ULTRA-
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LIGHT AN
VITAMIN
IN NU-
TRITION

BLUNT
AND
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THE UNIVERSITY OF CHICAGO
HOME ECONOMICS SERIES

LYDIA J. ROBERTS
Editor

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ULTRAVIOLET LIGHT AND VITAMIN D IN NUTRITION

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FOREWORD

In his recapitulation of the progress of the last quarter-century Mr. Mark Sullivan credited scientific medicine with having done more for mankind than any other branch of human activities. Preventive medicine, he pointed out, had freed man from the fear of disease. There is, however, much more to preventive medicine than its negative aspect. Modern preventive medicine is constructive; it promises not only additional years of life but additional years of healthfulness and of strength and of achievement.

Among the most notable features of the progress of the last quarter-century has been the development of our knowledge of the vitamins. These important substances are essential to growth and to health and therefore to life. Of all of the vitamins most seems to be known concerning vitamin D, which forms the subject of this book. Vitamin D must be a significant portion of the diet of the growing child or animal, or that child or animal will develop rickets. It is, of course, possible to get vitamin D into the body in other ways. Heretofore the richest known source of vitamin D has been called cod liver oil, "bottled sunshine." Vitamin D is not, however, sunshine made solid or material. Sunshine acting on the living tissues of man or animal or on other organic substances produces in them, from its precursor substance ergosterol, the product vitamin D. Once this fact was established the biochemists were able to irradiate ergosterol and thus to make a highly concentrated vitamin D preparation. Such preparations are now standardized and several of them have been accepted by the Council on Pharmacy and Chemistry of the American Medical Association for inclusion in its book, *New and Nonofficial Remedies*. To these preparations the name Viosterol has been given. Now the infant who needs vitamin D for the prevention of rickets or for the cure of that disorder, the person with diseases of the bone or teeth who should have vitamin D, may obtain all that he needs in a preparation that can be taken in drop-doses, and without the smell, the taste, or the other disagreeable qualities of cod liver oil. By irradiation vitamin D may be produced in milk products and in cereals and in other food substances. The adult who wishes to keep his vitamin D balance at a high level may use irradiated foods, or may produce his vitamin D by getting plenty of sunlight, or by using one of the ultraviolet-producing lamps. Our knowledge

of the vitamins has demonstrated again the importance of very small quantities of potent substances for vastly affecting the nature and the health of man. Without vitamin D the child's legs are bowed, its ribs beaded, its teeth decayed, its stomach distended, its physical mechanism weak and ailing.

Only seven years have passed since the identification of vitamin D as distinct from vitamin A. Yet thousands of investigations have been made, thousands of articles have been published in scientific and popular literature, and such progress has been made as no one would have dreamed possible seven years ago. In this book Dr. Blunt and Miss Cowan have assayed the literature, have collected it under significant headings, skimmed the truth from the fantastic notions and the exaggerations of those commercially minded, and yielded what seems to me to be a fundamental work for all interested in this field. It will not be necessary for writers in the future again to review all that has been done in arriving at the point where the authors have paused to take inventory. They give the investigator and the writer of the future a firm basis on which to stand and from which to take further flights into the mysterious and beckoning unknown.

MORRIS FISHBEIN
Editor Journal of the American Medical Association

PREFACE

In this volume the authors have attempted to summarize the more important recent research concerning vitamin D and ultraviolet light, and in particular their influence upon the calcium and phosphorus of the body. The remarkable advances in this field during the last decade are of significance for the physician, the dentist, and the teacher of nutrition, for parents and all others interested in child health, as well as for the biochemist through whose efforts much of the knowledge has been gained.

The authors wish to express their appreciation to their colleague, Dr. Lydia J. Roberts, for her valuable criticism of the whole manuscript; to Dr. Morris Fishbein, editor of the *Journal of the American Medical Association,* for his encouragement and numerous points of help; to Dr. Milton T. Hanke, for reading and criticizing the chapter on "Tooth Development and the Antirachitic Vitamin" and for permission to use some of his own material in advance of publication; to their own graduate students, for their criticism; to Mrs. Grace Jasper for careful editorial assistance; and to VeNona Swartz, for assistance in final editing and preparation of the manuscript and in making the Index.

KATHARINE BLUNT
RUTH COWAN

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CHAPTER I

INTRODUCTION: POSSIBILITY OF IMPROVEMENT IN GROWTH

What has modern science to say to the adage, "Which of you, by taking thought, can add one cubit unto his stature?" Is it true that a child's height is fixed by the laws of heredity and is wholly beyond the control of the child himself or of his parents? The idea that it is has been accepted by the majority of people since the beginning of time. Yet within recent years scientific data have been collected which are making us modify our notions on the subject, for there are numerous cases on record in which both children and young animals have shown marked improvement in growth under improved conditions. The final limits to which one may grow seem to be sharply defined, but the nearness of approach to the limit may be controllable.

GAINS OF VASSAR STUDENTS AND OTHERS

The Vassar College student of today, for example, averages almost 2 inches taller than her predecessor of thirty years ago. In 1891–95 the average girl entering Vassar was 63.1 inches tall, weighed 117 pounds, and had a girth of 24.3 inches. By 1923–27 her height had increased to 64.9 inches, her weight to 123.9 pounds, and her girth to 25.4 inches. This change in height has been almost perfectly steady, a regular increase of a fraction of an inch for every one of the five-year periods in which the figures are analyzed, and this in spite of a slight decrease in the average age.

Not only have the women at Vassar been gaining in height but a similar increase has been taking place at Smith College and at Stanford University as well. Also children of various races which have been transplanted to this country often show prompt increase in height and weight. Japanese children in the United States, for instance, are both taller and heavier than those in Japan. The American children of prosperous Russian Jewish immigrants are often from 4 to 5 inches taller than their parents. For a more detailed discussion of some of these and other cases of improvement of whole groups or of single individuals, the reader is referred to Roberts' *Nutrition Work with Children*. The illustrations

cited in Dr. Roberts' book are based either on her own experience or that of other investigators.

There are too many factors which may have influenced these very marked changes in body build to be at all sure of the real cause or causes. The authors of the report on the Vassar students emphasize the much more active outdoor life which the young woman of today leads in contrast to her mother. Over all the years of the study information is available as to the number of sports—skating, tennis, walking, basketball, etc., in which the girls indulged with fair proficiency. The average early student practiced just one of these sports and the present-day student no fewer than eleven.

The young woman's looser, lighter, more sensible dress, too, is undoubtedly a factor in her physical improvement. So also are the better sanitary conditions under which she and her brother live, the purer water and cleaner milk which they drink, the scores of other public health gains to which they are heir. But probably by no means least influential even in the case of the fairly well-to-do student is the improved diet from babyhood on. Much more milk is consumed today and many more fruits and vegetables are eaten, especially throughout the long winters. Cod liver oil promises to become almost universal for young children and the value of sunlight is being more appreciated.

A STRIKING IMPROVEMENT IN LABORATORY ANIMALS

Dr. Henry C. Sherman and his co-worker, H. L. Campbell, of Columbia University, have within the last few years carried out a remarkable experiment with rats in their laboratory, which gives far more clear-cut results than can be expected from these human observations. Conclusions from rat experiments can be drawn much more quickly than with man since the life of the animal is only one-thirtieth as long, and they can be much more definite because the animals can be made to live under carefully controlled conditions, the experiment thus being limited to one variable instead of the many in human affairs.

The one variable with Sherman and Campbell was the food of their animals. Starting with rats from the same litter so that the heredity and early nutritive conditions were the same, they have kept their animals for generations, one family on a diet one-sixth whole milk powder and five-sixths ground whole wheat, and the other one-third whole milk powder and two-thirds ground whole wheat, both groups having also a little

common salt. The only difference between the two sets of rats is, therefore, the relative proportion of the milk and wheat which they have eaten.

The family on the smaller amount of milk has done pretty well—about as well as the average human family, one is tempted to think, though Sherman and Campbell make no such comparison. They grow to good size, are moderately long lived, have fair-sized litters of young, and the infant mortality is not high. According to the latest report of the experiment, rat families are still living on this diet to the twenty-first generation! Certainly the race of rats is being carried on adequately.

On the higher milk diet, however, the family is far superior in every way—size, length of life, length of reproductive life, number of litters for each female, and number of young per litter, etc. Here are some of Sherman's figures. The figures given in the first column are the average on the poorer diet, and those in the second, the average on the better diet.

TABLE I

SOME COMPARISONS OF TWO FAMILIES OF RATS

(Sherman and Campbell)

	On the Poorer Diet	On the Better Diet
Weight at age of 300 days	268.6 gm.	314.9 gm.
Age of females at birth of first young	155 days	112 days
Duration of reproductive life	186 days	322 days
Number of young reared per female	5.8	18.1
Total number of descendants in one year	77	368

As to actual length of life, the animals live almost exactly 10 per cent longer on the better diet than on the poorer. The difference looks like a striking improvement in the race, a clear distinction between "adequate" and "optimum" nutrition.

There are other laboratory experiments on animals that show similar improvements in growth with improvement of diet, but these by Sherman and Campbell are probably both the simplest and the most remarkable.

CONTROLLED EXPERIMENTS ON CHILDREN

It is seldom that really controlled experiments can be carried out relating the diet and the growth of children and having a scientific validity comparable with those on rats. Recently, however, an interesting approach to such an experiment has been made in a colony for boys outside of London. The report in regard to it gains in authority by its publication by the Medical Research Council.

Dr. Mann, the investigator, had several groups of boys ranging in

age from eight to eleven years, housed in different cottages of the "village" for from one to two years. One group he kept on the basic diet of the institution, which, according to his report, had been proved of "adequate physiological value" by the gains of ninety boys in a four months' preliminary experiment. Each of the other six groups was given this same basic diet plus a different supplement—a pint of milk, sugar, butter, water cress, casein, or vegetable margarine. The added quantities of the milk, sugar, butter, and margarine were of approximately equal caloric value.

