for example the oxalates, brought about an increase in irritability.

As early as 1905 this subject was introduced into the field of pediatrics by the work of Quest in Czerny's clinic. He analyzed the brains of 3 infants as well as of some animals for their content of calcium and other salts, and reported a diminution in percentage of calcium in the fat-free brain tissue of infants which had suffered from tetany. This work led to several similar investigations, in the course of which the results of Quest were controverted in some instances, and in others confirmed. Some investigators reported even that the calcium was increased rather than decreased in tetany. The sodium, phosphorus and magnesium content of the brain likewise were investigated, also with no uniform result. This method of approaching the question is not promising, as, quite apart from the possibility that different areas of the brain may contain varying amounts of these salts, the nature of their combination may be so different as to deprive the chemical analyses of physiological value.

The greatest advance in this field was made by MacCallum and Voegtlin, in a series of experiments begun in 1909. They demonstrated two outstanding facts which have been confirmed repeatedly: (1) That the calcium content of the blood decreases regularly in experimental tetany, and (2) that the tetanic symptoms disappear when a soluble calcium salt is introduced into the body, intravenously, subcutaneously or orally, and that the animal remains normal as long as the calcium level is maintained at a sufficiently high plane. These experimenters, like most of those who followed them, induced tetany in dogs by the removal of the parathyroid glands. The calcium in the blood of the dogs was reduced to about one-half its normal concentration, and also was decreased in the brain and the spinal cord. They were able to put their experimental observation to the test in the case of an individual who developed tetany following parathyroid extirpation, and definitely showed that the symptoms could be alleviated by means of calcium.

The question of the physiological relationship of calcium to tetany was approached from various angles by workers in the laboratories and clinics of many countries. In 1906 Erdheim, of Vienna, emphasized its significance in connection with his pathological studies on

the induction of tetany by means of parathyroidectomy. Rosenstern (1910), working in Finkelstein's clinic, and using galvanic irritability as the gauge of tetany, showed that when infants were given calcium, nerve irritability decreased, whereas it increased when they were given sodium. As early as 1907, Netter, making a direct clinical application of various laboratory investigations, showed in his clinic in Paris that tetany could be relieved by giving calcium chloride.

At about the same time several investigators analyzed the blood of infants suffering from tetany, in order to ascertain whether the condition which had been brought about in the laboratory could be identified with infantile tetany. Cattaneo (1909) found the blood calcium diminished; however, the method which he used and the figures which he obtained were clearly unreliable. Neurath, in 1910, reported a reduction in the calcium content of the blood in tetany, employing the simple but somewhat crude method devised by Wright. It was not until 1918 that it was unquestionably shown by Howland and Marriott that in infants suffering from tetany the calcium in the serum is distinctly diminished.

VARIOUS FORMS OF TETANY.

Phosphate Tetany.—Although investigations of tetany have concerned themselves mainly with calcium, other ions also have been made the object of study, especially *the phosphate ion*. In 1911, Greenwald, who has made such valuable contributions to this field, showed that for a few days following parathyroidectomy dogs excrete much less phosphorus than previous to the operation. Two years later he was able to demonstrate that there is a phosphate increment in the blood and the serum, due to an increase in the "acid-soluble" phosphorus, in other words in the phosphorus fraction which is not associated with the lipoids or proteins of the blood. This result has been confirmed by numerous investigators. However, he was unable to produce tetany by the injection of sodium phosphate. The investigation of Binger in 1917 led to the concept of a form of tetany due to an excess of phosphate, the so-called phosphate tetany. Binger injected larger amounts of phosphoric acid and its sodium salts, intravenously, into dogs and produced a fall in the calcium of the serum and symptoms resembling tetany. These changes came about only when a neutral, slightly acid or alkaline salt was injected. When an acid salt (NaH_2PO_4) was used, tetany did not ensue, although the calcium concentration fell. The conclusion was drawn that it was the phosphate ion which was the deciding factor and that at a certain pH it exerted a toxic action. Greenwald, however, interpreted the results as due to a dilution of the blood, an increase in sodium concentration, and perhaps an alteration of the perme-

ability of the cells to sodium. The question was taken up both in the laboratory and in the clinic a few years later (1921) by Jeppsson. He was able to produce the symptoms of latent and manifest tetany in animals as well as in children by administering solutions of potassium and sodium phosphate, and concluded that it was the phosphate ion which brings about tetany. He emphasized furthermore the importance of the phosphorus intake in connection with infantile tetany, attributing in general the greater galvanic irritability of artificially-fed infants as compared to breast-fed infants, to the relatively high content of phosphorus in cow's milk. It should be mentioned that the tests in which he fed cow's milk, which was supposed to have been largely deprived of phosphorus, have been justly criticized from a technical standpoint. Later investigations, particularly those of Rohmer and of Woringer, have shown that large amounts of phosphate given by mouth to normal children result in little or no increased irritability of the nerves, having such an effect only where latent or manifest tetany exists. These investigations accord well with those of Salvesen, Hastings and McIntosh (1924) in which definite tetany had been produced in normal dogs. It was shown that an addition of phosphate to the diet regularly brought about tetany and a decrease of calcium, and furthermore that this result came about quite independently of the reaction of the phosphates. They concluded that the diminution of the calcium was the deciding factor, but came to no conclusion as to how the lowering of the calcium was brought about. György, whose work will be considered in detail in connection with a discussion of alkalosis, has explained the action of the phosphates by introducing $HPO_4^=$ into the Rona-Takahashi equation, which results in a diminution in ionization of the calcium.

All in all, it would seem from the various experiments which have been conducted in the laboratory and clinic since 1911 that there is a relationship between the phosphorus and calcium concentration of the blood in tetany. Although the phosphorus is not regularly increased in infantile tetany, it generally is increased relative to the amount of calcium. In this connection attention may be drawn to the seasonal curve of inorganic phosphate described a few years ago by Hess and Lundagen, more especially to the sudden rise in the blood phosphate which comes about in the early spring, the period when the incidence of tetany tends to be heightened. Whatever may be the nature of the relationship between phosphorus and tetany, it is by no means constant and therefore not one of cause and effect, nor is it fundamental to the pathogenesis of tetany. It seems rather part of the regulatory mechanism of the body for the maintenance of the reaction of the tissues, which is accomplished largely by the excretion of phosphates in the urine. It may be added that although stress has been laid on the distinction between calcium

which is ionized and non-ionized, little attention has been paid to this differentiation in relation to phosphorus.

Some years ago Greenwald suggested *sodium* poisoning to explain the tetany which follows the injection of various sodium salts, including the carbonate, the bicarbonate and the phosphate. In the course of tests on the galvanic irritability of infants, Rosenstern was able to intensify the electrical reaction by the administration of sodium chloride. Tisdall, in a study on the "influence of the sodium ion in the production of tetany," came to the conclusion that the sodium-calcium ratio is the important factor in the production of tetany with the exception of the gastric type.

Some have emphasized the importance of *potassium* rather than of sodium. In 1921 Kramer, Tisdall and Howland found the potassium slightly increased in infants suffering from tetany, and the ratio of sodium and potassium to that of calcium and magnesium likewise increased. It should be noted, however, that this disturbed relationship was the result almost entirely of a decrease in calcium. Wernstedt also regarded potassium as the main cause of tetany, and Gross and Underhill concluded in 1922, as the result of an investigation of parathyroid tetany in dogs, that this condition resulted from a disturbed relationship between potassium and calcium. In general, it may be stated that the studies of the potassium content of the blood of infants suffering from tetany are but few, and that these are of doubtful value owing to the unreliability still inherent in the technique.

ALKALOSIS IN RELATION TO INFANTILE TETANY.

In 1921, Freudenberg and György suggested that infantile tetany is the clinical manifestation of an increased alkalinity of the blood or tissues. This alkalosis was pictured as the result of a slowing down of the intermediary metabolism and a consequent lack of the formation of acid products. A distinction was made between tetany of the blood and that of the tissues. As is well known, an alkaline condition leads to a diminished ionization of calcium, whereas an acid reaction intensifies ionization. This theory, therefore, would serve to explain the decreased physiological action of calcium in tetany. Hand in hand with this alkalosis or trend toward alkalosis, which leads to a diminished ionization of calcium, Freudenberg and György predicated an increase of the phosphates in the blood, a so-called "phosphate stasis," which might be absolute or merely relative to the concentration of calcium. The proofs, on which this theory was founded, were mainly indirect in nature. In the first place, deductions were drawn from the reaction of the urine. It was claimed that in cases of infantile tetany an abnormally high pH was found in the urine, associated with low

values for phosphate, NH_3 and N, in other words, signs of increased alkalinity, and the conclusion was drawn from this phenomenon that an alkalosis, or a trend in that direction, existed in the tissues or in the blood. The hypothesis that this trend leads to a decrease in ionization of the calcium was supported by the well-known equation of Rona-Takahashi in regard to the effect of acid and alkali on the calcium ions. This equation is as follows: $[Ca^{++}] = K\left[\frac{H^+}{HCO_3^-}\right]$ in which $[Ca^{++}]$ is the calcium ion concentration, $[HCO_3^-]$ the bicarbonate-ion concentration, $[H^+]$ the hydrogen-ion concentration, and K the constant depending only on the temperature. Freudenberg and György augmented the bicarbonate buffer system $\frac{H_2CO_3}{NaHCO_3}$, of the original formula by a phosphate buffer system $\frac{NaH_2PO_4}{Na_2HPO_4}$, as alkaline phosphate, as well as bicarbonate, can inactivate calcium. From what has been stated in the chapter on pathogenesis, rickets is, according to this theory, the antithesis of tetany, for it will be remembered that Freudenberg and György associated rickets with a speeding up of metabolism and an increase in the production of acid.

It would lead too far afield to discuss the various studies carried out on animals and infants during the past six or seven years, with the object of testing the validity of this theory. They have included an ever increasing number of chemical and physical manipulations of the blood—determinations of its ions, potentiometer readings, dialysis and ultra-filtration tests, calculations as to the Ca-ion concentration, studies of supersaturated solutions, in addition to ordinary clinical and laboratory procedures. Not a few of the experiments which have been resorted to have been so crude and non-physiological that they have but little value in an interpretation of tetany in infants. In general it may be stated that the theory of alkalosis in the strict sense of the term has not been substantiated. It should be added, however, that Turpin has upheld it fully as the result of a clinical study. There seems but little doubt that a true, in other words an uncompensated, alkalosis does not occur as a part of infantile tetany, for the pH values of the plasma are the same in normal infants as in those suffering from manifest tetany. In both groups Drucker and others have found the pH values to be about 7.4. The same is true of the alkali reserve and of the calcium-ion concentration, as calculated from the Rona-Takahashi formula. Table 26 gives the data of Drucker and Faber in a series of cases of manifest tetany and illustrates the fact that the pH values were not decreased and that, if anything, the alkali reserve of the blood was slightly less during tetany than after the disease had been cured. In his monograph on tetany, Drucker expresses his opinion as fol-

lows: "There is a tendency in most of the cases of latent and manifest tetany toward a decreased bicarbonate content. This diminution, which in conjunction with the corresponding normal pH values is an expression of *a compensated acidosis*, must in all probability be regarded as a secondary effect of the increased formation of lactic acid during excessive muscular exertion (tonic and clonic spasms). I have not been able to detect any primary alkalosis either during the course of latent or manifest tetany which would account for the occurrence of the tetany." The animal experiments of Hastings and Murray, and of Underhill and Nellans, have shown that there is no evidence of either increased alkalinity or of an increased CO_2-combining power after parathyroidectomy, a view which is shared by Greenwald. It may be added that the fact that infantile tetany can be relieved not only by calcium chloride but by calcium lactate, must be regarded as evidence in support of this point of view, as well as in favor of the standpoint that non-ionized calcium diminishes nerve irritability.

TABLE 26.—HYDROGEN-ION CONCENTRATION, BICARBONATE CONTENT, AND CALCULATED PERCENTAGE OF IONIZED CALCIUM OF THE BLOOD IN A SERIES OF INFANTS DURING AND AFTER TETANY. (FROM DRUCKER AND FABER.[1])

pH.			$BHCO_3$ (volume per cent).		CA^{++} (calculated) (volume per cent).	
Tetany.	After tetany.		Tetany.	After tetany.	Tetany.	After tetany.
7.31	7.29	−0.02	39.9	46.4	3.9	3.5
7.42	7.37	−0.05	47.9	48.8	2.5	2.7
7.45	7.39	−0.06	41.0	50.2	2.7	2.5
7.39	7.39	0.0	37.2	45.7	3.4	2.8
7.37	7.39	+0.02	39.9	40.3	3.4	3.2
7.46	7.43	−0.03	38.5	45.3	2.8	2.6
7.37	7.43	+0.06	36.5	56.2	3.7	2.1
7.43	7.42	−0.01	45.3	42.4	2.6	2.8
7.36	7.40	+0.04	42.2	45.3	3.3	2.8
7.50	7.45	−0.05	52.9	44.2	1.9	2.5
7.38	7.37	−0.01	46.3	47.1	2.8	2.8
7.40	7.40	0.0	48.2	43.9	2.6	2.8
7.30	7.42	+0.12	36.9	41.4	4.3	2.9
7.40	7.47	+0.07	36.3	41.4	3.4	2.6
7.40	7.41	+0.01	43.9	49.5	2.8	2.5
7.39	7.42	+0.03	32.9	36.9	3.9	3.2
7.47	7.41	−0.06	42.6	48.9	2.5	2.5
7.38	7.41	+0.03	38.1	54.0	3.4	2.3
7.41	7.32	−0.09	43.1	47.5	2.8	3.2
7.35	7.39	+0.04	41.0	42.3	3.4	3.0
Average: 7.40	7.40	+0.002	41.5	45.9	3.1	2.8
(7.41)[2]			(46.9)[2]		(2.6)[2]	

[1] Jour. Biol. Chem., 1926, **68**, 57.

[2] Average from 35 normal children.

As mentioned, a condition of absolute or relative "phosphate stasis" has been suggested as playing a part in the diminished ionization of the calcium. A large amount of investigation has been carried out likewise on this aspect of the subject. Some of the studies have been on dogs, such as those of Salvesen, others on children, as, for example, those of Klercker and Odin, Drucker and Faber, Woringer and Rohmer. In the main, the technique has consisted of injecting, or of giving by mouth, various phosphate solutions and of noting their effect on the reaction of the blood. The conclusions drawn from these studies accord well with one another. It has been found that even large amounts of phosphate, when given to normal children or animals, do not alter the reaction of the blood as judged by its pH or bicarbonate values. This is true whether an acid or alkaline salt of phosphorus has been used. On the other hand, it is important to note that where latent tetany exists, large doses of phosphate do bring about an increased irritability of the nerves as well as a diminution of the calcium content of the blood. In view of the well-known tendency for the concentration of phosphate to be increased, especially in its relation to calcium, in infantile tetany, this phenomenon cannot be cast aside in considering pathogenesis. It should be added, however, that in none of these experiments was a quantitative relationship established between the fall of calcium and the rise of the "acid-soluble" phosphate.

It is difficult and probably unwise at the present time to enter into a fuller discussion of the pathogenesis of infantile tetany. Although it is evident that this disorder is not associated with an uncompensated alkalosis, any alteration which brings about a trend toward alkalosis tends more or less to the induction of tetany. As a rule, tetany is associated merely with a diminution in the calcium of the serum, which is, as far as we are able to judge, quite unaccompanied by an increase in the alkalinity of the blood or of the tissues.

It should not be forgotten that the chemical nature of all the calcium in the blood is not yet understood. It is known that the serum contains a total of about 10 mg. of calcium. Of this amount about 60 per cent is in a diffusible form and 35 to 45 per cent non-diffusible. The diffusible calcium is partly ionized and partly non-ionized, the chemical and physical nature of the latter fraction being entirely unknown. The ionized calcium constitutes about 2.5 mg. per 100 cc. of serum, as calculated by the Rona-Takahashi formula; in other words, it represents about one-quarter of the total calcium of the blood, which leaves about 3.5 mg. as non-ionized diffusible calcium. The function of this fraction is not known, but it has been suggested by Salvesen and Linder that it forms a reserve on which to draw when the calcium-ion concentration of the blood

becomes low. Meysenbug and McCann and others have shown that in tetany there is no change in ratio between the diffusible and the non-diffusible fraction, which is bound largely to protein. In all the discussion there is one point on which there is universal agreement, namely, that the total calcium is always low in tetany. It is thought that the ionized calcium is likwise reduced. All in all, until we have further information, it would seem the part of wisdom to emphasize the importance of the lowered calcium concentration in the pathogenesis of infantile tetany and, tentatively, to accept the point of view that this decrease is accompanied by a diminution in ionization. It should be mentioned that in nephritis the Ca is just as low, but that tetany does not develop, in spite of the fact that the inorganic phosphorus is at a high level and the CO_2-combining power of the plasma undiminished. This failure of reaction has been explained by taking into account the ultrafiltrable fraction of calcium, which recently has been investigated by Pincus, Peterson and Kramer. In tetany this fraction is greatly reduced, whereas in nephritis its concentration remains unchanged.