The gains in height and weight were markedly in favor of the milk,

TABLE II

GAINS IN HEIGHT AND WEIGHT OF THE BOYS IN MANN'S STUDY

DIET	NO. OF BOYS	CALORIES	ANNUAL GAINS	
			Weight (Lb.)	Height (In.)
Basic	61	1,724	3.85	1.84
Basic plus milk	41	2,112	6.98	2.63
Basic plus sugar	20	2,074	4.93	1.94
Basic plus butter	26	2,111	6.30	2.20
Basic plus margarine	16	2,103	5.21	1.84
Basic plus casein	30	1,808	4.01	1.76
Basic plus water cress	26	1,724	5.40	1.70

with the butter second. The main figures of the study, which are given in Table II, show this great advantage from the milk and the butter, and also show at least some improvement whenever there was a real addition in the calories of the diet. The gains on the basic diet, which supposedly was adequate, were far below the six to eleven pounds which should be expected in a year for boys of those ages, so that its real adequacy seems very doubtful.

The striking point is that those boys could be made to grow faster and their general spirits could be raised merely by slight improvement in the diet on which they had been living.

THE SCOPE OF THIS BOOK

It is such problems of growth and particularly of skeletal development that are discussed in this book. The experiences of the young women students, the schoolboys, and the animals may be taken as setting the problem to the scientist. Exactly what were the factors in the improvements in growth, what were the details of the bodily changes, how and how much is the improvement within human control?

We are much nearer to real answers to those questions than we were a short time ago. Within the last ten years we have seen a remarkable increase in knowledge of bone growth, of the storage of the chief bone constituents, calcium and phosphorus, in the normal healthy body, and also of the childhood disease rickets, which is characterized by abnormal calcium and phosphorus metabolism. The new information about the normal, as is often true in physiological investigations, has come in large part through the study of the abnormal, through experiments on rachitic animals or children. Specifically, the gains are chiefly due to the study of how ultraviolet light and vitamin D, the antirachitic vitamin, affect the normal and the rachitic body.

The authors have attempted to bring together some of the great mass of recent research along the lines of the calcium and phosphorus of the body, especially as they are affected by vitamin D and light. Their survey is by no means complete, but an effort has been made to separate clearly the well-substantiated facts and the well-proved conclusions from material which may be highly suggestive and a stimulus to further research but so far can be accepted only tentatively. In a fast-growing field like this, however, such distinction is often very difficult. Enough detail of the experimental method has usually been given so that the reader can see the basis for the conclusions drawn.

The investigations to be reported have been made by biochemists in the laboratory and by physicians in the clinic. They have been carried out on animals, on well and ill children, and on adults. Their remarkable success means both that a serious disease of infancy, rickets, is well on the way to moderation in severity or even to extinction, and also that children who without this newer knowledge might have been only fairly well will now have increased chance for vigorous health. The doctor, the mother, the teacher of nutrition all therefore may rejoice at the gains. Even the dentist, who until recently has not had so much close touch with developments in nutrition, has an important share in this new chapter.

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CHAPTER II

THE BEGINNINGS OF THE STORY

There may be said to have been two beginnings to this chapter in nutrition, one eleven years ago, showing the control of bone development by diet, and the other ten years ago, demonstrating its control by light. The two lines developed more or less independently till 1924 when a striking new discovery knit them together.

THE DIETARY CONTROL OF BONE DEVELOPMENT

The discovery of the antirachitic vitamin.—The first scientific knowledge of the dietary control of rickets should be credited to the Englishman, Mellanby. He worked with puppies, doing almost four hundred experiments, the accounts of which he published in 1918 and 1919. His puppies developed real rickets on the limited diets which he fed them, with soft bones, bowed legs, and other deformities much like those of rachitic children. He made sure of the disease not only by the outward appearance of his dogs, but by X-ray photographs which demonstrated clearly the poor bone calcification, by chemical analyses of the bones, showing their low calcium content, and by histological observations—all methods much like those used today (see Figs. 1 and 2).

In some of the puppies he succeeded in curing the rickets by giving cod liver oil, or, less effectively, by butter fat or suet, and in others he failed entirely to cure it by lard, or by cottonseed, olive, or linseed oil. He thus clearly placed rickets among the diseases due to a deficient diet, the substance necessary to prevent it being present in some fats and oils and not in others. This was his great contribution at this time.

Less happy were his conclusions as to just what the deficiency consisted of. The fats which he had found richest in antirachitic power, cod liver oil and butter, were also those which five years earlier had been shown to be richest in the "fat-soluble, growth-promoting vitamine A"—which we now more simply call "vitamin A." It was, therefore, natural enough to conclude that this vitamin cured the rickets, that it was "the antirachitic accessory factor," or "the antirachitic vitamine."

In this country investigators were somewhat loath to accept Mellanby's conclusions as to this new rôle for the fat-soluble vitamin. Dr. Al-

fred F. Hess in New York City, to whom frequent reference will later be made because of his important work on rickets, found that some babies having a diet rich in milk and cream (and hence in vitamin A) developed rickets more readily than other babies having a diet with skimmed milk very low in A—clearly a contradiction of Mellanby's idea.

The differentiation of vitamins A and D.—In 1922 came the clear-cut proof that the antirachitic factor in cod liver oil is distinct from vitamin A. McCollum and his co-workers at Johns Hopkins University, realizing that vitamin A is fairly easily oxidized, passed a stream of oxygen through the heated oil, and then fed it to two sets of rats. The rats on a diet devoid of vitamin A were no longer cured of their eye disease, xerophthalmia, by the oxidized oil as they had been before its oxidation; that is, the oil had completely lost its vitamin A. Yet those on a rickets-producing diet were cured of rickets; the oil still contained its antirachitic factor.



FIG. 1



FIG. 2

FIG. 1.—Photograph of one of Dr. Mellanby's dogs after thirteen weeks on the rickets-producing diet but protected from rickets by cod liver oil.

FIG. 2.—Photograph of another dog after thirteen weeks on the same diet with olive oil instead of cod liver oil, showing well-marked rickets. (From *Medical Research Council Special Report Series*, No. 93.)

Here, then, was a new vitamin, distinct from vitamin A, and judging from the prevalence of slight or severe rickets, of great significance to mankind. For a while it was merely called "X" but gradually it has come to be known as vitamin D or the antirachitic vitamin.

Cod liver oil was thus well established on a scientific basis as practically a specific against rickets, and infantile rickets was on the way to complete eradication. But let it be again said with emphasis—this vitamin is not only curative and preventive of an abnormality, rickets, but is of influence in the normal formation of bone and in other aspects of the normal activities of calcium and phosphorus in the body.

The knowledge of the usefulness of cod liver oil is not new. Fisher folk on the coast of England, Holland, and France have used it as a remedy from time immemorial. Its employment by physicians has gone through various cycles, and with the development of the cautious skepticism produced by the scientific method of thinking toward the latter half of the nineteenth and the beginning of the twentieth centuries, doubts were prevalent. Dr. Gamble, in his excellent and delightfully written article in *Chemistry and Medicine,* entitled "No Child Need Have Rickets," says: "To an even mildly critical attitude of mind the belief that oil from the liver of codfish is specifically curative of a human ailment was obviously a quaint bit of archaic medical lore." The rediscovery of the action of cod liver oil in "irreproachably scientific terms" was necessary for its intelligent use.

A point that should be mentioned now and will be explained more fully later is that in the laboratory diets, which produce rickets in rats, lack of vitamin D is not the only deficiency. For the rats to get rickets, the ratio of the calcium and phosphorus in their food must be wrong. It was the recognition of the latter fact almost simultaneously by investigators at Columbia and at Johns Hopkins in 1921 that has made possible the remarkable series of researches which have resulted in the control of rickets and all the associated abnormalities of calcium and phosphorus metabolism by vitamin D and ultraviolet light.

THE ANTIRACHITIC POWER OF LIGHT

The other beginning of this chapter in nutrition came from Germany in 1919 and 1920. Huldschinsky, working in Berlin just after the war, found an appalling prevalence of rickets even among older children. The children with whom he started his work were in the Oscar-Helene Home for Crippled Children. His patients were mostly from three to five years of age and all showed severely deformed limbs or spinal curvatures, were

extremely backward in growth, and all were in a state of active rickets. He experimented by giving these children radiations from the quartz mercury lamp and sunlight. He was most encouragingly successful and could demonstrate by X-ray photographs the rapid and complete healing of the rickety bones. The children's bad deformities, however, were not cured. He, therefore, next turned his attention with much success to the more hopeful field of the prevention of the rickets in younger children by his ultraviolet light treatment. Huldschinsky gives an interesting account, in English, of his work ten years ago and his more recent activities at a Public Welfare Center in Berlin, in the September, 1928, *British Journal of Actinotherapy*.

This German investigator, like Mellanby and the Johns Hopkins workers, had predecessors in his own line. The tendency of rickets to appear in children kept in the crowded, dark rooms of city tenements had long been known, though it was often ascribed to "bad air" or "noxious gases"; and a few physicians and laboratory workers had used sunlight for cure, but not with the definite results and proofs that Huldschinsky secured with his artificial ultraviolet and sunlight.

Many other workers soon confirmed the favorable effect of the artificial ultraviolet light, and then in 1921 Hess and Unger in New York City showed that sunlight alone could quickly and effectively cure infantile rickets. In the laboratory, too, rats that developed rickets on a diet adequate in calcium but low in phosphorus were cured as effectively by short exposures to sunlight as by the addition of a definite small amount of phosphorus to their diet.

Here, then, were the two lines of research well started—the control of calcium and phosphorus metabolism in general and rickets in particular, on the one hand by vitamin D, and on the other by sunlight and artificial sources of ultraviolet light.

It is easy to realize how baffling the co-ordinating of these two sets of facts seemed to the investigators—two such entirely different influences as cod liver oil and radiant energy from sunlight apparently accomplishing the same effect in the body. Why? What is the relation between the two?