On the other hand, Klinke has explained the peculiar difference in nerve irritability between these two disorders by taking into account differences in adsorption—in tetany there is stated to be an increased adsorption of calcium to the colloids of the serum and the tissues, a condition which does not exist in nephritis. Recently, Baar has shown, in an interesting study, that hyperirritability is closely associated with the amount of water which is bound to the colloids, and that by giving a diuretic, such as theocin, the galvanic reaction can be rendered much less sensitive. Some years ago Finkelstein showed that this result could be brought about by means of a salt-free diet. The work of Holt and his collaborators is also against the point of view that ionization suffices to explain tetany. It may be remembered that they injected solutions of NaOH as well as of $NaHCO_3$ intravenously into dogs and found that in some instances convulsions disappeared in spite of the fact that alkalosis must have been increased.

Tetany is not an entity from a pathogenetic point of view. In this regard it may be compared to epilepsy. It is merely a symptom-complex resulting from and giving evidence of, an increased irritability of the nervous system and may be incited by a variety of factors. Loeb's quotient, $\frac{Na + K}{Ca + Mg}$, must be regarded merely as a framework, representing the various agents which are constantly working toward or against the development of tetany in the animal body. Almost every chemical and physical agent in the tissues plays its part in determining the physiological status of the nerves.

Although infantile tetany cannot be regarded as the manifestation

of alkalosis, there are some forms of tetany which are associated with an increased alkalinity of the blood and tissues, or with a shift in the alkaline direction.

In 1920, by means of a simple technique, Grant and Goldman and Collip and Backus turned our attention in a new direction. They showed that the typical signs of tetany could be brought about in adults by means of forced respiration. It is worthy of comment that a simple and well-conceived experiment was able to furnish greater information than had been afforded by elaborate experimental technique. This so-called *hyperventilation tetany* is accompanied by a fall in alveolar CO_2 tension, by reduction in the amount of combined CO_2 and by a rise in pH value to 7.5 or 7.6. The urine becomes more alkaline and the NH_3 excretion diminishes. In other words, we have a true, uncompensated alkalosis, a disturbance of the equilibrium $\frac{H_2CO_3}{BHCO_3}$. It is important, however, to bear in mind that the concentration of calcium in the serum remains unchanged. According to Grant and Goldman and others, the tetany which is brought about is the result of a decrease in ionization of the calcium. It has been suggested that other factors may be at work besides an alkalosis. For example, Greenwald has shown the importance of a disturbance in the function of the respiratory center—of tissue anoxemia resulting from the increased stability of the oxyhemoglobin. It is, however, unnecessary to discuss this aspect in connection with infantile tetany. The tetany of hyperventilation is mentioned merely as the classic example of a form of tetany which is attributable mainly to uncompensated alkalosis.

TABLE 27.—VARIOUS TYPES OF CLINICAL AND EXPERIMENTAL TETANY.

Type of tetany.	Etiology.	Blood.			Remarks.
		Ca.	P.	pH.	
Clinical.					
Infantile	Rickets	Diminished	Normal or increased	Normal	Compensated acidosis (Maxwell and Miles
Osteomalacic	Osteomalacia	Diminished	Normal or increased	Normal	
Adult (idiopathic)	Unknown	Diminished	Normal	Normal	
Parathyroprivic	Thyroparathyroidectomy	Diminished	Increased	Normal	Compensated acidosis
Gastric	Hyperemesis (loss of gastric juice)	Normal	Normal	Normal or alkaline	Marked loss of chloride
Experimental.					
Parathyroprivic	Thyroparathyroidectomy	Diminished	Increased	Normal	Dogs; rats irregularly; compensated acidosis
Phosphate	Low Ca, high P diet	Diminished	Increased	?	In rachitic rats
Starvation	Fasting	Diminished	Increased	Acid	In rachitic rats (Cavins)
Toxic	Guanidine	Normal	Normal	Normal	Dogs
Pyloric obstruction	Loss of gastric juice	Normal	Normal	Normal or alkaline	Marked loss of chloride
Hyperventilation	Forced breathing	Normal	Normal	Alkaline	
Hyperalkalinization	Administration of large amounts of $NaHCO_3$, etc.	Normal	Normal	Alkaline	

Bicarbonate Tetany.—The third form of tetany, which may be included in this group, is the bicarbonate tetany. In 1918, Howland and Marriott described tetany which came about as the result of giving large doses of bicarbonate of soda to children. Since then this condition has been studied by numerous investigators. Many have reported negative results even when large doses of bicarbonate have been given, for example, Tezner, and Drucker and Faber who gave 4 grams a day of this salt for a period of several days. "A shift in the alkaline direction" resulted and in some instances an intensification of the symptoms of latent tetany, but in others, for example, in two cases recorded by Drucker and Faber, the signs of latent tetany could not be rendered manifest by the oral administration of moderate doses of sodium bicarbonate. Holt and his colleagues came to the conclusion that the tetany which they induced was the result of a diminution in the ionization of calcium. This is the prevailing point of view. It is not clear why the reaction in infants should be so irregular following the ingestion of a large amount of bicarbonate of soda. Greenwald regards the convulsions brought about by injections of sodium carbonate or bicarbonate into dogs as the manifestation of "sodium poisoning."[1] There can be no doubt, however, that the so-called bicarbonate tetany is accompanied by a trend in the blood and tissues toward an alkaline reaction and that this change is a factor in heightening the irritability of the nervous system.

GASTRIC TETANY.

Another form of tetany which is intimately associated with a trend toward alkalinity is gastric tetany. In 1918, McCann showed that tetany can be induced in dogs by the application of a ligature to the pylorus. A similar condition comes about in man, adults as well as children, as the result of excessive gastric lavage or of long-continued vomiting, occasioned by obstruction of the pylorus of an organic or functional nature. Under these circumstances the blood yields its acid equivalents for the formation of HCl and consequently contains an excess of basic equivalents. The absorption of HCl from the intestine is prevented by the obstruction and a marked disturbance of the acid-base equilibrium follows. Associated with this form of tetany is an increase in the

[1] It has been suggested by Tezner that this irregularity may be in part a seasonal variation. In this connection, I should like to emphasize the marked difference between young and mature animals in their reaction to influences which affect the calcium level in the serum. Recent experiences in the laboratory have made it evident that the calcium concentration of the serum can be reduced in rats by a very simple measure, by a period of calcium starvation of twenty-four hours, but that this measure leads to little or no reaction when carried out on mature animals. In other words, the regulatory mechanism in regard to calcium is far less well developed, and the level of calcium far less stable in the young than in the adult animal.

carbon dioxide combining power of the plasma, a marked increase in the bicarbonate ions, as well as a marked loss of chlorine. Recently the condition has been termed "chloroprival tetany." This is a revival of a theory which was suggested by Kaufmann over twenty-five years ago. There is little or no change in the true reaction of the plasma and, according to Tisdall, who studied two cases of this kind, the calcium level of the serum remains normal. Gastric tetany must be regarded as due to a decrease in the ratio of acid to base, which probably results in a decrease in ionization and functional activity of the calcium.

THE PARATHYROID GLANDS IN TETANY.

In connection with experimental studies of tetany, mention has been made of the induction of tetany in dogs by the removal of the parathyroid glands. This is one of the most fascinating and important aspects of this question and furnishes a connecting link between the characteristic disturbance of calcium metabolism and the clinical manifestations. It is the prevailing opinion, founded on sound experimental and clinical evidence, that the parathyroid glands play an important part in the regulation of the calcium salts and, incidentally, of some other salts of the body. In 1893 Gley demonstrated the relationship between the removal of the parathyroid glands and tetany. However, he regarded the parathyroids merely as glands which are accessory to the thyroid. Their true independent function was demonstrated in 1896 by Vassale and Generali. It was later found that following their accidental removal in man, symptoms of tetany develop—nervousness, convulsions, increased mechanical and electrical irritability of the peripheral nerves, and a decrease in the calcium content of the blood which cannot be controlled by giving calcium. A similar train of symptoms develops when all the parathyroid glands are removed from a young dog, cat, monkey, etc., the symptoms varying somewhat in different animals, due partly to species peculiarity and partly to the fact that accessory parathyroid tissue may be contained in the thymus gland and continue to function after the operation. The tetany is more pronounced in young animals and in those which are pregnant or lactating—factors which have a similar effect in relation to human tetany. Greenwald showed that the opinion generally held, namely, that following removal of the parathyroids, the excretion of calcium is increased, is just the contrary of what actually happens. Logically we might expect an increased excretion in view of the diminution of calcium in the blood, but metabolism experiments show that it is rather decreased. The deficiency in the blood results from the fact that after the parathyroid glands are removed, the calcium in the bones seems to be no longer available for the

tissues of the body. Hand in hand with this change in calcium, and still more striking, according to Greenwald, is the decreased excretion of phosphorus in the urine. This alteration calls to mind the relative or absolute increase of inorganic phosphate in the serum which is met with so commonly in the tetany of infants and of adults. In fact, the symptoms of parathyroid tetany are remarkably similar to those of "idiopathic" human tetany. The differences are mainly of a quantitative nature—the onset more sudden, convulsions more common and severe, tachypnea and dyspnea greatly exaggerated and death far more frequent. This is as we should expect, bearing in mind that the function of the parathyroid apparatus is eliminated precipitously and that the animal is deprived of practically all of the glands. If only two of the four parathyroids are extirpated, no lowering of the calcium of the blood nor signs of tetany follows, whereas if three are removed, transitory symptoms are brought about associated with a lowered level of calcium to about 7 mg. per 100 cc. of serum.

It was stated at first by Wilson and his collaborators that a condition of alkalosis resulted following parathyroidectomy, a conclusion largely drawn from the fact that injection of hydrochloric acid relieved the tetany. This deduction has been shown by numerous investigators (Hastings and Murray, Underhill and Nellans, Salvesen, Greenwald and others) not to be justified. The titrable alkali of the blood and its CO_2-combining power remain unaltered. Hastings and Murray summarize their study by the statement that "no support is found for theories based on disturbed acid-base equilibrium," and Underhill and Nellans that "after the onset of tetany in general there may be a decided tendency toward a diminished alkali reserve."

Another important link which connects the function of the parathyroids with the development of tetany consists in *the action of the extract of these glands*, more particularly the purified preparation which recently has been elaborated by Collip. By means of this potent extract, when given subcutaneously, the nervous manifestations can regularly be controlled and the calcium of the blood raised to normal, or even supernormal levels. This reaction emphasizes the validity of regarding the parathyroid glands as intimately associated both with infantile tetany and calcium metabolism. Metabolic studies of the effect of parathyroid extract give support to this viewpoint. Greenwald and Gross found that injections of the extract into normal dogs increased the excretion of calcium and phosphorus, whereas just the reverse effect was brought about after parathyroidectomy. They interpret their results as indicating that the parathyroid hormone serves to keep the calcium phosphate in solution or, at least, that it is necessary for the preparation of such a hypothetical substance. The hypercalcemia which it induces

cannot be due to improved assimilation of calcium—for it occurs in animals fed a calcium-free ration—but rather to withdrawal from the bones, which in turn leads to increased excretion by the urinary tract.

Passing mention should be made of the fact that *other glands of internal secretion* have been associated by various investigators with the pathogenesis of tetany. Basch has insisted on the importance of the thymus, claiming that extirpation of this gland brings about convulsions and galvanic hyperexcitability, signs which, in his opinion, should be regarded as the counterpart of infantile tetany. Others have associated the suprarenal and the hypophyseal glands with tetany. There is, however, little experimental basis for linking tetany with a disordered function of these organs, although in view of the interrelation which exists between the various glands of internal secretion, it may well be that more than one of them is involved indirectly in the etiology of this disorder. In this connection mention may again be made of the tetany associated with pregnancy and lactation, but more particularly of the fact that susceptibility to tetany is heightened during the menstrual or œstral periods. Such susceptibility cannot be attributed to a drain or loss of calcium but suggests the interaction of the ovary or other gland of internal secretion.

THE TOXIC (GUANIDINE) THEORY.

Some believe that tetany results from *an intoxication*. The most common expression of this point of view is the *guanidine or methylguanidine theory*, which is based on the premise that these amines are formed as a decomposition product of muscle tissue. Others attribute the disturbance to an unknown toxic agent formed in the intestinal tract, or to dimethylguanidine split off from creatin, or to ammonia or carbamic acid. Viewed in this light, the parathyroids function as a detoxicating agent neutralizing these poisons. The basis of the guanidine conception is the investigation of Koch, who in 1912 isolated methylguanidine from the urine of parathyroidectomized dogs. Somewhat later Paton and Findlay and their collaborators pointed out that symptoms resembling tetany, associated with an increase in electrical irritability and perhaps a reduction of calcium in the blood, could be brought about by injections of guanidine or of methylguanidine. These investigators concluded, as the result of a series of experiments carried out in the course of years, that this type of tetany is due to an intoxication with guanidine bases. Burns and Sharpe, also of the Glasgow school, found guanidine in the urine of children suffering from tetany. However, as recognized by Paton, the methods for determining guanidine in the blood and urine are not satisfactory. Greenwald failed to find an

increase of guanidine, methylguanidine or dimethylguanidine in the urine of dogs following parathyroidectomy, and states categorically that "there are two and only two well-authenticated metabolic changes after parathyroidectomy; one is the lowered calcium content of the serum or plasma, and the other is the diminished excretion of phosphorus in the urine." A point of significance is the fact that parathyroid extract and guanidine do not exhibit the reciprocal control over each other which we should expect if the function of the former were the neutralization of the toxic effect of the latter. On the contrary, Collip and Clark found that the "simultaneous administration of a potent parathyroid extract and guanidine to normal dogs at regular intervals has resulted in a condition of tetany and of profound hypercalcemia. Death has resulted in such experiments within approximately the same time as in the case of animals receiving parathyroid extract only." It should be added that the evidence is conflicting in regard to the important fact as to whether the calcium is always reduced in guanidine poisoning, and whether the administration of calcium always results in allaying the characteristic symptoms of tetany. Salvesen (1923) failed to find it decreased.

Dragstedt and Peacock believe that the toxic substances which lead to tetany are absorbed from the intestinal canal, and that they are normally neutralized by a hormone from the parathyroids. They support this theory by the observation that parathyroidectomized dogs were partially protected from tetany by a diet containing large quantities of lactose which led to the development of an aciduric intestinal flora. In their opinion the parathyroid glands form part of the detoxicating mechanism of the body. They suggest that the production of acid as the result of feeding lactose plays an important part in allaying the symptoms of tetany.

Although it is true that most of the evidence in relation to the toxic theory of tetany is of an indirect nature, it cannot be brushed aside. For example, the control of parathyroid tetany which follows bleeding or the infusion of salt solution, or the intravenous injection of calcium-free Ringer's solution is, it must be admitted, most readily explained according to this hypothesis. The simple theory of a deficiency of calcium due to a lack of function of the parathyroid glands is not absolutely satisfactory. Some other factor seems to be involved. We do not find the parallelism we should expect between the degree of tetany in infants or in animals, and the decrease of calcium in the blood. In other words, although calcium and the function of the parathyroid glands play the dominant rôle, there seem to be other factors which qualify their effect in relation to the development of the symptoms of tetany. How otherwise are we to explain the fact that the increase in the excretion of calcium persists in spite of a greatly lowered level of calcium in the blood? It has been suggested that this phenomenon may result from a lowered

threshold or increased permeability of the intestinal mucosa. Again, the calcium in the blood may be as low as 5 mg. per 100 cc. some months after parathyroidectomy and nevertheless the animal show no signs of tetany. A mechanism of accommodation is at work which we do not understand.

There is no doubt that infants are born with a varying supply or "depot" of calcium in their bones, which constitute the great storehouse of calcium for the body, and that this congenital factor may play a rôle in susceptibility to tetany. Furthermore, it is a well-established fact that the absorption of calcium is defective in the bottle-fed infant. Not only rickets, but to a still greater extent tetany develops in far greater ratio in the bottle-fed than in the breast-fed infant. The degree of gastric acidity also plays a rôle, a low acidity tending to decrease the solubility of calcium. The investigations of Babbott and his colleagues are signif cant in this regard. They conclude that "a lowered gastric acidity and diminished gastric emptying-time are found in manifest tetany and that there is a return of the gastric content to normal acidity and of the gastric mobility to normal activity coincident with the rise of serum calcium to normal, and with the disappearance of clinical symptoms of tetany." They suggest that the effect of fever in inducing tetany may be accounted for in this way. It may be added that Hastings and Murray described a similar diminution in gastric acidity in dogs suffering from tetany following the removal of the parathyroid glands.

The function of the parathyroid glands, which has been considered in some detail, may be summarized by the statement that their office seems to be the stabilization of calcium metabolism. Rickets places a heavy burden on their activity, leading frequently to hypertrophy of the glands, as demonstrated by Erdheim. It is quite possible, as has been surmised, that when rickets has lasted for a long period, the parathyroid glands become incapacitated and are no longer able to maintain the normal level of calcium in the body and in the blood, and that this deficiency of calcium brings in its train an increased irritability of the nerves. Loeb has shown that the blood contains only sufficient calcium to protect the body from the stimulating action of the sodium and potassium ions. As he puts it: "We are therefore indebted to the calcium concentration of the blood that our muscles do not constantly twitch." In this connection the characteristic seasonal incidence of tetany, in infants as well as in adults, may again be referred to, a peculiarity which calls to mind the work of Seidel and Fenger, who showed that the average iodine content of the healthy thyroid gland of sheep, of cattle and of hogs is in general about three times as great for the months of June to November as for the months of December to May. It would be interesting to ascertain whether a similar variation holds true in regard to the specific hormone of the parathyroid glands.

Some have stretched the relationship of the parathyroid glands to tetany still further and suggest that the congenital and hereditary factors in its etiology are due to differences in the activity of these glands. Iselin, for example, drew this deduction as a result of finding that the offspring of rats which had been deprived of their parathyroid glands were more susceptible to the development of tetany than the offspring of normal rats. This point of view is in line with the interpretation of the hereditary factor in some other metabolic disorders, for example diabetes, in which undue susceptibility is attributed to a hereditary functional disability of the specific secretion of the pancreatic gland.

THE METABOLISM OF TETANY.

The *metabolic tests* on infants suffering from tetany have been few—surprisingly few when compared with similar studies on rickets. This is probably due to the fact that tetany generally runs a short and irregular course, and that it is associated with rickets, a relationship which renders it extremely difficult to study the metabolism of uncomplicated tetany. In 1906, v. Cybulski analyzed the intake and output of a seven-month-old infant suffering from tetany—convulsions and laryngospasm, associated with an increase in electrical irritability. As this case has been regarded for many years as a classic example, I have reproduced its data in the accompanying table (Table 28). It will be noted that during the first period an

TABLE 28.—CALCIUM METABOLISM IN A CASE OF INFANTILE TETANY (V. CYBULSKI).

	Calcium intake.	Calcium output.		Retention.	Duration of test.	Remarks.
		Urine.	Feces.			
Period I	1.7560	0.0074	1.3824	0.3662	3 days	Cow's milk
Period II	0.9969	0.0088	0.4526	0.5355	3 days	Woman's milk
Period III	1.5310	0.0310	0.1650	1.3350	4 days	One month later

excessive amount of calcium was lost in the feces, that during the second, when woman's milk was substituted for cow's milk, retention was markedly increased, and that this increase reached even an abnormally high level during convalescence. This investigation has been criticised because cow's milk was fed during the first period, whereas woman's milk was given during the succeeding periods. However, this criticism seems unwarranted in view of the fact that the retention was increased following a change to a diet low in calcium. Schabad, whose metabolic work in rickets has been so

valuable, reported in 1910 two studies on tetany in older infants. In these instances likewise there was a diminished retention of calcium, the excretion both of calcium and of phosphorus being increased. However, the infants had definite rickets as well as tetany, so that the changes represent the metabolic product of these disorders, and it is impossible to gauge the effect of the tetany apart from the rickets.

Recently (1927) Hoag, Rivkin and their co-workers published metabolism tests of 2 cases of tetany as part of a study of the effect of parathyroid extract on the calcium balance; the report included metabolism tests of 1 normal infant, 4 infants having rickets, and 2 with manifest tetany. This investigation has significance owing to the fact that it was controlled by radiographs of the epiphyses, as well as by repeated analyses of the blood for inorganic phosphorus and calcium, and that care was taken that the intake of calcium and phosphorus was adequate. One of the infants, suffering from tetany, was a colored boy, aged nine months, who had convulsions. The serum calcium was 7.1 mg. per 100 cc. The calcium balance was studied during a fore-period of two and two-thirds days without any treatment and showed that output was practically equal to intake. During this period the serum calcium concentration rose to 7.9 mg. It may be added that subsequently large doses of parathyroid extract brought about a rise of calcium to 8.8 in three days, and that the calcium balance changed from −0.03 to +0.01 gm. The second case is still more interesting. As it represents one of the few studies of the metabolism of tetany carried out with the aid of modern technique, I have reproduced its data in full (Table 29). The infant was a white boy, weighing 15 pounds (6.8 kg.) with symptoms of manifest tetany. The diagnosis was verified by a cathodal opening contraction with slightly less than 5 milliamperes, and a concentration of serum calcium of only 4.4 mg. In addition there were clinical and roentgenological signs of moderate rickets.

It will be noted in the table that during the fore-period, that is, the period of untreated tetany, there was but slight retention of calcium, a faintly positive balance. It should be borne in mind that this was an unusually severe case, the serum calcium having fallen to a level that is rarely met with. Evidently an equilbrium had finally been established in regard to calcium. The effect of large doses of parathyroid extract was not great. There was a tendency to an increase in retention, a result which we should not have expected in view of metabolic tests on parathyroidectomized dogs.

Shohl and his collaborators recently found that Collip's extract led to an acid retention in infantile tetany, the urine becoming less acid and the stool more alkaline. From its effect on the potassium balance they concluded that there is some abnormality of potassium metabolism in tetany.

TABLE 29.[1]

	Fore-period 4/19-4/22 (2¾ days).			Test period 4/22-4/26 (4 days).		
	Calcium, gm.	Phosphorus, gm.	Silicon dioxide, gm.	Calcium, gm.	Phosphorus, gm.	Silicon dioxide, gm.
Urine	0.00	0.23	..	0.001	0.27	..
Stools	0.60	0.26	6.76	0.60	0.23	7.90
Total daily output	0.60	0.49	(70.2%)	0.60	0.50	(79.0%)
Total daily intake	0.66	0.51	9.63	0.62	0.52	10
Daily balance	+0.06	+0.02	..	+0.02	+0.02	..
Gm. per 1 gm. silicon dioxide in stool output	0.089	0.038	..	0.076	0.029	..
Calculated on Basis of Same Excretion of Silicon Dioxide in All Periods.						
Daily average output of silicon dioxide	..	..	7.44	..	..	7.44
Theoretical daily total output	0.66	0.52	..	0.57	0.49	..
Theoretical daily balance	0.00	−0.01	–	+0.05	+0.03	..

		Parathyroid extract.	
		Days.	Units.
		4/23	160
		4/24	80
		4/25	120
		4/26	60
		15.5 units per kg. per day	
Mg. per 100 cc.	Serum, 4/19 Calcium, 4.4 Phosphorus, 6.7	Serum, 4/24 Calcium, 6.4 Phosphorus, 5.4	
	Serum, 4/21 Calcium, 4.9 Phosphorus, 7.2	Serum, 4/26 Calcium, 6.5 Phosphorus, 5.3	

THE PROGNOSIS OF TETANY.

In general the prognosis of tetany is good. A distinction must be drawn in this regard between latent or mild tetany and the severe cases associated with repeated convulsions. In contradistinction to rickets tetany may be the immediate cause of death. This comes about either as the result of heart failure, following spastic contraction of the heart muscle or respiratory failure of cerebral origin; death from "broncho-tetany" has also been described. Happily, such a result is infrequent as there are many therapeutic measures available for rapidly controlling the convulsive seizures, and as tetany is generally a self-limited disease. Some cases, however, resist all measures. The percentage of calcium in the blood of these resistant cases may be no lower than in those which respond promptly to acid medication, ultra-violet light therapy, parathyroid extract or irradiated ergosterol.

[1] Hoag, L. A., Rivkin, H., Weigele, C. E. and Berdiner, F., Am. Jour. Dis. Child., 1927. **33**, 910.

It has been shown repeatedly that some indication of tetany may persist for many years, especially the facial phenomenon and galvanic hyperexcitability. This latent irritability of the nervous system may lead to a tendency to convulsions in early childhood beyond the third or fourth year of life. Such seizures are apt to be precipitated by the intercurrence of an infectious disease, for example, scarlet fever, whooping cough or pneumonia, and especially when these diseases are acquired in the spring.

In regard to the ultimate outlook in tetany, there is a striking incongruity between statistics which have been culled from various child-caring institutions and the general impression gained by the practising physician. The former presents a gloomy prospect, whereas the latter regards tetany as a mild disorder. For example, Thiemich and Birk report that among 155 pupils in a school for backward children, 36 or 23 per cent gave a history of having had convulsions or other signs of tetany in early life; 8 a history of convulsions and laryngospasm, 19 merely convulsions and 9 laryngospasm. Forty to 45 per cent of the children who had had convulsions were mentally subnormal and some others showed definite nervous symptoms, for the most part psychic in character; indeed, only one-third of the children seemed to have been entirely spared. Potpetschnigg came to a similar conclusion, based mainly on a study of the children frequenting the clinic in Graz. Among 109 children about three-quarters showed evidences of disability, mainly disturbances of the nervous system of a psychic nature. Vogt studied 116 children in a similar school and found that 28.5 per cent had suffered from convulsions, but that none of these was epileptic. The data of Escherich are somewhat more favorable; he, on the other hand, emphasizes the high mortality among such children, quite apart from the fatalities occurring during the convulsive attacks. Viewing these statistics in the light of non-institutional experience, it would seem that they are open to the criticism, which some of the authors fully appreciated—that the material forming the basis of the data cannot be regarded as typical or representative of childhood. Moreover, the figures in regard to mental retardation are not accompanied by similar data for children of the proletariat living under similar social conditions. Furthermore, the question naturally arises as to whether the convulsions which the children suffered from in early life should be accepted as manifestations of tetany or were due to other causes, a subject which will be considered in connection with the relation of tetany to epilepsy. There can be no doubt, however, that tetany, especially when accompanied by convulsions, sometimes inflicts permanent damage on the individual. It is probably the experience of most physicians that such children present evidences of various nervous manifestations in later childhood. But, viewing tetany broadly, such residual damage is the great exception.

This subject has been given especial attention by Stheeman, who followed a series of tetany cases for many years. He found irritative symptoms involving principally the vegetative nervous system, especially the abdominal vagus, the sympathetic and the vasomotor nerves. Many of these children had a tendency to diarrhea or to abdominal colic and pseudo-appendicitis; some had spastic anemia, pallor which was not accompanied by true anemia, and various forms of angiospasm. He also attributed numerous cases of enuresis to this constitutional defect, the basis of which he believed to be a lack of calcium. However, determinations of the calcium of the blood, made before exact methods had been devised, are not convincing. It would be very interesting to have for comparison a similar study of the sequelæ of tetany and its late clinical manifestations in cases in which reliable analyses of the blood were available.

The question of the *relation of tetany to epilepsy* is one of importance. Although the subject has been carefully studied by many clinicians, a marked difference of opinion still exists as to whether tetany ever predisposes to epilepsy. The difficulties in deciding this question are at present almost insurmountable. For example, if a case of epilepsy shows signs of latent tetany, such as the facial phenomenon or galvanic hyperirritability, should it be regarded as having tetany? Some have designated such cases as "tetanoid epilepsy." Again, if a child has had convulsions or other signs of tetany during infancy and later develops epilepsy, shall we consider this epilepsy a sequel to tetany? Birk gives the following differential points in the diagnosis between tetanic and epileptic convulsions: The epileptic attacks occur much less often; there is no distinction between children who have been breast-fed and bottle-fed; they have no association with the season of the year; they show no galvanic hyperexcitability, and the usual antitetanic therapy, especially woman's milk, is ineffective. He states, and in this he is in agreement with Potpetschnigg, that he has never encountered a history of epilepsy in a case of tetany. Of course, if the calcium in the serum is diminished the diagnosis of tetany is definite. These differential criteria are of value, but hardly satisfactory. In this connection, the opinion of v. Frankl-Hochwart, who must be regarded as the greatest student of adult tetany, should be recorded. He writes: "The epileptic attacks which are occasionally observed in those suffering from tetany should be properly regarded not simply as complications, but as part of the symptom-complex."

There would seem to be a clinical relationship between tetany and epilepsy, but at the present time it is impossible to state the nature of this relationship, or how frequently it is manifested. Escherich's opinion is interesting in this connection: "It is by no means out of the question," he writes, "that epilepsy, just as other nervous diseases, leads to tetany in an individual who is predisposed to this

disorder, or that in an individual suffering from chronic tetany true epileptic attacks should come about, perhaps as a result of tetany." One is dealing with two very similar disorders, the essential nature of neither of which is understood, so that it is clearly impossible at present to state whether and to what extent they are interrelated.

THE DIAGNOSIS OF TETANY.

The recognition of tetany is as a rule not difficult. What has been stated in regard to the diagnosis of rickets is equally pertinent to tetany—errors are due more often to oversight than to a failure to recognize. *In its mildest forms tetany ranks among the disorders of infancy which most often pass unsuspected.* It should be remembered that the tetany age is essentially from the third month to the end of the second year.

There are three mainstays in connection with diagnosis, all of which have been discussed in treating of symptomatology: The Chvostek sign or mechanical irritability of the facial nerve, a manifestation which, however, it is often difficult to interpret unless the reaction is marked. Second, Erb's phenomenon, electrical hyperirritability of the peripheral nerves—more especially a cathodal opening contraction or a cathodal closing tetanus obtained with less than 5 milliampères, or the so-called anodal reversal AOC < ACC. In connection with this sign it should be remembered that the excitability may be absent for some hours after a convulsion. Finally the diagnosis may be established by a chemical analysis of the blood. Percentages of less than 8 mg. per 100 cc. of serum must be regarded as indicating tetany. Border-line cases will have to be interpreted in the light of other clinical manifestations. In manifest tetany the calcium frequently falls to 5 or 6 mg. per 100 cc. This sign is of particular significance as the concentration of calcium in the blood is an exceptionally constant phenomenon, and is rarely reduced in any other clinical condition. If the inorganic phosphate is at the same time somewhat increased, the diminution of calcium points all the more strongly to tetany.

Its differential diagnosis from epilepsy has been discussed. Although points of difference between the two can readily be set down on paper, cases having marked convulsions, extending over protracted periods, frequently cause one to hesitate in prognosticating the future. At times the laryngismus of tetany is confused with *false or spasmodic croup*. The differential diagnosis between these two conditions is, as a rule, not difficult. Spasmodic croup occurs usually in older children—those above the age of three. The child usually is well on going to bed and wakes up with an attack

characterized by a loud, barking, metallic cough which wakes and often terrifies the household; the bark or stridor is long-continued and does not last merely for a few seconds as does true laryngismus; there are usually no signs of nerve hyperexcitability, nor is the disorder associated with rickets; there is a history and frequently signs of a cold, the voice may be hoarse and the chest present evidences of bronchitis.

A much rarer condition which might be confused with the laryngismus of tetany is *congenital laryngeal stridor*, a condition attended with crowing inspiration. This disorder occurs, however, within the first few days of life, which distinguishes it from true laryngismus stridulus, which is rarely met with before the second or third month. The infant does not seem to be perturbed by the inspiratory difficulty, although the retraction of the chest wall shows that there is more or less obstruction.

A clinical phenomenon described some years ago by Neumann and by Ibrahim, which has been termed *nervous holding of the breath* may be confused with laryngismus. When the condition occurs in children under three years of age the points of similarity are marked. This nervous manifestation is probably hysterical and to a greater or less extent under the control of the child; there is no crowing inspiration, but following a fit of anger or a shock, the young child will suddenly hold its breath, become cyanotic and just as it seems about to choke, draw a deep inspiration. This may occur several times a day, or at intervals of days or weeks. The significant points of differential diagnosis are that it is not accompanied by a crowing inspiration, that usually there are none of the signs of latent or manifest tetany, and that the onset of the attack gives one the impression of its being to some extent under the control of the child.

Some cases of tetany resemble *meningitis*. Where there is retraction of the head with opisthotonus, strabismus, or inequality of the pupils, the diagnosis may be perplexing. Reliance will have to be placed on the various signs of tetany which have been described. Bulging of the fontanel is generally a sign of meningitis and not of tetany. It may be necessary to perform a lumbar puncture in order to establish the diagnosis; usually, this will be found unnecessary if the child can be seen a second time.

There may be a combination of tetany with some other clinical condition which tends to induce convulsions. Recently, Powers has drawn attention to the association of tetany with pertussis in infants who develop convulsions in the course of this disease. The recognition of the underlying basis of the convulsions under such circumstances is most important from a therapeutic point of view.

THE TREATMENT OF TETANY.

The treatment of tetany has undergone a great change within the past few years and has become much more satisfactory. Our efforts should primarily be directed toward preventing its occurrence. In this regard a great deal has been incidentally accomplished through the wide-spread employment of cod-liver oil in the prophylaxis of rickets, as this medication is also efficacious in the prevention of tetany. Something no doubt has already been achieved through the recent introduction of direct ultra-violet irradiation. High hopes are entertained from the extended use by the community of either irradiated ergosterol preparations or irradiated dried or fluid milk. Apart from medication, the main reliance in prevention lies in breast-feeding, in giving the baby woman's milk instead of cow's milk. Just what constitutes the essential superiority of woman's milk is not well understood, but all are agreed on the relatively few cases of tetany which develop among nursing infants. If the baby must be fed cow's milk, care should be exercised that it should not be overfed. Most cases of tetany, but by no means all, come about in babies which have received too much cow's milk and are either too fat and pasty or have developed some alimentary disturbance as the result of unwise feeding. It will be noted that the same factors are emphasized as in considering the prophylaxis of rickets—the importance of breast-feeding and of not giving excessive amounts of cow's milk. This parallelism extends to other factors in the prophylaxis of these two disorders—the recommendation of Ibrahim that the best prophylaxis is woman's milk, sunlight and air, applies equally well to rickets and to tetany.