THE INTERRELATION OF VITAMIN D AND LIGHT

In 1924, the first part of the answer to this puzzle was secured, and, as has happened so often in the rapid development of the field with its many workers, by two investigators almost simultaneously. Certain foods

which were themselves without antirachitic power were discovered to develop it on irradiation with ultraviolet!

Hess in New York irradiated cottonseed and linseed oils and found them as potent to cure rickets in his rats as cod liver oil. Steenbock and his co-workers at the University of Wisconsin irradiated the whole mixed diet of the rat—with equal success. Thus ultraviolet light was apparently making vitamin D where no vitamin D had been before.

These investigations have been followed by the irradiation of many foods and their successful feeding to rachitic animals and even children (see chapter ix). Particularly important was the discovery that the potent part of an active fat is contained in its small non-fatty part or the "unsaponifiable fraction," and that the unsaponifiable fraction of a rachitically inert fat may be activated by irradiation. It is the sterols (solid alcohols) in the foods that can take on this potency, in particular one called ergosterol. One of the most sensational discoveries of biochemistry in recent years has been the proof that from ergosterol, by a chemical action induced by light, vitamin D is formed. It is probably the formation of vitamin D from the ergosterol in the skin of man or of animals that explains the antirachitic action of ultraviolet light. All of these points are discussed in greater detail in the chapters to follow.

The two lines of research have thus been firmly knit together.

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CHAPTER III

METHODS OF WORK WITH RATS

THE RAT COLONY

A visit to one of the great rat laboratories is an interesting and illuminating experience to specialist and layman as well. Mendel's laboratory at Yale, McCollum's at Johns Hopkins, Sherman's at Columbia, Steenbock's at the University of Wisconsin are among the best known for their nutrition research. A great room, or rooms, well-ventilated and scrupulously clean so that there is little or no animal odor, is filled with shelves of rat cages in double tiers one above the other like a library, with aisles between, each cage tagged with the number and kind of experiment going on inside.

The visitor entering the colony hears the rustle of the movement of the hundreds or thousands of white or piebald rats used as test material for the diets being investigated—the richness of different foods or food concentrates in the several vitamins for example; the effect of high iron or copper or some protein constituent on anemia or on growth; the conditions for good reproduction. At one side, especially quiet, are the breeding cages equipped with bedding material for the female and young, where the young, looking at birth like fat, red worms an inch or two long, grow with remarkable speed into lively, well-shaped animals.

Near at hand are the balances for weighing the rats and the diets; the equipment for preparing the food on a large scale for hundreds of animals or on a small scale for an experiment on half a dozen or a dozen rats; the chemical laboratory for analyzing food, bones, and excreta; microscopes; a lamp for ultraviolet irradiation; even possibly an X-ray machine for photographing bones.

Managing such a rat colony is no small undertaking. The investigator in charge must have first of all the rare combination of creative imagination and analytical power to conceive fruitful problems for research and plan the details with all the variables involved for carrying them out. He must train his assistants for the many tasks in care of the animals; he and they must constantly observe the rats and be alert for unexpected happenings; and, by no means least, they must keep detailed

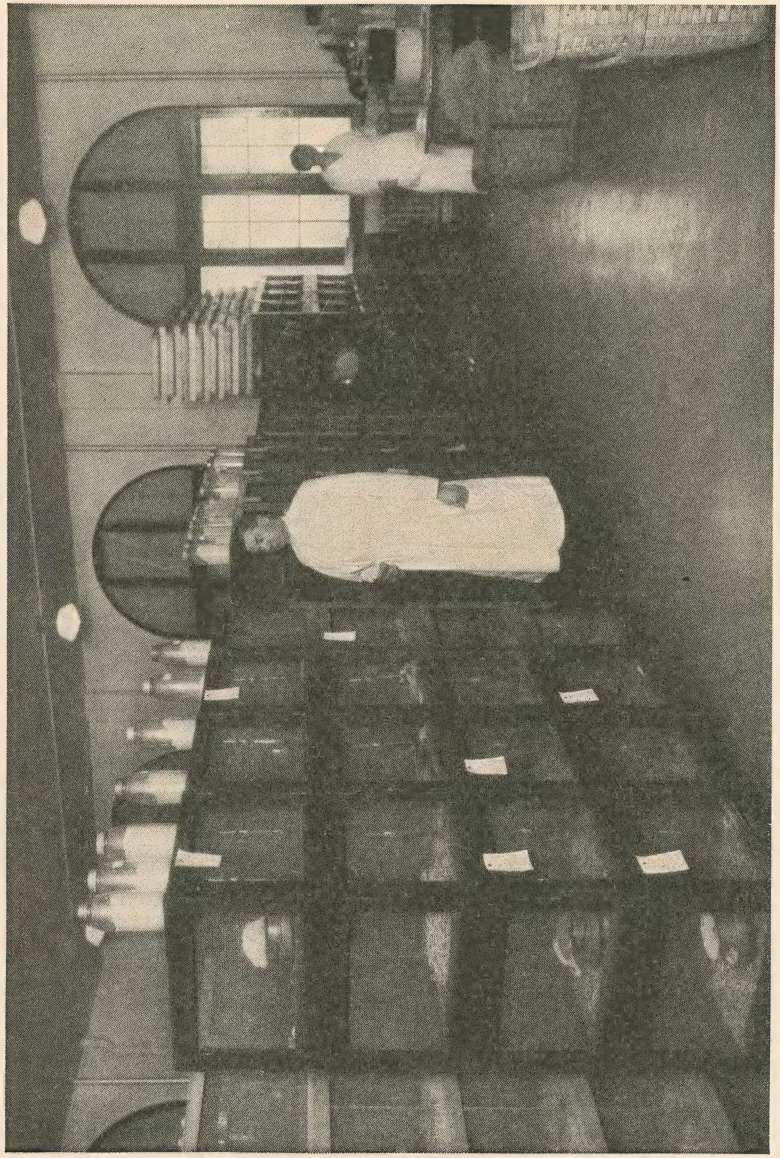


FIG. 3.—A section of Dr. McCollum's rat colony

and accurate records from which the final conclusions of the experiments will be drawn.

From such laboratories has come a goodly share of the remarkable progress in nutrition of the last two decades, a progress greater or at least more striking than in all time preceding.

In order to weigh the conclusions to be discussed in this book, the student will wish some description of the special laboratory techniques used in the study of calcium and phosphorus metabolism, normal and abnormal, including the methods of producing and curing rickets. The reader with less technical interest may wish to skip the rest of this chapter.



FIG. 4.—A normal rat family

HOW TO PRODUCE RICKETS IN RATS

The many investigators have come to agree on the whole rather closely in the methods they use to produce rickets. The experimental rats are always started young, for it is young, rapidly growing animals, like young children, that are most apt to have rickets. At the time when the rats naturally would begin to stop nursing and to eat the mother's food, from twenty-one to twenty-four days of age, they are taken from the mother and put on the special diet. In the best controlled experiments care is usually taken that the diet of the mother before the birth of the young and during the nursing period shall contain only a moderate amount of antirachitic vitamin so as to prevent the transfer of much of it for storage in the bodies of the young.

The rickets-producing diet.—These vigorous, sleek young rats are put immediately on a special diet limited in such a way as to cause them to develop rickets within a comparatively short time, from five to ten days for some signs of the disease, two or three or even four weeks for others. Several of these rachitogenic diets are in use, developed by dif-

ferent investigators. They are alike, of course, in lacking vitamin D completely, and also they all have an abnormal proportion of calcium and phosphorus—a dietary condition necessary for the production of rickets in rats. In the more commonly used diets the calcium is high and the phosphorus low, the ratio being 4 or 5 to 1 in contrast to a normal ratio of 1 or 2 to 1. High phosphorus-low calcium diets do produce rickets but they are not so satisfactory for work with rats, though not infrequently used with dogs.

TABLE III

COMPOSITION OF CERTAIN STANDARD RICKETS-PRODUCING DIETS

SHERMAN AND PAPPENHEIMER DIET 84

	Per Cent
Patent flour	95.0
Calcium lactate	2.9
Sodium chloride	2.0
Ferric citrate	0.1
Calcium:phosphorus=6.5:1 (computed by authors)	

MC COLLUM DIET 3143

	Per Cent
Whole Wheat	33
Whole yellow corn	33
Wheat gluten	15
Gelatin powder	15
Calcium carbonate	3
Sodium chloride	1
Calcium:phosphorus=4.04:1	

STEENBOCK DIET 2965

	Per Cent
Yellow corn	76
Wheat gluten	20
Calcium carbonate	3
Sodium chloride	1
Calcium:phosphorus=4.25:1	

OSBORNE AND MENDEL (MODIFIED BY OUTHOUSE, ET AL.)

	Per Cent
Egg albumin	18.00
Dextrin	71.75
Yeast	6.00
Salt mixture xxx (contains no calcium or phosphorus)	2.60
Calcium carbonate	1.55
Phosphoric acid	0.10
Butter fat	3 drops daily
Calcium:phosphorus=5:1	

Other points which have been kept more or less definitely in mind in working up the diets are that they must be good enough for fair growth, and adequate for the prevention of deficiency diseases other than rickets, at least during the brief time of the experiment.

Three of these standardized diets are being or have been extensively used in this country—Sherman and Pappenheimer's No. 84, which was formulated early and is now usually considered too severe, McCollum's No. 3143, and Steenbock's No. 2965. A modification of a diet originally suggested by Osborne and Mendel has recently been used with very good results by Outhouse, Macy, and Brekke. These are all given in Table III.

The diets differ in the source and quantity of their protein and also in their vitamin A. The Sherman and Pappenheimer diet contains practically no vitamin A, the McCollum and the Steenbock diets contain varying amounts derived from the yellow corn, and the Osborne and Mendel ration has the vitamin added in the form of three drops of butter fat daily. Vitamin B is present in adequate amounts in all but the Sherman and Pappenheimer diet. This very severe diet No. 84 is sometimes modified by the substitution of 5 per cent dried milk for an equivalent amount of flour, so that better growth is obtained, but the degree of rickets is unaffected. McCollum also suggests certain modifications of his Diet 3143, but the unmodified diet is much more commonly used. The McCollum, the Steenbock, and the Sherman and Pappenheimer diets are made up of a mixture of complex food stuffs, while the new Osborne and Mendel diet consists more nearly of single purified food substances and contains a salt mixture of approximately the same proportions as the Osborne and Mendel standard salt mixture, with the necessary exception that in the rickets-producing ration the calcium and phosphorus are omitted so that they may be added separately in any amount and in any ratio desired.