Particular attention should be paid to prevent the occurrence of tetany in premature infants as they are especially susceptible. In fact many premature babies will develop latent tetany in spite of maternal nursing, and even though they obtain cod-liver oil in addition. It would seem advisable to give these infants the advantage of heliotherapy, irradiation with ultra-violet light from artificial sources, or activated ergosterol.

In cases of active tetany attention was centered, until recently, on dietetic treatment. Although this aspect must not be neglected, we are able now to bring about quicker and more certain relief by means of various forms of medication. If the tetany is manifest, for example, if there is laryngospasm or carpopedal spasm, it is of advantage to give the infant a restricted diet for a few days, introducing this period of comparative starvation with a twelve-hour period of absolute starvation, during which nothing is given but large amounts of water. The fat, well-nourished type of child may be treated in this way for a longer period than the thin poorly-nourished baby, to whom a loss of weight is of greater significance.

Finkelstein has emphasized the advantage of substituting for cow's milk a dietary rich in flour or carbohydrates, in other words, various cereals; possibly the benefit from such food lies in its low content of salt. The baby should be kept quiet. Thomson's observation in this connection is interesting: "The frequent bad effects by the removal of these children to hospitals have already been referred to. Ward clinics constitute a real danger in bad cases; I have seen a fatal attack of laryngismus occur in the course of a clinical demonstration."

Calcium Therapy.—During the past few years we have learned the great value of calcium therapy in infantile tetany. It is surprising that calcium was not introduced earlier for this purpose in view of its undoubted effect in the tetany of animals. However, twenty years ago Netter reported "the good effects of the administration of chloride of calcium in tetany, spasm of the glottis, laryngismus stridulus and convulsions." He treated 3 cases successfully in this way, giving as much as 2 grams a day.[1] Calcium may be given in various forms, as the chloride, the lactate, the bromide or the phosphate. My experience has been confined to the first two preparations, which have proved entirely satisfactory. It should be emphasized that calcium must be given in large doses. The chloride, which to my mind is the medication of preference, should be prescribed in doses of 1 gram every two hours in severe cases and every three hours in the milder forms. Six grams a day will generally be found sufficient, although 6 to 9 grams may be given. It acts both as an acid and as a source of calcium (Table 30). The acid effect of this salt depends upon the fact that HCl is liberated in the intestinal tract, through the combination of the calcium with the bicarbonate, phosphate and fatty acids. According to Gamble, Ross and Tisdall 1 gram of $CaCl_2$ is equivalent to the ingestion of 75 cc. $\frac{N}{10}$ HCl, a very considerable amount. Experiments show that its effect is rapid, coming about in approximately one-half hour, reaching its maximum in two to three hours, and disappearing in three to four hours. It is thus evident that *it has but a temporary action* and can in no wise be regarded as a specific therapeutic agent for tetany. If not given in conjunction with a true antitetanic agent, it should be continued for a month, the dosage being reduced gradually, so that the infant obtains about 3 grams a day toward the end of this period. The amount necessary can be

[1] In an interesting historical account Shipley recently has called attention to the fact that the English physician, Walter Harris, in 1689 referred to the treatment of tetany by means of calcium. In "De morbis acutis infantum" he writes about a baby scarcely a year old, suffering from severe convulsions: "I undertook the treatment of this poor child and accomplished a cure by no other medicine than a few ounces of crabs' eyes mixed with crystals of tartar." The bodies which the apothecaries sold under the name of crabs' eyes were in reality the gastric teeth or "gastroliths" from the gizzard of the common crayfish. Shipley estimates that in this instance the child was given about 10 gm. of calcium salts at a time.

1689

gauged by the clinical symptoms, among which the facial phenomenon is of particular value. The calcium should be given in milk, especially the chloride which is irritating to the stomach, and sugar may be added in order to render it more palatable. If the crystalline salt is employed, rather than the dried preparation, the dosage should be doubled. In some cases calcium chloride leads to vomiting and must be discontinued; in such instances calcium lactate will often be found to be tolerated when suspended in milk. This salt must be given in double the amount on account of its low content of calcium and because it does not function as an acid. The bromide of calcium has been recommended and may be given in the same dosage as the lactate. Schabad believed that calcium acetate is particularly well tolerated by the stomach. Some have advised the

TABLE 30.—EFFECT OF CALCIUM CHLORID INGESTION ON THE FIXED ALKALI, BICARBONATE CONCENTRATION AND CHLORID OF THE BLOOD. (AFTER GAMBLE, ROSS AND TISDALL.[1])

A. Measurements of fixed alkali in blood serum from infant H. (tetany) before and after calcium chloride injection.

	Before $CaCl_2$ period, cc. N/10 per 100 cc.	At end of $CaCl_2$ period, cc. N/10 per 100 cc.
Sodium	139.0	138.2
Potassium	6.1	5.6
Calcium	2.6	4.0
Magnesium	1.5	0.9
Total base	149.2	148.7

B. Measurements of bicarbonate concentration in serum before and after calcium chlorid injection.

	Infant W. (normal), per cent of bound carbon dioxide by volume.	Infant H. (tetany), per cent of bound carbon dioxide by volume.
Before $CaCl_2$	54.1	50.4
After $CaCl_2$	40.9	40.0
Decrease	13.2	10.4
Percentage of decrease	24	21

C. Comparison of chlorid increase with bicarbonate reduction in serum from infant H., before and after calcium chloride injection.

	Cl^-, cc. N/10 per 100 cc. serum.	HCO_3^-, cc. N/10 per 100 cc. serum.
Before $CaCl_2$	106	23
After $CaCl_2$	112	18
	+6	−5

[1] Am. Jour. Dis. Child. 1923, **25**, 454.

[2] Chlorids as grams NaCl per 1000 cc.: Before $CaCl_2$, 6.13 gm.; after $CaCl_2$, 6.53 gm.

employment of calcium intravenously. This is a measure which is attended with some danger and has been followed by collapse; it is a procedure to which it will rarely be necessary to resort.

Hydrochloric Acid.—Scheer has recommended hydrochloric acid in the treatment of infantile tetany. He gives the following preparation: 740 cc. of whole milk, 260 cc. of $\frac{N}{10}$ HCl, which is slowly mixed with the milk, boiled and then heated until the curds are dissolved; 4 per cent of cane sugar is then added. This therapeutic agent has been found to be satisfactory according to all reports. The mixture is very acid and there may be difficulty in giving it to some infants. Scheer has recommended that the percentage of hydrochloric acid be increased in cases where a favorable result is not obtained.

Ammonium Chloride.—Freudenberg and György recommend the use of ammonium chloride, an agent which has been shown by Porges and by Haldane to increase the acidity of the tissues. They give 5 to 7 grams a day in a 10 per cent solution, and have found that this preparation acts promptly in overcoming the tetanic symptoms. The action also is ephemeral and purely symptomatic (Table 31). The physiological action of these various preparations is thus given by Gamble and Ross in a summary of their recent investigation: "The administration of ammonium chloride does not raise the lowered calcium content of the plasma found in tetany. The therapeutic action of this salt may be entirely referred to an increased metabolism of hydrochloric acid, which causes a lowering of bicarbonate and an increase in hydrogen-ion concentration in the plasma, both of which alterations operate to produce an increased ionization of calcium. In consequence, a physiologically adequate concentration of ionized calcium is obtained from a lowered total calcium content. The therapeutic action of calcium chloride and hydrochloric acid in tetany is in this respect identical with that of ammonium chloride."

TABLE 31.—THE COURSE OF THE ACIDOTIC ACTION OF NH_4Cl (2 GM.) ON THE TRUE REACTION OF THE BLOOD. (AFTER DRUCKER).[1]

Time.	pH.
10:15	7.42
10:45	7.30
11:15	7.33
11:45	7.37
12:15	7.40
12:45	7.40

Magnesium.—Magnesium was recommended by Berend for the treatment of severe cases. This medication is given subcutaneously, 8 per cent magnesium sulphate solution is injected, giving 0.2 grams per kilogram of body weight. The reports of this form of treatment, which are few in number, are favorable, no signs of intoxica-

[1] Acta Paediatrica, 1927, supplement vol. vi, p. 137.

tion having been noted. However, the fact that it has to be given subcutaneously and that calcium, which functions in a similar way, has been found to be most satisfactory, renders the magnesium therapy superfluous. It has been claimed by some that calcium acts more particularly on the central nervous system, whereas the seat of action of magnesium is peripheral, and that, therefore, the latter is especially indicated in cases with severe carpopedal spasm.

Cod-liver Oil.—It should be remembered that the above measures are merely symptomatic forms of treatment and *must be combined with specific antitetanic therapy such as cod-liver oil, irradiated ergosterol or direct ultra-violet irradiation.* The action of cod-liver oil is slow as it is in rickets; indeed, its main action seems to be on the rickets rather than directly on the tetany. As in rickets, no result is usually noted for about a fortnight, which is too slow for an acute disorder such as tetany. Finkelstein found that of 50 cases of tetany which were not treated, in only 2 did the electrical excitability (cathodal opening contraction) fall to normal within a period of five weeks, whereas among 32 children treated with phosphorus and cod-liver oil, 24 or 75 per cent showed a normal reaction within this period. Rosenstern's study of electrical reactions also demonstrated the value of cod-liver oil in tetany. In his opinion phosphorus combined with the oil is superior to cod-liver oil alone, twice the amount of oil being required to produce the desired effect when it is not given in combination with phosphorus. In some instances cod-liver oil fails to relieve tetany just as is found to be the case in rickets; this failure is often due to a deficiency in the dosage. The effect of cod-liver oil depends essentially upon its content of active ergosterol, which will undoubtedly replace it in this condition.

Irradiated Ergosterol.—Irradiated ergosterol is quite as effective in tetany as in rickets. One of the distinctive characteristics of this remarkable substance is that it raises the level of either inorganic phosphorus or of calcium, depending on which is in low concentration in the blood or tissues. In this respect, its action is similar to that of ultra-violet irradiation or of cod-liver oil. *In tetany activated ergosterol is characterized by its rapid action.* Table 32, which indicates the results of this medication in rickets includes several cases of tetany; we may note that in one instance within a period of nine days, the calcium level was raised from 6.4 to 10.1 mg. per 100 cc. of serum. Although time is not an essential factor in the treatment of rickets it is of the greatest moment in respect to infantile tetany.

Up to the present time it has been difficult to state the exact dosage of irradiated ergosterol. But, as will be brought out in connection with the treatment of rickets, solutions of irradiated ergosterol are about to be standardized so that they will be one hundred times more potent than high-grade cod-liver oil. Maximal doses should be given in infantile tetany. Fifteen drops a day in

latent cases and 20 or even 30 drops in manifest tetany. These large amounts should be reduced to about 10 drops daily after about a fortnight, and continued at this level for a month or more. There is, naturally, no danger of inducing hypercalcemia while tetany is acute.

I quite agree with Bakwin and his colleagues that the treatment of choice in the tetany of infants is a combination of calcium chloride and irradiated ergosterol.

It may be added that recently when confronted with two cases of marked tetany in which convulsions had been almost continuous, an oily preparation of activated ergosterol was given intravenously in a single dose of 10 mg. The convulsions ceased in both cases. In the one, the calcium rose from 6.9 to 10.4 within seven days, and in the other from 5.2 to 10.6 within ten days. This form of therapy is not recommended, but is mentioned merely as a possible recourse in extreme circumstances.

Ultra-violet Irradiation.—Ultra-violet irradiation is a specific agent for tetany, both from a prophylactic and curative point of view. In my experience this therapeutic measure has never failed in the treatment of a full-term infant, whereas cod-liver oil has in several instances. The mode of carrying out the irradiation is the same as in rickets and will be given in detail in connection with the treatment of that disorder. It is advisable to give all premature babies the benefit of ultra-violet ray therapy direct or indirect, irradiated milk or ergosterol, in order to ward off tetany, to which they are peculiarly susceptible. This treatment must be carried out throughout the winter months, for if it is suspended for a period of eight weeks or more, signs of latent tetany often return. In Hoag's experience irradiation brought the calcium to a normal percentage after an average of fourteen days. As mentioned in connection with the relation of season to the onset of tetany, ultra-violet rays at first may intensify nerve irritability, so that it is well to use a feeble intensity of irradiation in the beginning, and to give calcium or acid therapy at the same time. The temporary heightening of irritability may be manifested merely by a lowering of the threshold of the galvanic reaction, rarely by the sudden development of convulsions. It is due probably to a transitory decrease in the calcium concentration of the tissues and the blood, and may be noted in the serum twenty-four to forty-eight hours after irradiation has been instituted.

Parathyroid Extract.—Very recently gland therapy was put on a scientific basis by the work of Collip, who succeeded in preparing a purified preparation by means of acid extraction of the parathyroid gland. When given subcutaneously or by mouth, this preparation raises the calcium content of the blood in normal animals as well as in those deprived of parathyroid glands. At first it seemed that an ideal medication for tetany had been discovered. But

now that the extract has been used in various clinics for two to three years, it has not been found perfectly satisfactory. The clinical results are irregular and the rise in calcium variable. In one instance the symptoms of manifest tetany will yield rapidly, whereas in another no effect whatsoever can be noted. Furthermore, some infants react with marked depression associated with pallor, vomiting and mild diarrhea—symptoms which may give cause for alarm. As yet it has not been possible to obviate these disadvantages. However, even if they are overcome, the significant fact remains that the extract does not act as a curative, but like so many other of the therapeutic measures, is purely symptomatic, increasing the calcium in the blood merely by drawing on the calcium reserve of the bones. In other words, it does not accomplish any more than can be and has been brought about by simpler and more reliable methods—by giving calcium as such, or hydrochloric acid or ammonium chloride. As these forms of medication have been found satisfactory, it is probable that they will not be supplanted by the new extract of the parathyroids.

Symptomatic Treatment.—In addition to the specific treatment of the disorder, symptomatic treatment frequently is necessary, particularly to allay the convulsions and to a less extent the laryngospasm. Our main reliance in this connection is chloral hydrate. This drug is preferably given by rectum, suspended in mucilage of acacia, in doses of 0.5 to 1 gram. Infants have a marked tolerance for chloral hydrate and this dosage may be repeated if the convulsions do not subside quickly. Some give the chloral hydrate by mouth. I have always found it to work successfully when given by rectum. In one case in which by mistake 2 grams were given by rectum to a baby, aged six months, merely undue somnolence resulted. Where there is twitching of the face or of the extremities 0.5 gram of chloral hydrate may be given by mouth every three or four hours until this sign disappears. Luminal also is recommended in a dose of 0.05 to 0.1 gram. Some give bromides or a combination of bromides and chloral, or calcium bromide. In spite of having given calcium, twitching of the extremities and electrical hyperexcitability often persist for days or even weeks until the effect of the specific therapy, cod-liver oil or direct or indirect irradiation, makes itself felt. If the convulsions continue, or a status eclampticus develops, resort may be had to lumbar puncture, a measure which is indicated especially when the fontanel is bulging, which is an exceptional symptom. Its use has been advocated in connection with severe cases of tetany complicated by whooping cough, where the tension of the spinal fluid may be exceptionally high.

In connection with laryngospasm reference has been made to attacks of apnea endangering life. For this accident, massage of the cardiac area should be resorted to, as well as artificial respiration and the subcutaneous injection of the usual heart stimulants.

CHAPTER XV.

THE TREATMENT OF RICKETS.

"Sol maximum remedorum est."—Pliny.

THE treatment of rickets centers around cod-liver oil and ultra-violet light, including in this term, irradiated foods and irradiated ergosterol. It would seem of interest to preface a discussion of the therapeutic indications of these agents by a brief historical account of their introduction into medicine. The history of cod-liver oil is especially instructive and may well serve as a lesson to the medical profession in regard to its attitude toward popular remedies.

VICISSITUDES OF COD-LIVER OIL THERAPY IN RICKETS.

It is usually impossible to ascertain just when and where a remedy not elaborated by man, such as cod-liver oil or fish oil, was first used as a therapeutic agent. There are indications that it was employed by the peoples who lived along the shores of the Baltic and the North Sea, as well as by those on the coast of Scotland, many years before the attention of physicians was directed toward its virtues. The earliest reference to its medicinal use, which we have been able to find, does not emanate from a district bordering on the sea but from the inland city of Manchester, England. The introduction of cod-liver oil into medicine must always be associated preëminently with Manchester.[1] Although we are not informed as to the year in which it was first prescribed for patients of the Manchester Infirmary, we learn from a letter written in 1782 by Dr. Robert Darbey, the house surgeon and apothecary, that the annual consumption of this oil, soon after its introduction in 1766, was from 50 to 60 gallons. In 1789, Percival of Manchester states in his essay "On the Medicinal Uses of Cod-liver Oil," that "this medicine is dispensed so largely in the hospital here, that near a hogshead of it is annually consumed." Percival, himself, according

[1] The weather of Manchester seems to have had an unenviable reputation. The *Manchester Gazette* of October, 1824, comes to the defense of the city as follows: "We think Manchester does not deserve the character for humidity which it has obtained. . . . The narrowness of its streets, we imagine, has gained for this town its character for frequent rain. The sun's rays seldom fall on its pavements, which consequently continue long wet. . . . When we shall have one wide clean street, we shall complain less of the humidity than we do at present."

to the excellent account of Guy, introduced it into the British Pharmacopœia in 1771. The first description of its use is to be found in this letter of Darbey, written in 1782 and transmitted to us by Percival. He tells us that "about ten years since, an accidental circumstance discovered to us a remedy which has been used with great success" (for chronic rheumatism) "but is little known in any country except Lancashire." A woman was cured of chronic rheumatism and "about a twelve-month afterward her complaint returned with double violence, and the same remedy restored her to health again." "Encouraged by this second recovery Dr. Kay, one of the physicians of the infirmary prescribed it for other patients in similar cases; and it answered his most sanguine expectations." It would be interesting to know the nature of the "accidental circumstance." This completes our information in regard to the use of cod-liver oil until the nineteenth century.

One of the most complete accounts of cod-liver oil is to be found in the treatise of Bennett, published in 1848. He informs us that a Dr. Bardsley of the Manchester Infirmary, in the Medical Report of 1807, not only lauded the efficacy of cod-liver oil, but set indications for its use. Among these indications, the one which is of especial interest is its recommendation for "women whose constitutions have been worn out by repeated rheumatic attacks after parturition, and more especially in the decline of life." This undoubtedly refers to osteomalacia. In this connection a reference of Hull, another Manchester physician, should be mentioned; in discussing "the Cæsarean operation" he depicts a typical instance of puerperal osteomalacia which developed in a woman, aged twenty-eight years, following the birth of her third child, and was cured by means of cod-liver oil. Bennett, himself, definitely states that it is of benefit in "malacosteon," in other words osteomalacia, which he describes as a disease differing "from rachitis in its never appearing before puberty, in occurring more often in women than in girls and most frequently in those who have had children." Bennett did not, however, gain his knowledge and experience in England.[1] He had observed the efficacy of cod-liver oil on the Continent. In view of the experience in Manchester during the preceding century, it is odd to read in the dedication of his book of his desire "to introduce this Continental remedy into Great Britain; and again, in his preface, that he hopes "that it may prove as successful in the hands of the British as it has already done in those of German practitioners."

The first account from the Continent is given in the well known

[1] In view of the considerable percentage of rickets which Thomson found in Edinburgh recently, it is difficult to accept Bennett's statement that rickets was "a very rare disease" in that city at the middle of the past century. He writes: "during five years of dispensary practice, in which the diseases of children treated among the poor population at the Royal Dispensary were very numerous, I have only met with 2 cases." (Appendix.)

articles of Scherer or Schenck of Holland, the first of which was published in 1822. It is impossible to state whether the source of his inspiration was England, or originated in a personal observation of the value of the oil among the people dwelling on the shores of the North Sea. It is suggestive, however, that in his paper of 1826, he tells us that his venerated professor in Marburg recounted "that during his stay in England he had seen cod-liver oil used with striking success in rheumatism." A few years previous to this time, he had reported having treated 16 adults and stated that further patients would be observed at the Charité Hospital in Berlin. In this year he introduced the oil into the apothecary shops under the name of "oleum jecoris aselli." In January of the following year, the Society for Science and Art of Utrecht selected as the prize question for the year: "The curative action of cod-liver oil against rickets," this subject having been selected because many reputable physicians in Holland thought this oil of value in the cure of rickets. In 1826, Schenck published a paper in "Hufeland's Journal" on the remarkable value of cod-liver oil in "die Englische Krankheit des Kindes," an article which drew a note of appreciation from Hufeland. It records 3 definite cases of rickets in children about two years of age which were cured by the oil.

Two years before, in 1824, Schuette published case histories of adults and of children whom he had cured with cod-liver oil, and remarked that he had used this remedy for twenty-five years and found it "as specific and reliable as the use of mercury in syphilis." He suggests that the potency of cod-liver oil may be due to imponderable amounts of substances which produce marked changes in the body, but cannot be determined by the chemist. The first glimmer of the antirachitic factor! In the report of the first case, evidently an instance of osteomalacia, he mentions that, up to this time, cod-liver oil had been known only to the tanners. One wonders whether we have here a clue as to the origin of the therapeutic use of this oil; perhaps these workmen were the first to appreciate its medicinal value. *This is the first definite account of the employment of cod-liver oil in a case of rickets.* Schuette writes: "Friedrich Kraus was the first, as far as I know, to use Bergen cod-liver oil for the English Disease; in 1814 he gave it to both his sons, one five years and the other three years of age."

For the next twenty or thirty years the medical literature of Germany, especially "Hufeland's Journal," is replete with articles on the value of cod-liver oil as an "analeptic" or reparative agent, more particularly in cases of rheumatism, scrofula, gout, etc. In view of our newer knowledge regarding the action of vitamin A, it is most interesting to learn from Bennett that cod-liver oil was used for "strumous ophthalmia" (xerophthalmia of the present time) in the children's wards of the Charité Hospital, Berlin. He details 2

cases in which it manifested a curative action, one of scrofulous ophthalmia of four years' duration, associated with specks and ulcers of the cornea, and a case of "xerosis or atrophy of the conjunctiva and cornea."

It is an interesting commentary on medical bibliography that the introduction of cod-liver oil in medicine is frequently attributed to the great Trousseau of Paris or to his eminent teacher Bretonneau of Tours. As a matter of fact, France, as well as Belgium, was rather tardy in taking advantage of this specific remedy. In 1837 Roche communicated to the Medical Society of Paris an interesting account of how Bretonneau became aware of the efficacy of cod-liver oil. It seems that he was treating the child of a Dutch merchant for rickets and was told by the father that in Holland cod-liver oil was a popular remedy for this disorder. Accordingly he prescribed it and was struck by the rapidity of improvement. After that time he prescribed it extensively in rickets. This favorable experience led his pupil, Trousseau, to employ the oil, and in 1850, in an article on osteomalacia, he refers to the fact that it had given excellent results in the hospitals of Paris, both in this disease and in rickets. It may be added that, in this paper, Trousseau confuses rickets and scurvy, disorders which Glisson two centuries previously had sharply differentiated. Two years later Beylard, a student-physician from Philadelphia, published his thesis on rickets from the clinic of Trousseau. By this time the use of cod-liver oil had become wide-spread. In Beylard's opinion, fish oil was just as valuable as cod-liver oil, and preferable for the poor because of its low cost. This statement is somewhat too sweeping, but in general conforms with previous reports from the north of Scotland which recommended the use of the oil of the ray for "ricketty children." Gobley tells us that ray oil, which has a less disagreeable taste and odor, was used in the service of Professor Trousseau with results equal to those obtained with cod-liver oil. Exception must be taken, however, to the statement that Trousseau was able to replace the unpalatable cod-liver oil by a mixture of lard, butter and sugar and obtain equally good results. Recent investigations teach us that such could not have been the case. Since that time, about the middle of the past century, cod-liver oil has been accepted by most French physicians, and is highly recommended in the well-known treatise on rickets by Marfan.

A peculiar situation arose in Germany. In spite of the fact that the virtue of cod-liver oil gained early recognition, its efficacy has been the subject of controversy in that country for almost forty years. This resulted from the teachings of Kassowitz of Vienna, the recognized authority on rickets. It came about in a peculiar way. In 1872 the pathologist, Wegner, showed by experiment that elementary phosphorus exerted a "formative stimulus" on the bones of young rabbits. Wegner was cautious and stated that "it does

not seem probable that one has found a cure for this disorder (rickets) in phosphorus." Kassowitz, a man of quite different temperament, tested the value of phosphorus both in the laboratory and in the clinic, and proclaimed it "a specific remedy for rickets," "a direct, rapid and reliable therapeutic measure for rickets and its individual symptoms," and defended this position stoutly until his death. Incidently, he maintained that cod-liver oil was not to be regarded as a curative for rickets either "from a theoretical or empirical point of view," but that it was merely an easily digested oil. He fell into this error largely as the result of suspending the phosphorus in cod-liver oil, an oil which he chose because it did not turn acid in summer and was less expensive. For these reasons he used cod-liver oil in the dispensary as a menstruum for his phosphorus, suspending it in almond oil and sugar for his private patients. From this time the question of the antirachitic action of cod-liver oil was confused with that of elementary phosphorus, little or no attention being paid to the nature of the oil in which the latter was suspended. Some regarded cod-liver oil with favor, notably Gerhardt, Vogel and Henoch; Heubner suggested that the favorable effect of phosphorus might be attributable to the cod-liver oil in which it was given. However, such was the authority of Kassowitz and of the Vienna school, that numerous others, including Baginsky and Biedert, gainsaid its specific value absolutely. Even the classic metabolism experiments of Schabad in 1910, which clearly demonstrated the superiority of cod-liver over other oils in the treatment of rickets, did not overthrow the scepticism of the children's specialists.

In England and in America physicians have likewise differed in their appraisal of cod-liver oil, perhaps owing to the dominating influence of German medicine in pediatrics. In this country Jacobi—firm believer in the specificity of elementary phosphorus—went so far as to caution that it was doubtful practice to dissolve phosphorus in cod-liver oil, as long as the latter was not a uniform compound. The leading pediatrists, Holt and Rotch recommended it mildly. We read in Still's excellent English text-book, published in 1909, that "there seems to be no specific virtue in cod-liver oil, any other oil will do equally well." By many, cod-liver oil was prescribed merely as a tonic, supposed to be indicated especially for undernourished infants and children. Until recently, the pharmacologists shared and encouraged this point of view—Cushny[1] in

[1] In 1918, in the seventh edition of his well-known text-book, Cushny wrote: "Taken repeatedly, it (cod-liver oil) increases the weight and strength and improves the general condition. The same effects are obtained in healthy persons by the use of good foods and fats." "Its effects are obviously those of an easily assimilable food and it is not a drug in the ordinary sense of the term, and has therefore no place in pharmacology properly speaking, and should be classed along with other foods. It is always treated as a drug, however, because it has often been supposed to have some specific effect, quite apart from ordinary food." In 1924, in the next edition of his book, Cushny stated that "the value of cod-liver oil in malnutrition in the young and in rickets has long been recognized."

England, Meyer and Gottlieb[1] in Germany and others in the United States. Some believed in the antirachitic action of cod-liver oil. In 1917, Hess and Unger carried out a study of the "Prophylactic Therapy for Rickets in a Negro Community" and concluded that "cod-liver oil proved to be a more potent factor than breast-feeding in warding off rickets." In 1920 Howland recommended it mildly in the following words: "Cod-liver oil has been used empirically for a long time. It is regarded by many physicians as a specific in the treatment of this disease. This is perhaps too strong praise, but there is no doubt of its usefulness. Its effect, however, is not very prompt or marked."

Today cod-liver oil is universally acknowledged to be a specific for rickets, one of the few specific remedies with which medicine is blessed. What has brought about this sudden unanimity of opinion? It is due, as has been so frequently the case, to the introduction of new methods—in this instance, of methods which render us no longer dependent on subjective clinical interpretation, but furnish convincing objective evidence. In 1919 Mellanby, in his study of experimental rickets in dogs, published radiographs which left no doubt of the specificity of cod-liver oil and of its marked superiority over vegetable oils. In 1921 Park and Howland showed in a similar way that calcification of the epiphyses could be brought about in rachitic infants by giving this oil. The estimation of inorganic phosphorus in the blood furnished additional objective proof of its antirachitic value. Today the medical profession is fully convinced of the efficacy of cod-liver oil. It is a sad commentary on the fallibility of clinical medicine that a therapeutic action as well defined as that of cod-liver oil could not be conclusively established by means of bedside observation, carried out in many countries over a period of one hundred years, but that physicians had to await the proof of its specificity from non-clinical sources. It must be granted that the difficulties involved were not inconsiderable—chance exposure to the curative action of sunlight, the unnoted advent of spring, a retardation or acceleration in growth of the infant and still other hidden factors tended to confuse the picture and render judgment difficult.

SUNLIGHT AND ULTRA-VIOLET RADIATIONS IN TREATMENT OF RICKETS.

A full discussion of the direct action of sunlight and of artificial ultra-violet radiations will be found in the chapter on Etiology. This achievement will be associated with the name of Huldschinsky

[1] Meyer and Gottlieb, in the fourth edition of their standard work on experimental pharmacology, published in 1920, sum up the virtues of cod-liver oil in the sentence: "It is very effective because it is an easily digested food."

(1919). As early as 1904 Buchholz presented a communication before the German Pediatric Society, bearing the interesting title "Light Treatment of Rickets." Buchholz made use of a "Gluehlicht." It is difficult to surmise what kind of light this was. He tells us that the source was 16 to 25 candle-power lamps, and that a glass screen was placed in front of them. Evidently the intensity of ultra-violet light was weak and almost all of it must have been filtered out by the glass screens. This report of Buchholz's is not at all convincing and can be disregarded in connection with the history of ultra-violet irradiation in the treatment of rickets. On the other hand, the little booklet on Heliotherapy, published by Rollier in 1916, contains a statement which should be remembered. He wrote as follows: "Our experience allows us to state that sunlight exercises as marked an action on the local and systemic condition of the rachitic child as on patients suffering from bone tuberculosis," and again, "the sun cure is without doubt the treatment of choice in rickets." This early recommendation of heliotherapy has been completely lost sight of.

The History of the Activation of Foods by Ultra-violet Rays.—As is well-known, these rays may exert their action indirectly, changing inert substances to specific antirachitic agents, which are being used to an ever-increasing extent in the treatment of rickets. This aspect is so novel and of such broad scientific interest that it seems to merit a chronological review.

In 1924, Hess and Steenbock, independently and almost simultaneously, reported that various foods, for example cotton-seed and linseed oils, which were of no value in rickets, could be endowed with specific antirachitic properties by subjection to the rays of the mercury-vapor lamp. Not only could vegetable oils be metamorphosed by this means, but all vegetables and many foods, for example, spinach, carrots, wheat flour, as well as fluid and dried milk. On the other hand, sugar, starch, gelatin, oleic acid, mineral oil and glycerol could not be activated by the rays. The oils maintained their acquired potency, with slight diminution, for six months to a year.

It will be remembered that the wave lengths which confer protection on infants or on animals are limited to a narrow area of the ultra-violet, with its upper limit at about 310 millimicrons. It was found that this same area of radiations is responsible for the activation of oils and foods—a result which suggested that the process involved was essentially the same. Sunlight acted in a similar way, but owing to the low intensity of its short ultra-violet radiations, its specific effect was comparatively feeble. On this account lettuce grown and plucked in July failed to protect animals from rickets. As stated in considering etiology, the rays of the tropical sun differ in quality as well as in intensity from those in the temper-

ate zones. The tropical solar radiations were found to activate foods, as demonstrated by a comparison of the antirachitic potency of two lots of cocoanut oil which had been obtained from Trinidad—one lot which had been dried in the sun, and another which had been dried in a kiln. The former sample was found to be antirachitic, whereas the latter was inert in this respect. This result calls to mind a time-honored custom of some of the Chinese, who expose their vegetables to the sunlight.

The next question was—what is the relation of this artificial antirachitic agent to the natural specific factor in cod-liver oil? A good review of the principal researches of the chemistry of cod-liver oil will be found in a paper published by Bills in 1927. It had been shown by Zucker and by others that the antirachitic activity of cod-liver oil is inherent in its non-saponifiable fraction, and that the saponifiable or fatty moiety is entirely inactive. The same was found to hold true in regard to the irradiated vegetable oils—only the non-saponifiable fraction showed any antirachitic properties. As the main constituent of the non-saponifiable fraction of oils is cholesterol, inquiry was soon directed to this substance. It was found by Hess and his collaborators, and by Steenbock at the beginning of 1925, that although cholesterol possessed no antirachitic activity whatsoever, it acquired marked antirachitic properties after it had been irradiated for a short period by means of a mercury-vapor lamp; irradiation of a few minutes sufficed to bring about this remarkable change. If, however, the period of irradiation was prolonged for several hours, the cholesterol was rendered inactive, nor could it be rendered antirachitic again. Cholesterol maintained its antirachitic action when dissolved in oil but lost it rapidly when preserved in water or in a dry state. It was of protective value both for the type of rickets brought about by a diet low in phosphorus or low in calcium, and was active when given subcutaneously.

A series of investigations was carried out in order to determine whether the activation of cholesterol was due to a chemical change. By means of the spectroscope, it was shown by Hess and Weinstock (1925) that a chemical change had been wrought in the course of activation, a point of view which was corroborated and extended by the work of Schlutz and Morse. Irradiated cholesterol absorbed ultra-violet radiations in certain definite parts of the spectrum, to a less degree than ordinary cholesterol. A further study, undertaken to ascertain the nature of the change brought about by irradiation, indicated that the action of the ultra-violet rays involved the double bond in the cholesterol molecule, for when saturated reduction products of cholesterol and phytosterol were tested—dihydrocholesterol and dihydrophytosterol—it was found that they could not be activated and did not acquire antirachitic properties. Another indication that irradiated cholesterol had undergone a change was

furnished by a comparison of the cholesterol before and after it had been irradiated, in regard to its well-known property of hemolyzing red blood corpuscles, and of the power of digitonin to inhibit this action.