The exclusion of light.—In order to produce rickets in the rats, not only are they fed one of these high calcium-low phosphorus diets without D, but they are protected from ultraviolet light. They must be kept in rooms without sunlight, either artificially lighted or with the only daylight through window glass. The reason for this precaution is now generally known—that the portion of the sun's spectrum which is potent in prevention and cure of rickets, the ultraviolet, does not pass through window glass and is not obtained from ordinary incandescent lights.

SIGNS OF RICKETS IN RATS

Outward signs.—Rats with rickets are below par in appearance and exhibit many of the deformities of the bones seen in rachitic children. That is to say, the ends of the long bones become decidedly enlarged, the rib junctions are enlarged, and the thorax is small and often misshapen. In severe cases the animals often develop spinal curvatures which may be so extreme as to be readily apparent to the eye, and they usually develop a characteristic lameness in the hind legs. The most marked signs of rickets, however, are seen after the death of the animal, either when it is killed early in the experiment or when it dies after several weeks on the deficient diet.

The bones in rickets.—The bones are the part of the body where

signs of rickets are most plainly seen. Examination after death shows them to be very soft as compared with those of a normal animal. They may be easily cut, and the shafts of the long bones may be so fragile as to be easily crushed or broken. These gross signs, visible to the naked eye, are preceded by changes in the composition and internal structure of the bone which can be detected by much finer laboratory methods, so that it is possible to follow closely the onset of the disease even in its less severe phases or its healing after therapeutic measures are begun.

The growth and development of bone, normal or abnormal, may be observed in successive X-ray pictures and forms a fascinating histological study, details of which are beyond the scope of this book. It will be sufficient to say here that bones grow from centers of ossification, which in case of the long bones are located at the junction between the end of the bone (the epiphysis) and the shaft (the diaphysis). Here a cartilaginous material is first laid down, and then calcification rapidly takes place and the true bony tissue is formed. In rickets this calcification takes place less rapidly and less completely than in normal bone, so that the bones remain soft and pliable and in severe cases are easily drawn out of shape or even fractured by the pull of the muscles upon them.

The line test.—The ends of the long bones by microscopic examination thus reveal an alteration in structure proportional to the severity of the rickets. This is most sharply defined by the now famous "line test," first proposed by McCollum and Shipley several years ago, a test so delicate that slight degrees of rickets—or of healing—can be detected by its use. It has been called the most practical means of determining the effects of antirachitic agents and is now being carefully standardized in an attempt to make it quantitative.

The principle underlying the test is that when bone sections are soaked in dilute solutions of silver nitrate, silver phosphate is formed in the areas where calcification has taken place, and this silver salt, when exposed to intense light, is reduced to black silver. A distinct dark line of calcification appears at the ends of normal bones, no line at all in severe rickets, and a more or less sharp line in cases of healing rickets, according to the degree of recovery. Longitudinal sections from either of the bones of the leg may be used for the test, although the tibia is now considered the more satisfactory.

To make the test a quantitative measure of vitamin D, the rickets-producing diet fed during the experiment, and even the stock diet fed before the experiment is begun, are kept constant, even to the quantity



FIG. 5.—X-ray photographs of two female rats fed upon a rickets-producing diet. Both rats were of the same age and size at the beginning of the experiment, but Rat 2 (right) was exposed to ultraviolet light during the experiment while Rat 1 (left) was not. Note especially the difference in size, the density of the bones (indicated by the depth of the shadow cast), and the shape of the ends of the long bones. (From Steenbock, Nelson, and Black, *Journal of Biological Chemistry*, LXII [1924–25], 286.)

eaten; the substance to be tested for vitamin D is given exactly five days, and only rats used that do not lose weight. Loss of weight in itself may

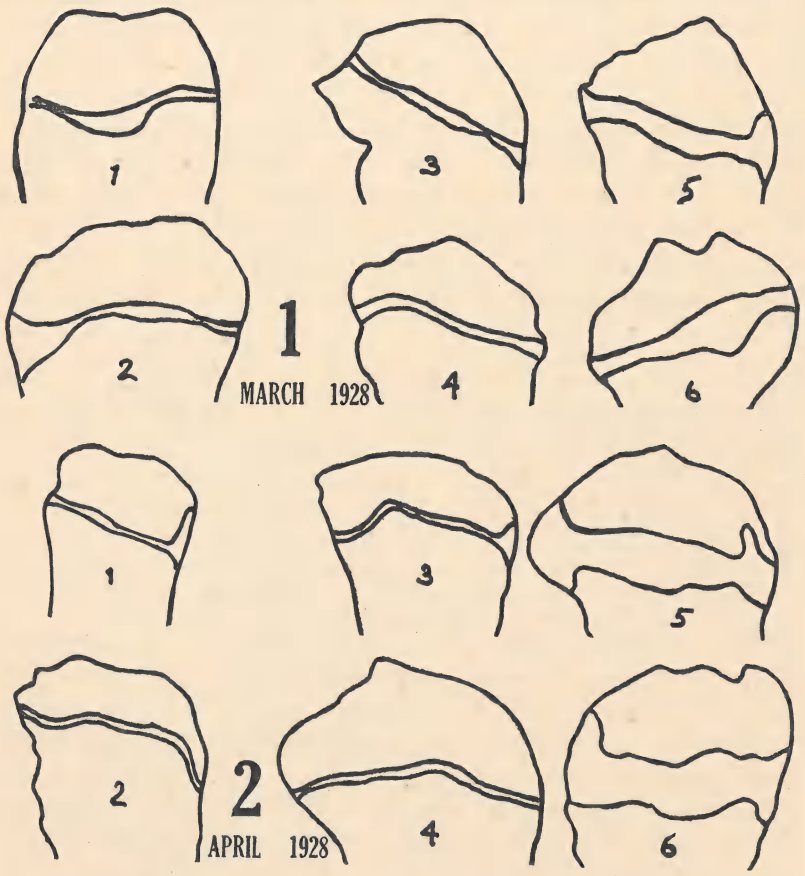


FIG. 6.—The line test. Simplified drawings of the split ends of rat knee bones. The narrowness of the "line" between the end of the bone and the shaft indicates degree of protection, the narrower the line the higher the protection. Rats 1–4 were free from rickets, having received a fair amount of ultraviolet light from New York sunshine through vitaglass, especially those tested in April; Rats 5 and 6, without ultraviolet light, developed rickets, more severe in April than in March. (From Eddy, *American Journal of Public Health*, Vol. XVIII [1928].)

sometimes bring about bone calcification, so this complication must be avoided. From the width and character of the line resulting under these

conditions a scale of from one to four plus signs is used to show the relative quantity of the antirachitic effect. The test is so sharp and so sensitive that it has been found that the minimum amount of irradiated ergosterol required for a positive line test is only 0.00001 mg. daily. (For further discussion of this point, see the material on irradiated ergosterol in chapter ix.)

Composition of normal and rachitic bone.—Normal bone may also be distinguished from rachitic bone by its chemical composition. The normal bones of young animals have a large proportion of water and a relatively small proportion of ash. During normal growth the proportion of water lessens, the proportion of organic matter increases very slightly, and ash increases markedly. The figures given in Table IV are typical for

TABLE IV

COMPOSITION OF HUMERUS OF MALE RATS

Age, Days	Ash Per Cent	Organic Matter Per Cent	Water Per Cent	Calcium		Magnesium		Phosphorus	
				Mg.	Per Cent	Mg.	Per Cent	Mg.	Per Cent
23.....	17.07	17.97	64.95	3.41	6.14	0.091	0.166	1.80	3.24
65.....	31.49	20.97	47.54	17.63	11.76	0.415	0.279	8.89	5.94
150.....	43.41	22.19	34.40	41.75	16.17	0.946	0.371	20.64	7.97

the humerus of the normal male rat at different ages. They have been selected from the wealth of data contained in a recent series of analyses made by Hammett of the Wistar Institute.

In rickets, with its delayed bone-growth, the total weight of the bones is less than for normal rats. Also, as would be expected, the composition is abnormal, with a decidedly lower percentage of ash and a lower percentage of calcium and phosphorus. For example, in some experiments by Macy, the dried, fat-free bones of her rachitic rats contained only 30 per cent or less ash, and her control with cod liver oil 40 per cent or more.

Bone analysis, therefore, may throw light on the severity of rickets or the completeness of healing when an antirachitic agent is supplied. The sensitiveness of the method is well illustrated by some recent figures of Roscoe which show that, in spite of earlier reports to the contrary, fresh spinach does have extremely slight antirachitic potency, though by no means as much as cod liver oil. Her control rats on a rachitic diet had 8.61 per cent of calcium in the dry, fat-extracted leg bones, those given

cod liver oil had 15.27 per cent calcium, and those with spinach 9.86, 9.06, and 9.56 per cent.[1]

Roscoe and a number of other English investigators also report what they call the A/R ratio, ash to extracted residue of the bones, which in

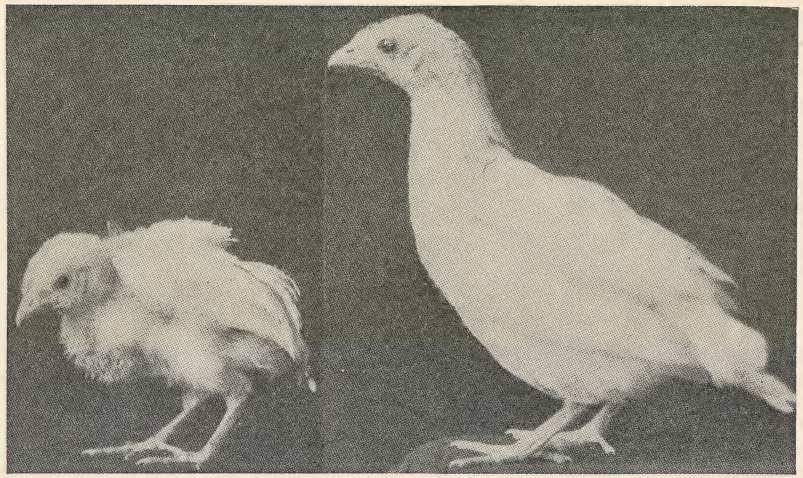


FIG. 7.—The effect of limited amounts of sunlight and a rickets-producing ration. The two chickens shown are of the same age—six weeks. The chicken on the right was exposed to sunlight all day and was apparently a normal specimen. The smaller chicken had sunlight only ten minutes each day and was definitely abnormal. (From Hart, Steenbock, Lepkovsky, and Halpin, *Journal of Biological Chemistry*, LVIII [1923–24], 42.)

the spinach experiment was 0.303 for the rachitic rats, 0.703 for those with cod liver oil, and 0.348 for those with spinach; that is, the ash is a much smaller part even of the fat-free residue of rachitic than of normal bones.

Not only rats, but dogs and pigs and chickens, have been shown to have these abnormalities of bone composition in rickets, and to have the abnormalities corrected either by giving vitamin D or by irradiation. Two chickens of the same age but different size are shown in Figure 7. Both

[1] These figures and Macy's, it should be noted, cannot be compared directly with those in Table IV for the normal rat, because the analyses, like many others reported, were made after the bone had been dried and extracted with ether. It has been found that more consistent results are obtained on this material than on the whole fresh bone.

had a poor diet with no vitamin D, but the large vigorous one spent all day in the sunlight, and the other spent most of the time indoors.

Other signs of rickets in rats.—Rats with rickets show not only abnormal bones, but abnormal phosphorus and calcium in the blood, and abnormal storage of these elements in the body. These abnormalities, however, unlike abnormal bone composition, have been studied extensively with children as well as animals. Discussion of them is therefore taken up in the next chapter, the work with animals and children being considered side by side.

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CHAPTER IV

THE CALCIUM AND PHOSPHORUS OF THE BODY

Children, like laboratory animals, may be thought of as young organisms, storing calcium and phosphorus more or less well, depositing elements in bones, maintaining more or less satisfactory balance in the blood, in short growing well or ill according to conditions. As with the animals, the processes are largely influenced by vitamin D and ultraviolet light.

CALCIUM AND PHOSPHORUS RETENTION

Positive or negative balance.—The young and the adult, human or animal, obtain their calcium and phosphorus from their food—milk, eggs, and some vegetables being the commonest sources of calcium, and meat, whole cereals, eggs, and milk the commonest sources of phosphorus. After the elements are eaten they are absorbed more or less completely from the intestinal tract into the blood, and thence drawn upon for bone formation or other use. Unused portions and those portions which the body has used and finished with are excreted in the urine or stools.

The adult, while he makes daily use of the elements in his bodily processes, does not increase his store of them. Day in and day out his output of them, if he is in health, is equal to his intake; he is in "calcium and phosphorus equilibrium."

The growing young, on the other hand, retains a fairly large proportion of the calcium and phosphorus eaten, in new bones and other tissues. He is excreting less than he takes in; he is always, if in health, in "positive calcium and phosphorus balance." When he is growing fast his retention is greater than when growth is retarded. The total retention over years has been greater for the tall youth with good bone development than for the undersized boy or girl. Presumably, therefore, conditions which increase retention of the elements may be expected to increase the chances of superior growth.

The usual laboratory method of studying retention of an element is a "balance experiment"—on children, adults, or animals—with careful, quantitative measurement of the intake and the output, and therefore by difference of the storage.

How a balance experiment is carried out.—The carrying out of a bal-

ance experiment is by no means a simple procedure, especially with children. All the food eaten in the carefully planned diet must be weighed and definite portions saved for analysis. The urine and stools must be quantitatively collected. As there is always a "lag" in the feces, those belonging to the experimental diet must be marked off with a colored line by taking a dose of carmine or charcoal just before starting the period and again at the end. Further, as excretion of the feces is usually somewhat incomplete and irregular, the experimental periods must be several days long, at least three, better five or six, in order to secure a fair picture of what is happening in the body.

An infant serving as subject for balance experiments is loosely tied on a hammock-like metabolism frame, with cleverly devised connections for collecting excretions. The usual baby will lie as quietly with this arrangement as in his own crib, and, provided he is taken up occasionally, may be a contented contributor to scientific research for several days at a time.

Older children offer a different sort of problem. To keep them contented and their energies happily directed under the experimental routine, to prepare and weigh all the food and get the children to eat it completely without undue pressure, to collect completely and to analyze all the excreta, require the combined skills of a mother, a nursery school teacher, a dietitian, and a chemist. As might be expected, the number of such experiments reported is not large, nothing like so large as on animals or even on adult men and women. Further, so that no possible harm may be done to the children, the scope of the experiments is sharply limited as to length, kind of diet, and other conditions. Yet the results obtained have a value, within their limits, far beyond those of animal experiments.

Balance experiments are also carried out on large animals, for instance on cows to find the drain of milk production on the calcium metabolism, and on dogs and other animals in the laboratory, special metabolism cages being devised to fit each case. Recently, satisfactory technique has even been developed for rats—a somewhat difficult procedure because with these small animals there is the double problem of preventing any scattering of food, so that food consumption may be accurately weighed, and of quantitative collection of a large enough amount of excreta for analysis.

SOME BALANCE EXPERIMENTS AND CONCLUSIONS DRAWN FROM THEM

Much the most striking point in the calcium and phosphorus balance experiments of recent years is the favorable effect of antirachitic agents. More of these two elements are stored by an infant or a young animal

given cod liver oil or irradiated with ultraviolet light than by an untreated companion. This is especially true in cases of rickets but also has been noted in well subjects.

Experiments on children.—A few of the many experiments proving this fact may be cited: First, one on children without rickets. Dr. Amy Daniels, of the Child Welfare Research Station and the Pediatric Department of the State University of Iowa, who has carried out numerous balance experiments on infants, co-operated with Dr. Harry Steenbock, of the University of Wisconsin, several years ago to show the effect on babies of his irradiated olive oil which had been proved to have antirachitic potency for rats. Two infants, one five and the other three months old, were given, in addition to their regular diets of milk, dextrimaltose and lactose, first 5 cc. of untreated olive oil and then 5 cc. of the irradiated oil. Three-day calcium balances were obtained for each oil.

Both babies stored decidedly more calcium on the irradiated oil than on the ordinary—0.39 gm. as opposed to 0.29 gm. daily for one child and 0.41 gm. and 0.36 gm. for the other. That is, the antirachitic agency brought about increased storage even by non-rachitic children.

Two years earlier Orr and his co-workers had made the important observation that three children with rickets who served as subjects for balance experiments were not retaining adequate calcium and phosphorus, although the quantity which they ate was adequate. One of them, twenty months old, was actually in slight negative calcium and phosphorus balance, losing the elements from the body rather than storing them. Their rachitic condition, that is, interfered with their normal storage.

Each child was given from eight to eleven treatments from a mercury vapor quartz lamp, and the balances again determined. The retentions were found to have gone up markedly, in the worst case from a negative balance of —0.10 gm. of calcium and —0.006 gm. of phosphorus during the four-day period to a high positive balance of 2.81 gm. and 1.79 gm., respectively. For other rachitic children irradiating the milk of the diet brought a similar improvement.

Within the last few months (February, 1929) Dr. Daniels, with co-workers, has reported an impressive extension of her work, including seventy-four metabolism experiments upon infants from two to nine months old, all except one apparently normal, but all artificially fed. In every case she found that both calcium and phosphorus retention were greatly improved by either cod liver oil, irradiated milk, or irradiated olive oil, the last being the most effective of the three. Some of her figures will be

used in discussing what is the quantity of the elements that a child at best really should retain (chapter x), and also, because she gets somewhat different results from different kinds of milk (pasteurized or boiled), they will be discussed further in chapter xi, on the effects of different foods.

In addition, Dr. Daniels has found and reports still later that "the infants receiving the cod liver oil were much heavier at the same age than those receiving no cod liver oil." They also weighed more than infants of their respective ages and birth weights would be expected to weigh. These facts suggest "that the accepted standards of growth for infants are too low. It seems probable that conditions which make for better utilization of calcium and phosphorus will result in larger and physically better developed children."

The question of what is the optimum retention for children of different ages still cannot be definitely answered. In spite of considerable work already done, much more is needed. One would like to do a year-by-year or even month-by-month series of balance experiments on a group of physically superior children, fed the best kind of diet now known. Instead, the children observed have been of all kinds, probably with a preponderance of them below par; the diets have often been designed to study the comparative value of one or another food, and have often been far from optimum; and the complete age-by-age series is lacking.

On pages 155–58, in Tables XVI and XVII, are brought together many of the important balance experiments reported. The discussion of the data in detail and the few conclusions to be drawn from them are postponed till chapter x after other relevant material has been considered. Here, the point to be emphasized is the increased retention affected by antirachitic factors.

Animal experiments.—Balance experiments on animals are so numerous that it is hard to decide which to choose for illustration. The most striking probably are those on rats made rachitic by one of the high calcium-low phosphorus diets already described. Such rats are found to be retaining a very small quantity of the elements, or else to be in negative calcium balance and to a greater extent in negative phosphorus balance. With the antirachitic treatment the calcium and even the phosphorus retention are brought way up. That is, vitamin D corrects the defect of the abnormal mineral ratio.

Puppies and pigs and rabbits, too, with experimental rickets or under certain other abnormal conditions have all been shown to be retaining abnormally low amounts of these two elements and to have the retention

improved by cod liver oil or irradiation. One young dog, for example, with cod liver oil was keeping in its body more than three-quarters of the calcium it ingested, and two others on the same diet, but with linseed instead of cod liver oil, were retaining considerably less than half of the intake (Shohl and Bennett).