It has long been established that cholesterol is present in almost every cell of the animal body and that phytosterol, its counterpart in the vegetable world, occupies a similar position. Although this wide dissemination pointed clearly to an important function of these sterols, no definite activity had been linked to cholesterol or to phytosterol, either in physiological or pathological conditions. It was, therefore, of particular interest that these substances acquired specific antirachitic potency after having been subjected to certain ultra-violet radiations. Of all the organs in the body, the brain and spinal cord, more especially the white matter, contain the highest percentage of cholesterol. Another organ which is especially rich in this constituent is the epidermis. The question suggested itself whether the protection or the cure which is brought about in infants by means of direct irradiation is not due to an activation of the cholesterol in the epidermis or adjacent parts. Tests made to elucidate this question showed that although the skin of a cadaver or of a calf showed no antirachitic potency, when tested biologically, it developed this activity following irradiation by the mercury-vapor lamp. In other words, not only could the sterol in the skin be activated in this manner, but the process evidently was one of chemical nature and quite independent of an intact nervous or circulatory system. From this point of view, as Hess, Weinstock and Helman stated in 1925, the superficial skin is an organ which reacts to particular light waves rather than a mere protective covering—the epidermal organ.

THE HISTORY OF IRRADIATED OR ACTIVATED ERGOSTEROL.

At the close of 1924 it seemed as if the origin of the antirachitic factor had been fathomed; that without doubt cholesterol had undergone the remarkable metamorphosis. But soon thereafter, a more searching study, carried out in the chemical and physical laboratories of England, Germany, and the United States, led investigators to question the correctness of this conclusion. The solving of the riddle is the story of the recognition of ergosterol as the precursor of the antirachitic vitamin and seems worth recording. In the summer of 1926, Rosenheim and Webster reported that ergosterol was one of the sterols which could be activated by means of irradiation. They failed, however, to carry out any quantitative tests, to determine whether the product was of high or low potency. On December 10th of the same year, three communications appeared independently, two in England and one in Germany, to the effect that irradiated

cholesterol contained an impurity! Rosenheim and Webster found that cholesterol which had been treated with charcoal could not be activated, and concluded that ordinary cholesterol was contaminated with a substance which they termed "vitasterol." On the same day Heilbron, Kamm and Morton, physicists of the University of Liverpool, reported that by means of spectral absorption tests they had noted an impurity in cholesterol which had been recrystallized, and Pohl of Goettingen likewise reported that a specimen of cholesterol, which Windaus had purified by means of bromination,

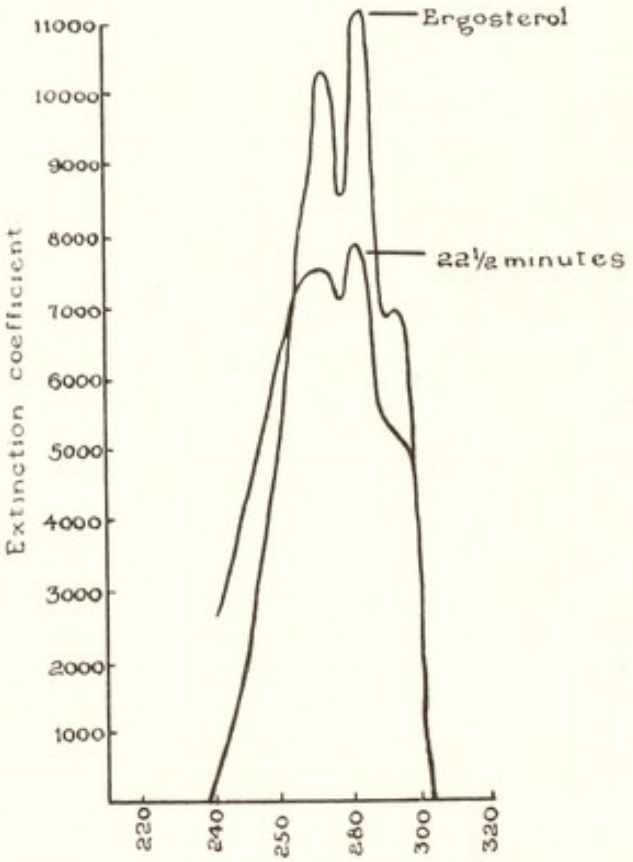

FIG. 51.—Effect of irradiation on the ultra-violet absorption of ergosterol dissolved in alcohol. The three bands with maxima at about 270, 282 and 293 $\mu\mu$ are apparent. After irradiation for twenty-two and a half minutes, the band at 270 has broadened, and (as shown in the succeeding figure) activation has reached its highest point. (Bills, Honeywell and Cox, Jour. Biol. Chem., 1928, **80**, 557.)

had, upon irradiation, failed to develop the characteristic bands of activated cholesterol. About two months later, January, 1927, Windaus and Hess announced that the contamination which had been met by the various investigators was ergosterol, and that this contamination, and not cholesterol, was the illusive "provitamin" of the antirachitic factor.

Although *ergosterol* was known to chemists, having been described by the French chemist Tanret in 1889 and in 1908, it had excited

but little interest. It had been extracted from ergot and various fungi and yeasts, but very little was known as to its distribution in the vegetable world, and nothing whatsoever in regard to its occurrence in the animal kingdom. It is a sterol which is highly unsaturated—it has three double bonds—is very unstable, and has a melting-point which has been placed at from 166° to 183° C., and an optical rotation which has recently been given by Bills and Honeywell as $[\alpha]\frac{20}{D} = -132°$.

The spectral absorption of ergosterol, which is reproduced in the accompanying graph (Fig. 51), indicates, as shown by Pohl and by Heilbron and his colleagues, that there are three main absorption bands—one at 293.5, another at 281.5 and the third at 270 millimicrons. These characteristic ergosterol absorption bands have been observed by Woodrow in a thin film of cod-liver oil by means of a sensitive photoelectric spectrophotometer. Very recently (1928) Bills and his co-workers have described a fourth ergosterol band, which is too feeble to be recognized with the spark. In view of the fact that light is effective only to the extent to which it is absorbed, the spectral curve illustrates in what regions ultra-violet light or energy exerts its action on ergosterol. It shows also why the rays from the mercury-vapor lamp, with their high intensity of short ultra-violet radiations, have such a pronounced antirachitic effect. It will be noted that absorption ceases in the neighborhood of 310 millimicrons, in other words at the uppermost level of what has been designated as the "antirachitic region" of the spectrum. In regard to the solar spectrum, the graph emphasizes anew how limited is the band upon which we depend for protection against rickets.

In connection with cholesterol, it was observed that, following activation, the ultra-violet radiations are absorbed to a less degree, but that if the irradiation is prolonged for some hours, the sterol becomes even less transparent than normally. This phenomenon holds true for ergosterol, indicating that the active factor is photochemically unstable. It is probable that ergosterol passes through various phases in the course of irradiation, that a series of substances are being formed and destroyed—that it is at one and the same time being specifically activated and deactivated. The accompanying graph (Fig. 52), prepared by Bills and his colleagues, shows the relation of the development of antirachitic potency to the duration of irradiation by the mercury-vapor lamp. These figures will differ, according to the source and nature of the irradiation, and the nature of the solvent. The curve shows a sharp rise in potency, which attains its maximum of 250,000 protective units in the course of twenty-two and a half minutes, and a steady loss of potency after that period. At the conclusion of three hours' irradiation, the ergosterol is once more inert. Bills and his co-workers

have followed the formation of the vitamin concurrently with spectroscopic and biological measurements. They found "that when the maximum antiricketic potency was developed 73 per cent of the ergosterol remained apparently unchanged, and the 27 per cent which was altered consisted of a mixture of vitamin D and other sub-

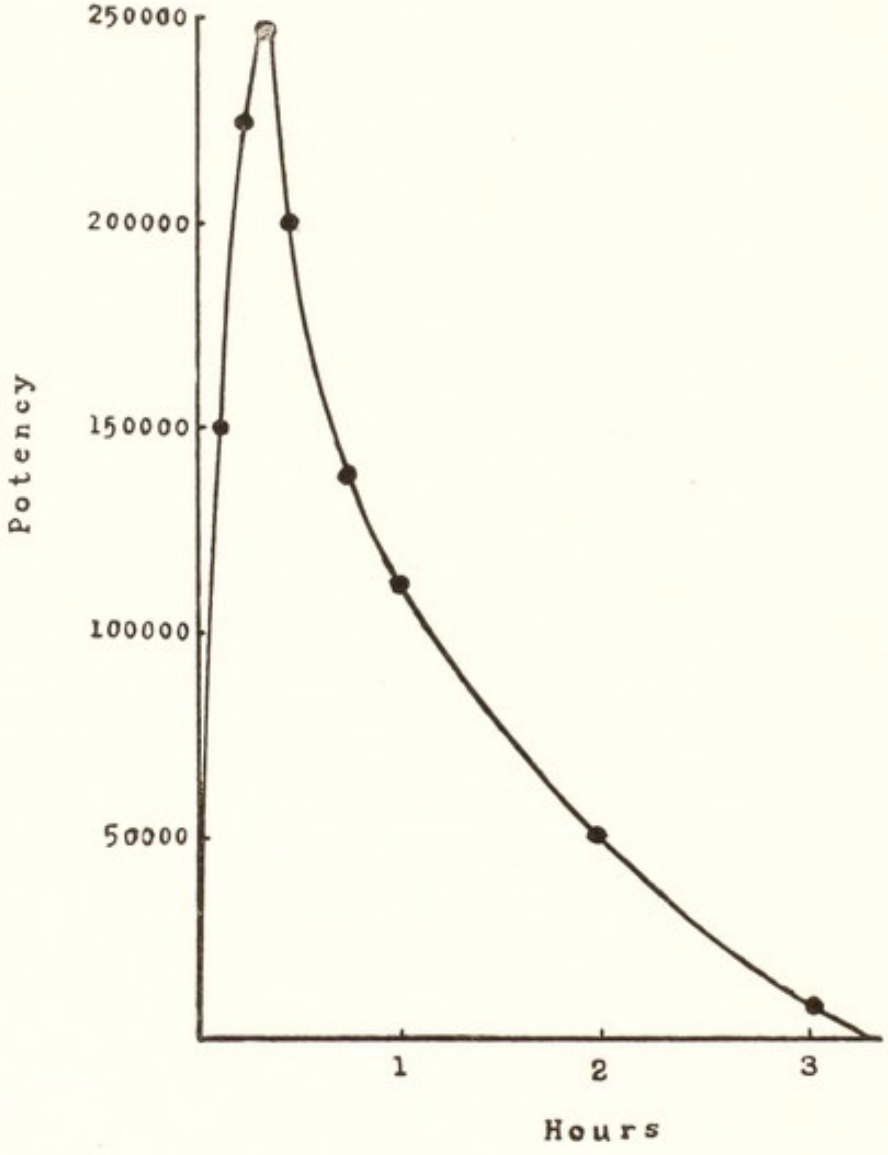

FIG. 52.—Effect of irradiation on the antirachitic potency of ergosterol (alcoholic solution). Graph plotted on the basis of units of standard cod-liver oil. Maximal biologic potency after twenty-two and a half minutes. (Bills, Honeywell and Cox, Jour. Biol. Chem., 1928, **80**, 557.)

stances. The reaction product was 250,000 times as potent as average cod-liver oil." They state: "Lately we have attained 400,000 × activation. That is to say, $\frac{1}{400000}$ of a milligram daily of a product that is known to be at least three-quarters inactive will suffice to prevent rickets in a rat. One millionth of a milligram daily is a

conservative estimate of the dose that would be required of pure vitamin D."

We have no exact knowledge of the chemical nature of the substance which, for want of a better name, we term "activated ergosterol," "the antirachitic factor" or "antirachitic vitamin." Following irradiation it is unchanged in its chemical constants, its specific rotation and its melting-point. As is true of cholesterol, ordinary ergosterol is precipitated quantitatively by digitonin, a property which is lost following irradiation. Although we do not know its chemical nature, it is certain that the active substance has the grouping of the sterol molecule and we can be sure that it develops from either ergosterol or a sterol with the same absorption spectrum. It may be that we are dealing with chemical bodies with certain configurations rather than with a particular substance, and that other substances may be found with this molecular configuration which can be rendered active photochemically. At present, however, this does not seem likely.

The relationship of ergosterol to the etiology of rickets may be rationalized as follows: Ergosterol is contained in the skin and probably in almost all animal tissues and cells, in combination with the omnipresent cholesterol. In order to be activated, it requires but a small intensity of ultra-violet radiations and the resulting product is needed in but a minute fraction of a milligram to bring about calcification of the bones. It is highly probable that the action of sunlight in protecting against rickets comes about through the mechanism of the activation of ergosterol in the skin and in its circulating blood. Kuester and Hoerth recovered about 1.5 mg. of ergosterol per liter from the blood of a steer. The same hypothesis holds good that was suggested a few years ago in regard to the relation of cholesterol to rickets—the point of view which regards the superficial skin as an organ rather than as a mere protective covering. In this connection there are still many questions which press for answer and which, undoubtedly, will be investigated in the near future. The main problem is that of the chemical nature of the substance which we term "activated ergosterol."

PREVENTIVE TREATMENT.

This question has two distinct aspects—the communal and the individual. From a broad point of view, rickets may be regarded as an economic problem, as it is brought about most often, and in its severest form, by conditions inherent in modern civilization. Although it is met with in the country, it is essentially a disorder of the city and of the urban population. In considering preventive measures, one has, therefore, to take into account social aspects, such as improved housing and dwelling conditions, for much will

be accomplished if the sunless tenement can be replaced by abodes which are light, airy and spacious. The importance of good housing in relation to the prevention of rickets and tetany was convincingly brought out some years ago by Miss Ferguson in her study of the occurrence of these disorders in two garden-cities of England, as compared to Glasgow. These are matters which physicians should elucidate, and public health authorities emphasize in their efforts for better living conditions.

Not a great deal can be expected from the use of *the newer window-panes*, which allow the passage of some of the antirachitic ultra-violet radiations. This measure is of value only under exceptional conditions—where access of sunlight is unimpeded and exposure of the body can be carried out; for example, in sunny children's wards or in some of the homes of the well-to-do. It is a device which will not play any rôle in the eradication, or even in appreciably lessening the incidence of rickets in large cities. Most of these window glasses filter out about 50 per cent of the specific radiations, and become less permeable soon after they are set up and subjected to "solarization" or "weathering." But the main difficulty is that the congestion of housing prevents the access of sunlight, and that the ultra-violet radiations, which are of low intensity in winter, are obstructed in the city by the moisture, the dirt and the smoke.

Up to the present time, little or no effort has been made to combat rickets by *prenatal care*, nor indeed is it known how much can be accomplished in this way. It seems probable that the predisposition or susceptibility to rickets is due partly to the faulty nutrition of the mother. To a certain extent, this can be obviated. Recently Hess and Weinstock made an attempt to prevent the occurrence of rickets in a group of infants by giving their mothers adequate amounts of cod-liver oil during the last two months of pregnancy. The attempt met with failure, almost all the babies developing rickets in the course of the subsequent winter. However, Korenchevsky seems to have found that, in rats, rickets can be prevented to a certain degree by feeding the mothers an adequate diet, a conclusion shared by Grant and Goettsch. Our experience in similar animal experiments is that, although rickets can be mitigated in this way, it cannot be prevented.

Breast-feeding is one of the most valuable measures for combating rickets, but should not be regarded as specific. However, infants who develop rickets in spite of having been nursed, almost invariably manifest the disorder in a mild form. Possibly, many of these mild cases might be prevented if the nursing woman were to receive a supplement of antirachitic factor as well as an adequate diet. The prospect of bringing about this result by giving nursing mothers cod-liver oil seemed hopeful, but experiments on animals have shown that the antirachitic potency of the milk is not greatly

increased in this way. Perhaps this goal can be attained by giving irradiated ergosterol, or by direct irradiation. In a recent study of the effect of direct irradiation on the nursing mother, Hess and Weinstock found that the antirachitic potency of the milk could be increased markedly by this means. This procedure may prove to be of practical value under special conditions.

Little can be accomplished in the realm of prophylaxis by modification of cow's milk. As stated in considering etiology, we do not know which constituents of cow's milk lead to rickets, nor, in general, which foods predispose to its development. According to common consent, the only definite factor in this connection is the deleterious effect of overfeeding. No infant should receive more than 1 quart of milk a day, and one showing signs of rickets should be given a smaller amount.

The only food which is of service in the prevention of rickets is *yolk of egg*. Babies under two months of age may be given one-half a yolk of a raw egg, and older infants an entire yolk incorporated in the daily quota of milk. Egg yolk is not as potent as cod-liver oil and therefore will often fail to afford complete protection. It possesses the advantage of being well taken, of adding to the calorific value of the diet, and of furnishing the fat-soluble A factor in large amount. I have used it satisfactorily in the clinic and in private practice for the past five years.

Chicken liver contains a moderate but variable amount of the antirachitic factor, and, with this quality in mind, may well be given to children in the second year of life. Bone-marrow was advocated some years ago by Amistani of Padua, and more recently by Bosányi, but must be regarded merely as an adjuvant. The "drippings" of beef fat are used at times by housewives, especially in England, but cannot be relied upon as a prophylactic to the same extent as yolk of egg.

Sunlight plays an important rôle in prevention, determining frequently whether or not rickets develops. We shall postpone discussion of the technique of heliotherapy and of artificial irradiation until we consider curative treatment. In general, it may be stated that exposure of infants to the air and to the sun's rays can, with safety, be carried out in the city to a far greater extent than is the custom today. It should be borne in mind that diffuse sunlight—"skyshine"—is also of marked antirachitic value; in fact, if infants had to depend for protection solely on the direct rays of the sun, rickets would be far more prevalent. At the present time, the fear that "the baby will catch cold" generally prevents its being exposed to the sun until the summer is almost under way. Under some circumstances, it is advisable not to rely on heliotherapy for protection, but to resort to artificial ultra-violet irradiation. This is particularly true in the case of premature infants and of twins.

Indeed, the former develop rickets so frequently, in spite of having received cod-liver oil, that, as a routine, they should be given ultraviolet therapy, irradiated ergosterol, or irradiated milk. Recently, Hottinger has reported that, at times, all of these newer and more potent methods fail to protect premature infants from rickets.

Cod-liver oil is a specific for rickets, either as curative or as prophylactic therapy. Unless other measures are employed, it should be given in a routine way to every infant whether nursed or artificially fed, much as orange juice or tomato juice is given to protect against scurvy. The marked distinction between cod-liver oil and milk-fat in relation to calcium retention is now fully appreciated. Infants generally tolerate cod-liver oil at two weeks of age. At this time of life 5 drops, three times a day, should be either incorporated in the cow's milk, given separately with a dropper or added to orange juice; a week later the dose may well be increased to 10 drops; after a month it should gradually be increased, so that 1½ teaspoonfuls are being given at three months of age; at four months and thereafter infants should receive 3 teaspoonfuls daily—given either as a teaspoonful three times a day after the bottle, or as 1½ teaspoonfuls twice a day, a method which has its advantages. It should be mentioned that Gerstenberger and Nourse find that as little as 3.5 cc. a day is sufficient to afford protection. Possibly the requisite dose varies according to the nature of the diet. It is true that infants may develop rickets of mild degree in spite of receiving proper amounts of cod-liver oil—an occurrence which Wilson recently has emphasized. Such partial failures are met with more often in the nursling than in the artificially-fed infant, probably due to the low calcium and phosphorus content of woman's milk. The rickets which develops under these circumstances is almost always of mild intensity, and not associated with radiological signs or a lowered concentration of phosphorus in the blood. If the baby has had the benefit of moderate exposure to sunlight, even this mild grade of rickets is exceptional.

PUBLIC HEALTH MEASURES.

What will be the method of choice in our attempt to prevent and to eradicate rickets, in order to equal what has been achieved in infantile scurvy? Until recently, the question was simple and revolved about the possibility of combating its development by means of cod-liver oil. Today it is far more complex. There are now four paths open to us, and, at present, it is not possible to decide which of these is the most practical. The first measure to be considered is the use of *cod-liver oil*. This medication has the advantage of being well-known to the public and of containing not only the antirachitic factor but also the fat-soluble A vitamin. It

has the disadvantages, however, of being disagreeable in taste and odor, of not being well-borne by some infants, and furthermore, of not always conferring complete protection against rickets. It will probably be largely replaced.

The second therapeutic measure is *direct irradiation of the infant* by means of ultra-violet light. This is a far more reliable antirachitic agent; in fact, it may be regarded as an absolute specific. It also is not without its disadvantages. First, there is the expense of the lamp, and the difficulties associated with the proper technique of irradiation. From the communal standpoint, it is not desirable to gather babies together in a clinic or welfare station in order to carry out this form of treatment. The dangers and the seriousness of infection during infancy are important contraindications to a wide application of this method of prophylaxis.

But, instead of employing direct irradiation, the indirect method may be resorted to, and the infants may be given *irradiated fluid or dried milk*. This procedure has the great advantage that it works automatically—that it is quite independent of the intelligence and the conscientiousness of the mother. It is a method which seems promising and is now being carried out by the city of Frankfurt, Germany, apparently with good results. It has been used for too short a time to warrant its being singled out as the method of choice.

The latest therapeutic agent is *irradiated ergosterol*. The pros and cons of this medication will be discussed in detail below. From a public health standpoint the question is whether it will be found safe to dispense such preparations promiscuously without medical supervision. It does not seem wise to follow the suggestion of adding this drug indiscriminately to the milk for infants.

In addition to these four methods, it is possible that by means of supplementing the fodder of the cow with concentrated antirachitic substances, or by the use of direct irradiation, a milk may be produced which will prevent the development of rickets in infants. This has been suggested but not put into actual practice.

From this short review of the present status of prophylactic therapy, it is evident that it holds great promise, but that the time is not yet ripe for a pronouncement as to which of the various measures is best adapted to practical use. The experience of the next few years, in this country and abroad, will no doubt furnish valuable information as to the best method of solving this important question.

CURATIVE TREATMENT.

Rickets is unique in the fact that we have at our disposal several specific remedies for its cure. It is evident, therefore, that the diagnosis once having been established, there is little difficulty in arresting the progress of the disorder. Although the liver oil of the

cod is used almost universally, other fish oils have similar antirachitic action. Biological tests which allow us to titrate the potency of these oils—much as we assay antitoxins—demonstrate that almost all the oils extracted from fish livers possess specific antirachitic activity. Puffer fish and menhaden oils are very potent, salmon oil of moderate potency, and seal oil of no specific value whatsoever.[1] The oil from the flesh of many fish also contains the antirachitic factor.

For the cure of rickets ½ teaspoonful of *cod-liver oil* should be given three times a day after feeding, to a baby three months of age. This amount may generally be doubled after a fortnight. *Dosage depends upon the rate of growth rather than upon the weight of the baby.* It is not unusual for infants six months of age or more to tolerate 6 teaspoonfuls of cod-liver oil daily for long periods without the least disturbance of appetite or of digestion. Without doubt, some babies do not tolerate cod-liver oil, either refusing it or regurgitating it soon after it is given; in such cases, it will be found generally that if one persists for a week or two, the regurgitation becomes less frequent or ceases entirely. Cod-liver oil may be given even when there is a tendency to diarrhea, as it exerts no laxative action. In Germany it is frequently combined with elementary phosphorus. The idea of incorporating phosphorus in the cod-liver oil had its origin in the investigations of Wegner some fifty years ago, and was introduced into pediatrics by Kassowitz. In my experience the addition of phosphorus has in no way increased the efficacy of the oil. Not long ago Miss Weinstock and I carried out a careful experimental study of the effect of elementary phosphorus in rickets. It was found that phosphorus was unable to prevent its occurrence to any degree whatsoever, and did not enhance the antirachitic action of cod-liver oil. It brought about a "phosphorus band" near the epiphyses of the long bones, but not calcification of the proliferating cartilage, nor did it prevent the excessive formation of osteoid tissue (Figs. 20, 21).

There is a general impression that the dark cod-liver oil is more potent than the pale yellow variety, but this is not based on reliable clinical or laboratory experience. A metabolism experiment of Schabad and Sorochowitsch showed that the dark and the light varieties were of equal value in bringing about calcium retention. Cod-liver oil varies markedly, not only in its content of the antirachitic factor, but of the fat-soluble A vitamin. The therapeutic significance of the latter vitamin is not known. This is a matter of

[1] Figures of the comparative potency of the liver oil of fish are open to the criticism that the oil varies greatly from season to season, and especially with the period of spawning. An oil should be used which has been tested and standardized biologically. Cod-liver oil retains its potency unless exposed for a long time to air or to light.

some importance at the present time, when antirachitic agents, more potent than cod-liver oil, but devoid of the fat-soluble A factor, threaten to replace the oil. Pharmaceutically cod-liver oil is often combined with malt in order to disguise its taste. Such preparations usually contain only one-third oil, so that they must be prescribed in three times the usual amount.

It is true that cod-liver oil fails to cure at times; but this is true of almost all remedies known to medicine. Our recent experiences with activated ergosterol lead us to believe that such partial failures must be ascribed merely to inadequate dosage. Unfortunately, this inadequacy cannot be overcome by giving large amounts of cod-liver oil. It has been recently met by fortifying the oil with small amounts of irradiated ergosterol. In my experience, cod-liver oil has never been injurious. This question is raised, because Agduhr recently has reported the development of cardiac lesions as the result of feeding large amounts of this oil.

Concentrates of cod-liver oil have been elaborated. Zucker has reported a method by which a product many hundred times as potent as the original oil can be produced, and Dubin and Funk have prepared a similar preparation which contains also the fat-soluble A vitamin. These preparations have shown their efficacy in laboratory tests, but it is probable that they will be superseded by irradiated ergosterol.

By far the most potent antirachitic—for infants or for animals—is *irradiated ergosterol*. Within the past two years, a rapidly increasing literature has sprung up, consisting mainly of reports of clinical experiences with preparations of this drug. It seems unnecessary to review these studies in detail, as they are in agreement. In almost every instance, the new therapeutic agent has been found to be reliable in the cure as well as in the prevention of rickets. It has been especially remarkable in its rapidity of action—the signs of rickets disappearing more quickly than has been accomplished heretofore by means of cod-liver oil, its concentrates or even by direct irradiation. Beading of the ribs has become less marked, calcification of the epiphyses evident within a fortnight, and craniotabes has disappeared almost miraculously. Very many have emphasized the rapidity with which the cranial bones regained their normal resistance, an effect noticeable frequently within one or two weeks. The phosphorus or the calcium, as the case might be, was brought back to its normal level—in other words, tetany as well as rickets responded to this treatment. In the accompanying table, instances may be noted of a rise in calcium from 8.3 to 11.4 and from 7.8 to 11.6 mg. per 100 cubic centimeters within a month's time, and from 7.9 to 10.9 mg. after an interval of two weeks (Table 32). The exceptional value of irradiated ergosterol in tetany is brought out in the chapter devoted to that subject.

TABLE 32.—EFFECT OF IRRADIATED ERGOSTEROL ON INFANTILE RICKETS AND TETANY.[1]

Case.	Age, mos.	Weight, lbs.	Antrachitic treatment.	Date.	Craniotabes.	Beading.	Blood.		Roentgenograms.	Comment.
							Calcium, mg. per 100 cc.	Phosphorus (inorganic) mg. per 100 cc.		
M. G.	5	12¼	Ergosterol, 2.5 mg., 3/1–3/23	Mar. 1	+++	±	7.9	6.7	.....	Latent tetany.
				Mar. 15	+±	±	10.9	6.6	Healing rickets	
				Mar. 23	±	±	....	....	Marked healing	
G. Y.	2	6½	Cod-liver oil, 15 gm., 1/16–2/20	Dec. 5	0	0	....	....	.....	Triplet; latent tetany; failure of cod-liver oil.
	4½	9¼	Ergosterol, 4.0 mg., 2/21–3/14	Feb. 21	++	++	8.3	6.2	Mild rickets; osteoporosis	
	5½	11		Mar. 14	+	+	11.4	5.4	Healing	
B. Y.	2	5¾	Cod liver oil, 15 gm., 1/16–2/20	Dec. 5	0	±	....	....	.....	Triplet; failure of cod-liver oil; rickets in spite of normal calcium and phosphorus.
	4½	8¾	Ergosterol, 2.5 mg., 2/20–3/15	Feb. 21	+++	++	10.1	6.3	Very slight rickets; osteoporosis	
	5½	11		Mar. 15	±	++	11.4	9.6	Slight healing	Diminished phosphorus in urine.
I. V.	7	11	Ergosterol, 6.0 mg., 4/4–4/13	April 4	+++	+±	6.4	4.7	Marked rickets; osteoporosis	Latent tetany; improved appetite; gain in weight; improvement of musculature.
	7½	11¾		April 13	+±	+±	10.1	4.7		
C. H.	9	12½	Vitaglass, 2/13–3/15	Jan. 16	+++	+	10.0	4.4	Definite rickets	Twin; improvement of craniotabes with progressive rickets.
			Ergosterol, 2.5 mg., 3/16–4/1	Mar. 16	±	++	9.9	4.2	Rickets worse	
	11	15		Mar. 29	±	++	11.2	6.2	Healing	
M. D.	4½	9¼	Cod liver oil, 15 gm., 1/27–2/16	Oct. 30	0	0	....	....	.....	Twin; latent tetany; failure of cod-liver oil.
			Ergosterol, 4.0 mg., 2/16–3/14	Feb. 16	++	+±	7.8	3.8	Mild rickets; osteoporosis	Diminished phosphorus in urine.
	5½	10¾		Mar. 14	±	+±	11.6	10.4	Healing	Sweating disappeared.
F. H.	2	6	Ergosterol, 0.5 mg., 5/4–6/19	May 3	++	+	....	....	Mild rickets; osteoporosis	Premature infant; hypercalcemia with progressive rickets; increase of irradiated ergosterol brought about healing within a week.
	3	8½	Ergosterol, 2.5 mg., 6/19–6/25	June 19	++±	+±	13.6	4.2	Rickets worse	
	4½	9¾		June 25	+ to +±	+±	12.3	6.0	Healing	

[1] Hess, A. F., Lewis, J. M., Rivkin, H.: Jour. Am. Med. Assn., 1928, **91**, 783.

Hottinger has reported favorable results in a case of adult tetany as well as in three instances of osteomalacia, and Starlinger was able to cure a case of long-standing osteomalacia which had resisted other measures. Meyer showed that it is also of value in the treatment of the type of rickets which is complicated by multiple fractures; in his case the concentration of inorganic phosphorus in the blood was only 1.6 mg.

The only disadvantage is that the inorganic phosphorus or the calcium may rise, in some cases, to abnormally high levels. This occurs especially in normal infants, where large amounts have been given for prophylactic purposes. The phosphorus may reach a concentration of 10 mg. or the calcium 15 mg. per 100 cubic centimeters of serum. Accompanying the hypercalcemia, there may be drowsiness, pallor, loss of appetite, and signs of irritation of the kidneys—all of which are quickly dispelled when medication is discontinued. Such symptoms are very exceptional. Strangely enough, they are scarcely mentioned in the reports from Germany, where irradiated ergosterol has been used most extensively. In a study of this question, Hess, Lewis and Rivkin were unable to determine why it was that certain infants reacted unfavorably to this drug. The fear of hypercalcemia should not militate against the use of irradiated ergosterol in rickets.

The problem of dosage, unsatisfactory in connection with all antirachitic agents, has assumed a new aspect in regard to irradiated ergosterol. There is no longer the question of being able to give sufficient of the antirachitic factor, in view of the fact that the new specific is many thousand times as potent as a high grade of cod-liver oil; 1 ounce (30 gm.) of average activated ergosterol is the equivalent of several tons of cod-liver oil. In the past it has always been difficult to administer an adequate amount of cod-liver oil. Today, on the contrary, care has to be exercised not to give an overdose of the specific. Indeed, judging from the biological titration of various preparations, it would seem that the tendency has been to give excessive amounts, decidedly more than is necessary to bring about protection or cure.

It is difficult, at the present time, to lay down exact rules in regard to the dosage of irradiated ergosterol. In the first place, clinical experience is as yet too limited. But, of far greater moment is the fact that the preparations differ so markedly, one from another, that there is no well-defined point of departure for discussion. Biological tests on rats have shown the potency of four widely used preparations—made in Germany, United States, France and England—to bear the following ratios to one another, 2500 to 100 to 80 to 14! That such differences should exist is not to be wondered at, when we bear in mind that there are marked distinctions in the technique of irradiation and in the strength of the solutions. Until

these irregularities are righted, until there is standardization of various preparations, clinical reports cannot be satisfactorily compared.

It is evident that a categorical statement of dosage expressed in terms of milligrams can have but little meaning. Even if we may not be willing to grant that the action of irradiated ergosterol is the counterpart of that of cod-liver oil, the most reliable standard for computing the dosage of the former is in terms of the latter.[1]

If irradiated ergosterol is to be used on a large scale and prescribed intelligently throughout the United States, the preparations must be of uniform strength; in other words, a drop must represent a definite amount of the antirachitic agent. The best way to bring about this highly desirable situation would seem to be to assay it so that solutions have a potency one hundred times that of a high-grade standard cod-liver oil. This basis has already been established for some preparations and might well serve as a measure for all. In the course of a considerable clinical experience with a pharmaceutical preparation of this titer, I have found that approximately 8 to 10 drops a day is *the prophylactic dose* for infants which are growing at the normal rate.

Premature and exceptionally rapid-growing infants must be considered as a separate group, and dosage gauged according to a different scale. They will require at least 15 drops a day. Even more should be given if signs of rickets develop. If loss of appetite or slight diarrhea should supervene, medication should be temporarily discontinued.

For cure, 15 drops of this standardized irradiated ergosterol should be prescribed in cases of mild rickets, and 20 drops for the moderate cases. Severe instances, such as are rarely met with, excepting in Italians and negroes, will require still larger amounts for a short period. This same higher dosage will probably be found necessary for cases of late rickets and for osteomalacia, which are notably refractory. Where exceptionally large doses are given for prevention, it would seem of advantage to control medication by occasional estimations of both the calcium and the inorganic phosphorus content of the blood.