For other examples, see chapter x, page 161, and chapter xi, page 172.

THE BONES IN NORMAL AND RACHITIC CHILDREN

Of the calcium retained in the child's or animal's body, all but a very small amount finds its way to the bones. Of the phosphorus, a large part goes to the bones and also considerable to the muscles and other tissues. The development of the bones of rats under normal conditions and in rickets has already been discussed in chapter iii on methods. In this section some of the much smaller amount of material on children's bone formation will be brought together and also a little on other animals.

Bone composition.—Children's bones, like those of animals, consist of organic and inorganic material (the latter chiefly calcium phosphate $Ca_3(PO_4)_2$ or $CaHPO_4$, with some carbonate and a little magnesium) and water. The inorganic material is laid down slowly—a smaller proportion in the very young than later on. In the human fetus, measurable amounts of calcium and phosphorus are beginning to be deposited by the twelfth to the sixteenth week of pregnancy, the daily quantity increasing gradually till the child is born. A normal, newborn baby may have in its body from 25 to 33 gm. of calcium, mostly in the bones (see page 181). These figures and others are obtained from analyses of the bodies of children who died at birth, some of them from accidents at time of delivery.

During the first two years of life comes the greatest skeletal development, but during the first four months of this time, according to Hamilton, part of this increase of the skeleton comes from a reserve of calcium deposited in the body during the last months before birth rather than all from food calcium. The proof of this is that in normal infants the ratio of calcium to body weight diminishes during the first four months, while the skeleton increases proportionately to this increase in weight. This reserve of calcium, he believes, explains why normal infants do not get rickets till four months of age and why premature infants almost always become rachitic. Whether or not this particular explanation is justified, the steady increase in ossification of the bones in babyhood is reason enough for routine antirachitic treatment.

Bone formation takes place normally when the calcium and phosphorus are retained in the infant's body in the proportion of approximately 2 to 1. This is not far from the ratio in human milk. With other ratios of retention, the body structure may be abnormal, as in rickets (see also chapter x). It is quite possible and even common for a child's retention to be in normal ratio, but in small quantity; then the skeleton will be of normal structure but small. The size of the skeleton depends on the amount of the calcium and phosphorus retained. Dr. Amy Daniels, to bring out these points in a public lecture by reference to her own small size, says, "Probably my mother did not give me enough calcium and phosphorus in my babyhood or enough vitamin D, so that I could store enough in my bones."



FIG. 8.—Roentgenographic appearance of a twenty-month-old child with acute rickets. (From Wilkes *et al.*, *American Journal of Diseases of Children*, XXXVII [1929], 489.)

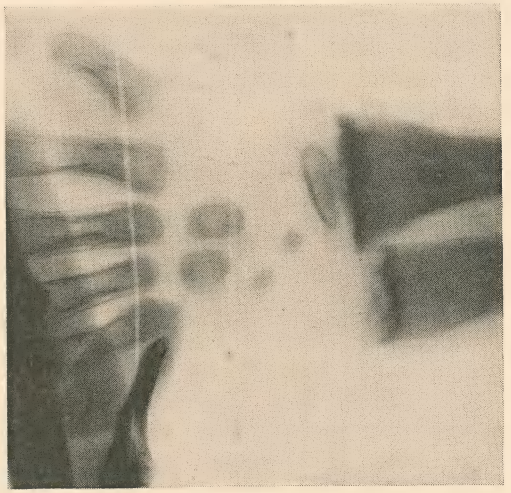


FIG. 9.—Roentgenographic appearance of the same child two months later, showing marked healing, almost complete trabeculation, and a thick line of calcium formation. (From Wilkes *et al.*, *American Journal of Diseases of Children*, XXXVII [1929], 490.)

X-ray photographs.—Normal ossification of children's bones from month to month can be followed most interestingly by X-rays, noting the increasing number and density of the small bones of the hand and wrist especially, as the child grows older. X-ray photographs are useful also in showing up slight rickets in cases too mild to be recognized by the usual clinical signs. The most frequently photographed bones are those of the baby's wrist. Typical examples of both normal and rachitic bones are shown in Figures 8, 9, and 10. It will be seen that normally the ends of the bones are convex in outline and the edges are sharply defined. In rickets, the ends of the bones develop a frayed appearance and finally may become "cupped," or concave instead of convex. Feeding the child cod liver oil, or irradiating it with ultraviolet light, causes the appearance, usually within two or three weeks, of dark bands or "chalk lines" at the end of the bones, and the gradual return to a normal outline.

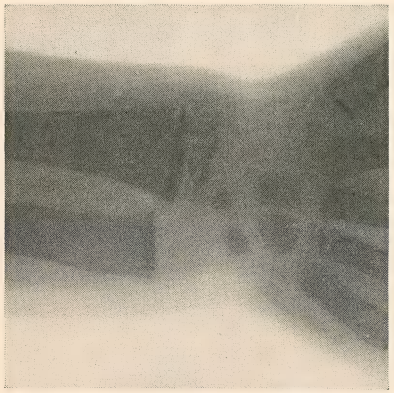


FIG. 10.—Roentgenographic appearance of the same child four months after treatment was begun. Except for some periosteal thickening the bones appear normal. (From Wilkes *et al.*, *American Journal of Diseases of Children*, XXXVII [1929], 494.)

Bone composition in rickets.—A German treatise by Czerny and Keller, which is a mine of information on children's metabolism, brings together some figures on the composition of bones of infants, normal and rachitic. Normal bones, for example, contain from 55 to 60 per cent of ash, but in rickets the ash content sinks to 32 or even 22 per cent. Thus in the rachitic child as in the rat, the inorganic part of the bone is formed more slowly than the organic.

The outward signs of the abnormal bone development of rickets are more or less familiar to people who work much with poorly fed children, though severe cases are fortunately becoming rare. Beading of the ribs, enlargement of the wrists and elbows (epiphyseal enlargement), flaring ribs, pigeon breast, and bowed legs are probably the commonest ones. Characteristic of human rickets also are delayed closing of the fontanelles, softening of the cranial bones (craniotabes), and bulging forehead (cranial bosses). Beading of the ribs and enlargement of the wrists are the first signs to appear, and may be almost the only ones, if the case is mild or checked at the beginning. All of these may be improved or cured by sufficient antirachitic treatment, provided the deformity has not gone too far.

The two structural divisions of bone calcium.—Most interesting proof has recently been found in the laboratory of the Massachusetts General Hospital, by Bauer, Aub, and Albright, that bones contain a section which can readily change and metabolize and which is distinct from the larger structural portion which serves for body support.

The active parts are delicate, lacelike structures known as trabeculae, most numerous at the ends of the bones. Here they are well situated by virtue of blood supply to receive calcium deposits in time of calcium excess and to give up calcium in time of calcium demand. The shafts of the bones, where these trabeculae are few, are not nearly so well situated for these purposes.

That they really do serve as a place of active calcium storage was shown by creating conditions of fluctuating calcium demand in animals and later observing by X-ray or by microscopic examination of removed bones how the number of trabeculae had changed. In one experiment some adult cats were fed a high calcium diet and others a low calcium diet and were found to be respectively in positive or negative calcium balance. At the end of several months the left forelegs of the animals were amputated at the shoulder joint under anesthesia, and the diets then reversed. After several months more the animals were sacrificed, thus allowing comparison of the humerus of each cat on the high and the low diets. Regardless of which diet was given first, the results were always the same. The bone removed after the high calcium feeding contained many trabeculae and its opposite member on the low diet showed a marked reduction. That is, the calcium reserve had been built up when much calcium was available and used when calcium was low (see Fig. 11).

By a method of intravital staining which works only on newly deposited bone the gradual formation of the trabeculae could be followed. Several cats, in another experiment, were put on a low calcium diet for eighty-two days so that the reserve would be used up. Then the dietary calcium was increased, the dye injected, and the cats killed at intervals thereafter. On the fifth day after the diet change, there were a few trabeculae faintly stained red, and on the fifty-fifth day there were many.

One more experiment of this series will be quoted proving the presence of this active calcium reserve in the bones. The parathyroid is known to have marked effect on calcium mobilization, and giving parathyroid extract is one of the quickest and surest ways of increasing calcium excretion and producing a negative calcium balance. Normal young rabbits on a high calcium diet were therefore injected with the extract parathormone. The usual results followed, including an abnormally high serum calcium. That the extra calcium came from the bones and in particular from the trabeculae was plainly shown by the X-ray plates; calcium was diminished in the bones and the trabeculae were much fewer.

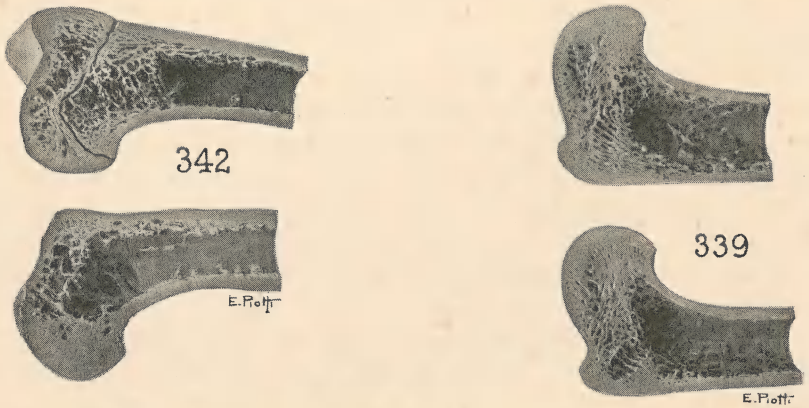


FIG. 11.—The effect of diet on the amount of cancellous bone (cats 342 and 339). The upper humerus in each case represents the high calcium diet and contains many more trabeculae than its opposite member (the lower humerus), representing the low calcium diet. (From Bauer, Aub, and Albright, *Journal of Experimental Medicine*, Vol. XLIX [January, 1929].)