No doubt these directions will have to be modified in the light of future experience. It is preferable that we shall have to increase, rather than decrease the dosage. As there is a tendency for irradi-

[1] For the young rat, the minimal protective or curative dose of a good cod-liver oil is about 7 mg. daily. The average amount of oil given to an infant is about 3 teaspoonfuls or 15 gm. daily, so that we now give the infant somewhat more than 2000 "rat units." The protective or curative dose for the rat of an average preparation of irradiated ergosterol is about 0.0001 mg., thus 2000 "rat units" of this sterol is equal to about 0.2 mg. If we prescribe, as suggested, from 0.5 to 1 mg. of irradiated ergosterol, we are giving the equivalent of about 7 to 14 teaspoonfuls daily of cod-liver oil. A daily dose of 5 mg. represents about 70 teaspoonfuls of cod-liver oil, an unnecessarily large amount.

ated ergosterol to continue to exert its effect for a considerable period after it has been discontinued, it may be of advantage to give it interruptedly for prophylaxis or perhaps only a few times a week. Such details will have to be worked out in the clinic and cannot be solved by observations in the laboratory. The difficulty which we are experiencing in setting the therapeutic dosage for activated ergosterol is one which is associated with the introduction of any new preparation. Irradiated drugs and foods constitute the newest chapter in therapeutics and pharmacology, and are being investigated with all the approved methods of modern medicine. In view of the high degree of activity and ease of administration of irradiated ergosterol, it should prove a most valuable addition to our rapidly increasing fund of specific antirachitic agents.[1] As stated in 1927, "instead of ergosterol, *irradiated yeast* may be used as an antirachitic. This product has been found highly effective in animals and in infants." There may well be a field for this preparation, especially where the matter of expense is of prime importance. Activated yeast can be prepared at low cost and is sufficiently potent for all therapeutic purposes. It is now being used to prevent "leg-weakness" in chickens.

Ultra-violet irradiation is a far more potent and reliable specific than cod-liver oil. It may be secured from the sun's rays or from an artificial source such as the mercury-vapor or the carbon-arc lamp.

The difficulty connected with heliotherapy in this climate is that it is not available in sufficient intensity during the very season when rickets is most marked and wide-spread. Although infants, if properly protected, can be exposed to the sun during the winter months, the specific radiations are of such feeble intensity at this time of the year that they bring about but slight calcification of the epiphyses. A few years ago I made a careful therapeutic test of the curative value of heliotherapy during the months of January, February and early March and found it unsatisfactory. A special garment was devised for the infants in order to keep them warm. This consisted of a heavy woolen outer garment with elastic bands at the axillæ and at the groins to prevent the cold air from entering beneath the clothing and chilling the body. The feet and hands were also well protected, but the legs and the arms were left bare and exposed. Our main difficulty was that, owing to the inclemency of the weather, the babies could be exposed only about every other day and for periods of merely an hour or two. After carrying out the treatment throughout the month of February,

[1] It might be thought that cod-liver oil could be rendered more potent by means of irradiation. It has been found, on the contrary, that its antirachitic value is decreased following exposure to ultra-violet rays. This subject has been carefully investigated by Adam from a chemical and physical standpoint.

it was found that practically no healing had taken place, as judged by the radiographic picture and the inorganic phosphorus content of the blood. The Vienna Commission, composed of Chick, Dalyell and others from the Lister Institute, cite an instance where exposure of the face, hands and legs for a total of thirty-one hours on ten sunny days between December 22d and January 11th did not prevent the development of rickets. Such failure is not surprising when we consider that Dorno has estimated that in Davos, Switzerland, the ultra-violet radiations at midday, at this season of the year, are only one-twentieth as intense as in July. In view of the fact that artificial irradiation can be employed more easily and is so much more effective, it seems preferable in this latitude from the beginning of December until April.

The technique of carrying out *heliotherapy* is as follows: At first the legs are exposed, the feet being protected by socks in the early spring and autumn. The first exposure should be for ten minutes and is to be regarded as a preliminary test to gauge the susceptibility of the individual. On each successive morning the treatment may be prolonged five minutes until the infant is being exposed for one-half hour daily. On alternate days, the arms are treated in the same way—at the beginning for ten minutes and increasing the period as with the legs. As soon as weather permits, the trunk is exposed, the baby being clad merely in a diaper with the hands and feet covered. The head should always be protected with a light cap; the eyes may be shielded. Mothers and nurses are often greatly concerned lest the sunlight prove harmful to the eyes, but in my experience neither conjunctivitis nor any other injury to the eyes has ever resulted. As is well known, blondes are in general more sensitive to ultra-violet rays than brunettes, but there are exceptions to this rule, so that care should always be exercised at the beginning of treatment. Every year I see one or more infants who have developed painful blisters or bullæ on the face, as the result of exposure to the sun in the early spring. This burning can be prevented by applying a thin coating of oil or vaseline to the face, previous to placing the babies in the sunlight. It is not necessary to extend the exposure beyond one hour a day; in fact, in the warm weather longer periods are contraindicated. In the summer, it is well to carry out heliotherapy during the early morning or late afternoon hours and not between eleven and three o'clock, when the heat is greatest. Following treatment, the infant should not become pale, nor should its rectal temperature rise. The results of heliotherapy in rickets are remarkable—the epiphyses rapidly calcify, the inorganic phosphorus in the blood increases, and there is marked improvement in the nutrition of the skin and the muscles. Benefit can be noted often in a fortnight. The presence of marked anemia delays the cure, especially when it is associated with

an enlarged spleen. This is true of treatment with irradiation, cod-liver oil or irradiated ergosterol. On the other hand, I have seen an infant with but 75 per cent hemoglobin improve definitely following irradiation, in spite of the fact that the hemoglobin decreased. Another case with only 48 per cent hemoglobin responded promptly to irradiation.

Artificial irradiation may be substituted for heliotherapy. The sources most suitable for this purpose are the air-cooled mercury-vapor and the carbon-arc lamps. The former emits ultra-violet rays of far shorter wave lengths than those of the sun, the spectrum from the carbon-arc resembling more nearly that of the solar radiations. The technique of artificial irradiation is still highly empirical, as no satisfactory method has been devised for measuring the dosage, although many gauges have been suggested for this purpose. In the use of the mercury-vapor lamp, the guide to the proper intensity of irradiation—in other words to duration of exposure and distance from the burner—is the induction of slight and the avoidance of marked erythema. As a matter of fact, neither erythema nor pigmentation is an accurate gauge of dosage, for by employing short and frequent irradiations, it is possible to cure rickets without occasioning either. Our therapeutic procedure, which as stated, is purely empirical, is as follows: For the average case, the child is irradiated every other day for a total period of four weeks. In a severe case, the time may have to be extended to eight or ten weeks. If treatment is begun after January, it will not be necessary to repeat the course of treatment during the winter, but if it is begun in the autumn, a second series of irradiations should be given before March. The lamp is placed at a distance of 3 feet from the body and exposures of the front and of the back are carried out alternately. The exposures are at first for two minutes, and are increased by one minute at every session, until a total of thirty minutes is reached. These rules can serve merely as a general guide and must be modified according to the individual case. Special care must be observed in the treatment of blondes and of infants which are markedly atrophic.

The effect on the rachitic process brought about by irradiation with the mercury-vapor lamp is remarkable. Within ten to fourteen days radiographs show new calcification at the epiphyses as well as calcification of the carpal centers. However, neither irradiation from the sun nor from any artificial source confers a prolonged protection against rickets. Time and again, as emphasized in considering "Recurrent Rickets," I have observed a second attack develop in spite of a thorough course of irradiation during the previous winter. The following case shows that even two periods of ultra-violet irradiation may fail to prevent a recurrence:

Case 8.—M. E. was admitted in February when six months of age, showing definite signs of rickets; the roentgenographic picture disclosed some transverse lines at the epiphyses. When eighteen months of age, in February of the subsequent year, the child again showed rickets as judged by beading of the ribs, enlargement of the epiphyses and rachitic changes of the distal ends of the radius and of the ulna. These signs of rickets, like those of the first attack, disappeared as a result of ultra-violet irradiation. Much to our surprise, a routine examination during the following September, when the baby was twenty-six months of age, revealed a third attack of rickets, that is to say, a second recurrence. Again the evidences were definite both clinically and objectively. Irradiation by means of the carbon-arc lamp was instituted, and the third attack of rickets yielded as had the others.

For prophylaxis, a mild intensity of irradiation is sufficient. Exposures of five minutes (at a distance of 3 feet), given once or twice a week, will be found to afford protection under average hygienic conditions. There can be no doubt that the prevailing tendency is to irradiate more than is necessary. All infants should be given some kind of preventive treatment, which should be carried out until the child is three years of age.

Artificial irradiation cannot be regarded as the counterpart of heliotherapy, as is evident from the difference in pigmentation which they occasion. The pigmentation which develops following exposure to the rays of the mercury-vapor lamp is of a more brown and a less ruddy hue. Furthermore, although the texture of the skin is improved, it does not become as elastic nor as firmly bound to the underlying connective tissue as when heliotherapy has been employed, nor does the turgor of the muscles become quite as good. These differences between natural and artificial irradiation were emphasized a few years ago in a group of children which had been irradiated regularly from November to March by means of the mercury-vapor lamp. At the beginning of April a few exposures to sunlight brought about pigmentation of a quite different shade and an improved texture of the skin.

In judging of the curative process, the main criterion should be the radiographic picture, and only secondarily should we rely on the chemical analysis of the blood. It must be borne in mind that changes in the beading of the ribs may lead to a false interpretation, as the rosary may become firmer and more pronounced due to calcification and a lack of fluid at the costo-chondral junctions. Thus, healing may be readily interpreted as an intensification of the rachitic process. Naturally, bowing of the legs, the frontal bosses and other malformations of the skull will be unchanged by treatment. On the other hand, craniotabes undergoes very rapid healing. Frequently, but by no means always, there is a general tonic effect,

the appetite is stimulated, sleep is sounder, and the child is more vigorous. In an investigation of "grippe," it was found that the development and frequency of respiratory infections were uninfluenced by systematic treatment with the mercury-vapor or the carbon-arc lamp, nor was the percentage of hemoglobin nor the weight of the infants definitely improved.

In this connection, it should not be forgotten that solar radiations shorter than 295 millimicrons do not reach the surface of the earth, and, therefore, that man, in the course of his evolution, has never had to become adjusted to rays of a shorter wave length. No evidence has been adduced to show that radiations of less than 295 millimicrons exert a harmful effect on the tissues or cells of the body, but as is true of many biological phenomena with which clinical medicine is confronted, it is difficult to appreciate harmful reactions of mild degree. Until we have reliable data on this important subject, it would seem preferable to interpose appropriate filters so as to intercept rays which are shorter and more irritating than those of the sun. As the result of a study of the antirachitic activity of monochromatic radiations, Sonne and Rekling state that wave lengths of about 280 millimicrons are most potent, those about 300 millimicrons are effective, and those around 260 millimicrons are of no value.

Instead of the mercury-vapor, the *carbon-arc lamp* may be used. From a practical therapeutic point of view, each of these sources of ultra-violet rays has its peculiar advantages. The mercury-vapor lamp costs more initially, but is less expensive to operate. It is more practicable, due to the fact that it can be attached to the ordinary electric light socket, and, therefore, can readily be employed in the household. Its main disadvantage is that, owing to the shortness of its ultra-violet radiations, it may cause superficial burns unless the intensity of irradiation is carefully supervised. The carbon-arc lamp, on the other hand, requires at least 15 ampères and, therefore, cannot be adjusted to the ordinary light socket and is more expensive to operate. Furthermore, the carbons have to be replaced after the lamp has been used for a few hours, and their ignition produces a disagreeable ash. On the other hand, this type of lamp does not induce burns and can be manipulated by an unskilled or untrained person. As pointed out above, its spectrum approaches more nearly that of the solar rays.[1] The technique of using the carbon-arc lamp is similar to that of the mercury-vapor lamp, except that the duration of exposures must be about twice as long. A group of babies in the clinic or the hospital may be

[1] In referring to the action of the rays from the carbon-arc lamp, I have in mind carbons in general use. It is possible to obtain carbons with various "cores," which emit rays of shorter or of longer wave lengths.

exposed to the rays of a centrally placed carbon-arc lamp. However, this procedure involves the danger of contact infection.

A still greater effect may be obtained when cod-liver oil is given in conjunction with ultra-violet therapy. Combined treatment of this kind is to be recommended especially for premature babies who frequently fail to be fully protected by even large doses of cod-liver oil. In my experience, ultra-violet light has failed only once to protect or to cure an infant from rickets; this was in the case of a baby that suffered also from diabetes. However, there are reports of failure in uncomplicated cases, even with the combined therapy. An exceptional case, which resisted treatment with cod-liver oil as well as repeated irradiation from a carbon-arc lamp, has been reported recently by Schier and Stern.

In addition to specific therapy, massage and warm baths may be used to advantage. Findlay has strongly advocated *massage and exercise*, measures which must be regarded as adjuvants to improve the nutrition of the muscles. The arms and legs should be massaged daily, if possible, and passive exercises employed. Standing and walking, which are frequently retarded in rickets, may be hastened by these means. Warm saline baths, about 250 gm. of salt to the bath, have been recommended as a stimulant to the nerves of the skin and as a general tonic. French clinicians believe that the climate at the seashore is preferable to that in the mountains, and several health resorts for the cure of rickets have been established along the coast of the North Sea and the Bay of Biscay. It is quite possible that the superiority of the seashore lies in the marked intensity of sunlight to which the children are exposed while on the beach.

In addition to the cure of the active process, measures should be taken to alleviate the damage which has resulted from rickets which is past and healed. The most common deformities are those of the legs, of the thoracic wall, and of the spinal column. It is surprising to what degree Nature may bring about a spontaneous cure of bowed-legs. On this question orthopedists are apt to differ with pediatrists. In my experience, even bowing of moderate degree has frequently become straight by the time the child has reached the age of six or seven years. As mentioned previously, we have a striking example of this spontaneous curative process in relation to negro children in New York City. Although rickets is almost universal among negro infants, the great majority of the children of school age have straight legs and bodies. Among the children of a public school where the attendance is composed almost entirely of negroes, I have repeatedly noted that bow-legs are not especially prevalent among the pupils. Knock-knee also disappears, but not so readily.

Infants which show a tendency to bowing of the legs, especially

those which are above the normal weight, should, if possible, be kept off their feet. Similarly, infants with curvature of the spine, for example a slight kyphosis, should not be allowed to sit, or should be permitted to maintain this posture for only short periods. While being nursed, they should be placed in a recumbent rather than in an upright position. As infants which have marked craniotabes are apt to develop asymmetry of the skull from pressure on the soft parietal bones, the position of the head should be changed from time to time. Rickets tends also to bring about marked deformity of the thoracic wall. Such malformations, the most common of which is the Harrison's groove, may persist to a greater or less degree throughout life. Children having thoracic deformities of this kind should be given breathing exercises as soon as they are able to coöperate, which is at about four or five years of age. It will be found that by means of forced breathing, the deformity of the chest wall often can be corrected. For flat-foot the well-known exercises of rising repeatedly on the toes, or of walking about on tiptoe are of value.

Reference should be made to books on orthopedics, in regard to treatment by means of braces and other appliances. It may be stated, in general, that braces are used to a much less extent than formerly, partly due to the fact that severe cases of rickets are far less common. Apparatus of this kind is rarely needed; the wearing of a metal brace may change an active, vigorous child into one who is inactive and does not care to join his playmates. The principle should be to promote the function of the muscles by means of active and passive exercises, rather than to hinder their activity. Exceptionally marked degrees of bowing of the legs will have to be treated by means of osteotomy, an operation which generally gives excellent results; this treatment may well be followed by heliotherapy, artificial irradiation or medication with irradiated ergosterol.

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CHAPTER XIV.

Infantile Tetany.

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CHAPTER XV.

Treatment.

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Deformity of pelvis

Glisson, Mellis. Anatomists & Clinicians

Mayow & scurbo & itch in healing of Rickets.

Coal measures & infantile mortality

Margarine in Faroe I.

arrested growth – hypercalcification!

Expt rickets: clinical v. experimental

? PAI report on osteomalacia ? red or yellow marrow

Line test.

Get Erdheims Monograph

Starvation in rickets.

Growth & xerophthalmia: A. !!

Ergosterol & hypercalcaemia.

Low Ca rickets.

Rickets in adult rats & osteomalacia

Antirachitic zone of spectrum. – 290–310 μμ

Paralysis of hind limbs in rat rickets caused by Sr.

Rats low P: Human low Ca common c̄ tetany

low Ca rare; Human low P rare.

? Note rat parathyroid deficiency. III only | American J. Anat 1929

human — adequacy III & IV

85 Christeller. Rickets in Apes

85 Get growth curve of chicks.

90 Foetalization. centres earlier in negro than in white!

91 Fromme. Late rickets ♂/♀ 15/1 Growth curve? Menstruation?

115 Sonne & Reckling 240–248 μμ NBG.

118. 120 NB 128 "There can be no doubt that A– leads to osteoporosis

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Umbanzone & Thomas
[illegible]
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Plot distribution of Sr. in child & adult skeleton

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Rachitic rosary normal enlargement.
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Macewen's Case H O A ??
Stress rate of growth in determining distribution in ♂
dent." + menstn." in ♀
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