Probably in children or adults on limited diet, in pregnancy, lactation, and other conditions of excessive calcium demand, without extra supply in the diet, the extra calcium comes first from the reserve in the trabeculae.

THE CALCIUM AND PHOSPHORUS OF THE BLOOD

The material deposited in the bones gets to them from the intestinal tract, of course, only through the blood. The minute amounts constantly present in the blood serve definite functions there and also act as exchange between different parts of the body.

Variations in children's blood.—It was only after sufficiently accurate methods had been developed for determining tiny amounts of mineral in small samples of blood that Drs. Howland and Kramer, of Johns Hopkins University, in 1921 reported values for calcium and inorganic phosphorus that have stood the test of time and have been repeatedly confirmed by other investigators. They found that for normal children the blood calcium averaged the very small amount of from 10 to 11 mg. per hundred cubic centimeters of blood and the inorganic phosphorus even less—between 5 and 6 mg. The twenty-five rachitic children whom they examined had in each case a normal or only slightly low blood calcium (minimum about 9 mg.). The blood phosphorus, however, was distinctly less than normal, the values ranging from 0.6 mg. to 3.2 mg., with an average of 2.0 mg.

Howland and Kramer did not rest content with the mere observation of the abnormality. They wanted to know whether these values could be brought back to normal, and accordingly treated the rachitic children with cod liver oil (from 2 to 4 cc. three times a day). Such treatment brought the serum phosphorus up (5.5 mg.) in from two to five weeks, and caused at the same time a general improvement in the clinical signs. The blood calcium was not much affected by the cod liver oil, although there was a slight rise in some cases.

About a year later Dr. Hess and his collaborator, Margaret Gutman, in New York, were able to show that proper light treatment, as well as cod liver oil, will also bring up the serum phosphate. These two people treated a number of infants with mild rickets by placing them in the direct sunlight (not screened through window glass or clothing) for from one-half to several hours, the time varying according to the sun's intensity, the clemency of the weather, and the sensitiveness of the baby. Exposure of the arms and legs only proved to be sufficient, although exposure of the trunk also was preferable if the temperature permitted. Care was always taken to keep the children warm. In all cases the inorganic blood phosphorus was low at the start, but gradually, within seven weeks for some and four months for all, rose to the normal level, parallel with the child's general improvement. For example, one infant seven months old had an initial blood phosphorus of 2.80 mg. per hundred cubic centimeters. Within two months this value had risen first to 3.75 mg. and then to 4.14 mg. These striking changes in the blood phosphorus have decided historic interest, for, as Hess and Gutman themselves say, "They furnish the first

definite evidence of metabolic change in the animal body brought about by the solar rays."

At about the same time blood phosphate increases were also observed in rachitic children after irradiation with an artificial source of ultraviolet light, the mercury vapor quartz lamp. The changes were even more marked than with sunlight, the increase being from an average of 2.9 mg. per hundred cubic centimeters to 6.0 mg.

It was thus early observed that parallel with the clinical signs of rickets in the body there is present also an abnormal blood picture, and that both may be improved by treatment with cod liver oil, sunlight, or artificial source of ultraviolet light.

Animal observations.—The more extended experimental work with animals has given results in most respects very similar to those reported for children. A slightly different technique is required for some animals, however. For children, the samples of blood needed for analysis are so small that they can easily be taken from the infant's vein week by week without pain or harm to him. The larger laboratory animals like dogs may be treated in the same way. Unfortunately, rats have so little blood in their bodies that all of it is usually needed for a single analysis, so that the changes in blood composition must be followed, not on a single rat, but on groups, each group living under the different conditions of the experiment.

Rachitic rats, especially those on the usual high calcium-low phosphorus diets, like rachitic children have a normal or slightly low blood calcium, and a decidedly low inorganic phosphate, frequently as low as 2 or 3 mg. per hundred cubic centimeters instead of the usual 8 mg. or thereabouts, which is normal for the rat. Only four weeks on a rachitic diet has been known to reduce the blood phosphorus from 7.5 mg. to 1.6 mg. Irradiating the rachitic animals or giving them cod liver oil or irradiated food or irradiated sterol (see chapter ix) brings the phosphate to normal, coincident with the healing of the rickets. So clear-cut are the results in some cases that Hess has found that he could make a definite comparison between healing by sunlight and healing by the addition of phosphate to the high calcium-low phosphorus diet which he was using. He states that the exposure of his rats to sunlight was equivalent to the addition of at least 75 mg. of phosphorus to the diet in the form of basic potassium phosphate.

A winter and summer fluctuation in blood composition.—Rickets occurs with greater frequency in the winter than in the summer months,

and many cases of rickets appear to heal spontaneously in the summer time. In view of these facts it is not surprising to find that the inorganic phosphate of the blood of rachitic children is distinctly lower in the winter than in the summer and autumn months. That normal children should also show this fluctuation in blood composition seems surprising and disturbing. It was Hess, again, with another of his collaborators, Marion Lundagen, who first observed this variation in 1922. Monthly examinations of sixty infants, from December to June, showed a steady decrease

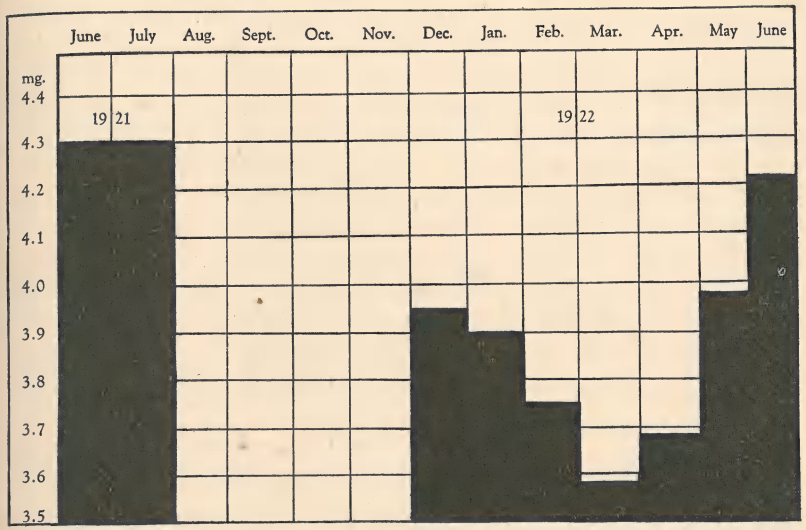


FIG. 12.—Seasonal tide of blood phosphate (inorganic). (From Hess and Lundagen, *Journal of the American Medical Association*, LXXIX [1922], 2210.)

in blood phosphorus from 3.92 mg. in December down to a minimum value of 3.58 mg. at the end of February and the first of March. From this time on the phosphate increased until, when the last observation was taken early in June, it had reached 4.22 mg., a value considerably higher than that found at the start in December. Ten older children, of from two to three years, showed a smaller but still a definite "seasonal tide" (see Fig. 12).

Even the less variable blood calcium may fluctuate with the seasons, though not so much as the phosphorus. Around 9.0 mg. from January to May, about 9.7 mg. in June, and up to 11 mg. in October were the average values found for some New York babies—not very marked differences,

but, taken in connection with the greater phosphate fluctuation, enough to show relation to the marked seasonal variation of rickets itself.

This seasonal variation seems to occur in many portions of the globe, since German nurslings have also been reported to show a rise in blood phosphate in summer and a drop in winter; and even in New Orleans where severe rickets is rare, and where the annual level of phosphate is higher than Hess found in New York, the same kind of fluctuation has been reported both for phosphorus and for calcium.

The variation in the antirachitic potency of the sunlight from month to month is probably largely responsible for these variations in blood calcium and phosphorus—a point that will be discussed in detail in chapter vi. The winter increase in colds and other respiratory infections may also be an important factor, for prolonged febrile infections, such as pneumonia, are known to cause a marked diminution of blood calcium.

Whatever the cause, the average baby, or even the young child, apparently has a low blood calcium and a lower blood phosphorus all through the winter and early spring. Probably the only means of avoiding this annual depression, especially in our northern climates, is the administration of cod liver oil or other antirachitic treatment during the winter months.

The calcium-phosphorus product.—Several investigators have found it illuminating to consider the *product* of the quantities of calcium and phosphorus in the blood in relation to rickets. They thus, logically enough, regard as significant the amounts of the two elements taken together rather than the amounts of each one separately.

Normal children with 5 mg. of inorganic phosphorus on the average and 10 mg. of calcium have a product (calcium×phosphorus) around 50. In rachitic children the product is almost always low. Howland believes that a product under 30 always means active rickets. From New Orleans, where rickets is apt to be milder than in the northern parts of the country, two physicians, Drs. DeBuys and von Meysenbug, have reported the blood findings in sixty-eight infants. The group that had a product of only 18 to 30 all showed positive rickets by roentgenographic examination, and 42 per cent of this group showed marked rickets. Half of those with a product from 31 to 45 showed more or less rickets, but of those with products from 45 to 62.8 only a quarter showed evidence of the disease, and in every case but one it was either healed or healing. The size of the product, therefore, did run rather closely though not perfectly parallel with clinical signs. Other excellent examples of the increase in

the product which accompanies healing rickets are given in Table VIII, on page 85.

A theory as to the relationship between the concentration of calcium and phosphate ions in the blood and the deposition of calcium phosphate in the bones has been worked out tentatively by Holt and his co-workers. The idea of these authors is that normally blood serum is greatly supersaturated with respect to calcium phosphate, so that that deposited in the bone is precipitated from a supersaturated solution. In rickets, the supersaturation is much less, so that deposition is much slower. In mathematical terms, it has been found that in normal blood or in cases of healing rickets, the ion product $(Ca^{++})^3 \times (PO_4^{=})^2$ is greater than 8×10^{-25}, and in rickets lower. While the idea of the supersaturated condition of the blood serum has been challenged, the significance for bone formation of the concentration of the blood calcium and phosphorus is undoubted.

Tetany.—Another childhood disease which must be mentioned here, because of the blood abnormality which accompanies it, is tetany, the chief outward symptom of which is convulsions. A child with tetany always has low blood calcium. The disease may occur alone or simultaneously with rickets, and it is subject to the same seasonal variations as rickets. In laboratory animals it can be induced by a low calcium-high phosphorus diet in contrast to the high calcium-low phosphorus which has been emphasized as the rickets-producing diet so far in this book.

Both in children and in animals it can usually be cured by the same means as are used to cure rickets—ultraviolet radiation, cod liver oil, or irradiated sterol, sometimes with the addition of calcium salts. As the tetany subsides, the serum calcium goes up to normal. In eleven infants studied by Hoag, only fourteen days' irradiation on the average was required to bring the serum calcium up to the normal. The cure was so definite that the statement could be made that fifty minutes' exposure was the average time for an increase of 1 mg. per hundred cubic centimeters of serum.

Recently Bakwin and Bakwin, of New York, have confirmed this observation of Hoag's and have found that even more striking cures could be obtained with irradiated ergosterol. In the twenty infants thus treated the serum calcium rose to normal in seven days on the average, and in only one case were convulsions present after the first day.

Thus it will be seen that either a low blood phosphorus or a low blood calcium can be raised to normal levels by dosage with vitamin D or ultraviolet light. If both calcium and phosphorus are low, they will be

raised together. It is interesting to note here, however, that if one value is very low, as for example, the calcium, and the other normal or above, the result of antirachitic treatment is usually to remedy the deficiency without affecting the level of the other mineral in the blood.

AN ATTEMPT TO FIND HOW THE ANTIRACHITIC FACTOR WORKS

Low retention of the elements in the body, low concentration of them in the blood, delayed deposition in the bones—this is the picture so far of the condition in the rachitic child or animal, and sometimes in the normal on an inadequate diet, and all these abnormalities are subject to improvement by treatment with vitamin D or ultraviolet light. What is back of the disturbances? Are they dependent upon low absorption from the intestinal tract? Is there an unusual condition in the intestinal tract that prevents or lessens absorption? The questions are under debate and the evidence available by no means conclusive.

The absorption of the calcium and phosphorus from the intestinal tract does seem to be definitely higher for the normal than the rachitic child and to be increased by antirachitic treatment. This is shown by changed distribution of the elements between the urine and the stools. The fecal calcium and phosphorus are made up both of unabsorbed material and of material absorbed and re-excreted into the tract. The urinary content is all material that has been truly inside the body, absorbed from the tract. Differentiating the two sources in the stools is difficult, but a lowering of the total quantity there and an increase in the urine is significant.

As a part of Dr. Daniels' recently quoted experiment on the retention of calcium and phosphorus by normal children, she observed the distribution between the urine and stools. On milk alone, without antirachitic treatment, the fecal calcium was as high in some cases as 94 per cent of the total intake and the fecal phosphorus 43 per cent. When the babies were given cod liver oil, the excretion in the feces was much reduced (to about 67 and 23 per cent, respectively), and with irradiated olive oil the figures were still lower (only 57 and 13 per cent). In contrast to these results, one rachitic child examined was excreting 100 per cent of the calcium and 72 per cent of the phosphorus by way of the intestine. At the same time that the intestinal excretion was being reduced by antirachitic treatment, the calcium and phosphorus in the urine was considerably increased—clear evidence that more of the minerals were being absorbed from the intestines.

Why these differences occur is uncertain, but an attempt has been made to find out by studying the acid or basic reaction of the feces and intestinal tract.

HYDROGEN-ION CONCENTRATION OF FECES AND INTESTINAL TRACT

It is well known that the solubility of the calcium phosphates depends upon the reaction of the medium. In acid media we have the readily soluble acid or primary calcium phosphate, $CaH_4(PO_4)_2$, in alkaline, the extremely insoluble tertiary calcium phosphate $Ca_3(PO_4)_2$, and in mediums which are faintly acid or near to neutral, we may have the slightly soluble secondary salt $CaHPO_4$ in equilibrium with larger or smaller amounts of the others.

A very attractive hypothesis, based on these differences in solubilities, is that absorption of the calcium and phosphorus from the intestinal tract can take place only when the material there is sufficiently acid to keep some of the calcium phosphate in solution. The data in support of this hypothesis are, however, incomplete and contradictory.

Animals.—Early work was done on feces, not on the less easily secured intestinal contents, and gave results in accord with the hypothesis. With normal rats the feces were distinctly acid, the hydrogen-ion concentration ranging from pH 5.2 to 6.5, and with rats on the rachitic diet they tended to the alkaline side of neutrality, pH 6.4 to 7.4.[1] More recently (1927), Yoder has extended and confirmed the results of earlier workers and has observed not only feces but intestinal contents. The contents of the whole intestinal tract of his rats, divided into sections immediately after death, were on the average distinctly less acid for the animals on the rachitic régime than for normal animals; for example, for the ileum the pH value was 7.39 instead of 6.90 or 6.85. Parallel with these changes the percentage utilization of the calcium of the feed was also poorer on the rachitic diet.

Normal and rachitic dogs, too, have been found to show similar variation in pH of gastro-intestinal contents and feces. The stomach contents were always found most acid (pH 3.40 to 3.93) and when the dogs were on a normal diet the contents of the whole intestinal tract, obtained in sections by ligation immediately after death, were also acid (pH 5.68 to 6.84). Dogs on Mellanby's rachitic diet, on the other hand, showed a

[1] The modern method of recording acidity or alkalinity is in terms of hydrogen-ion concentration, of which pH is one of the technical expressions. A pH of 7.0 indicates neutrality; smaller numbers, acidity; and larger numbers, alkalinity.

higher pH in all the six sections of the intestine which were observed, rising to 7.05, 7.27, and 7.44 in the lower, small intestine, caecum, and colon. When the dogs were fed cod liver oil or were irradiated, these values went down approximately to normal.

However, the conclusion that the feces and intestinal contents of rachitic animals are always less acid than that of normal is apparently not justified. Shohl and Bing, at Yale, have recently confirmed earlier results of the Englishman, Zucker, when rats were fed Zucker's particular rachitic diet, but not when Steenbock's diet was used. With the latter no marked change in fecal pH was apparent when the rats were cured of their rickets by cod liver oil or by irradiated diet or additional phosphate. On the Steenbock diet the fecal pH curves were often irregular, though in general the values were higher in rickets than when curative or preventive measures were used. The most definite observations are that the acidity of the colon of the normal animal was higher than that of the rachitic—a significant point since it is in the colon that reabsorption of calcium and phosphorus may take place.

Nevertheless, though the pH of dog or rat feces does not *always* vary with the rachitic or non-rachitic condition of the animal, an interesting quantitative method for vitamin D can be made to depend upon the variation. *When the conditions of the experiment are carefully controlled,* the rat diet having a very high calcium-phosphorus ratio and a very small amount of the two elements, and especially when relatively large and concentrated doses of vitamin D are tested, then the fecal pH does vary with the quantity of D eaten. Bacharach and Jephcott have just replied to the criticism of their earlier work and have shown that they can distinguish between samples of non-irradiated cereal and samples irradiated 5, 15, and 30 seconds, respectively. The fecal pH of the rats fed the four cereals was 7.16, 6.97, 6.76, and 6.57. "The specificity of the pH test depends on a knowledge of the conditions under which it will work, and on the exercise of the reasonable minimum of care and skill required to maintain these conditions."

Observations on children.—The interesting work on animals, of course, pointed the way to similar observations on the stools of children who were normal or rachitic or recovering from rickets. The problem has been investigated by Redman, in England. Her first observation on single stools from twelve children of the out-patient department of a Liverpool hospital who were recovering from rickets were decidedly encouraging, for all showed acid reaction. The pH values ranged from 4.21 to 6.24, with

only one above 5.90. Her several other much more elaborate series of experiments, however, gave indefinite and disappointing results, no correlation being obtained between different stages of the disease and the pH of the feces. For example, fourteen children of from two to three years and two fifteen-months babies, all with severe rickets, and also one normal child, were all given a standard diet with milk, cream, egg, etc., and then all, except the normal child, were given light treatment or irradiated ergosterol or cholesterol or a cod liver oil extract. The rickets was healed or almost healed in every case in the thirty to sixty-three days of the experiment, but the fecal pH values fluctuated up and down irregularly without reference to the stage of healing.

What further work on pH of feces or intestinal tract may bring forth cannot, of course, be predicted, but it looks now as if more variables were involved in its fluctuations than merely the rachitic or non-rachitic condition of the animal or the infant.

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CHAPTER V

TOOTH DEVELOPMENT AND THE ANTIRACHITIC VITAMIN

THE PROBLEM OF THE CAUSE OF TOOTH DECAY

Why do teeth decay? This problem has perplexed and vexed successive generations at least since the days of ancient Greece. Yet until about ten years ago we seemed no nearer to a solution than was Aristotle, who put the question, "Why do figs, when they are soft and sweet, produce damage to the teeth?" and answered it by saying, "Perhaps because the viscous softness of the fig causes small particles to adhere to the

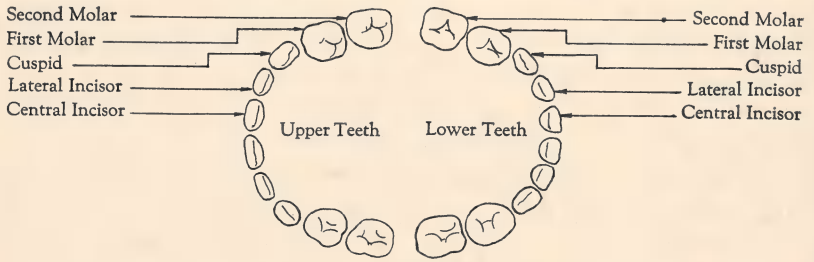


FIG. 13.—The temporary teeth. Age at which they erupt: central incisors, 4 to 9 months; lateral incisors, 7 to 10 months; first molars, 12 months; canines or cuspids, 18 months; second molars, 2 years.

gums and insinuate themselves into the dental interstices, where they very easily become the cause of putrefactive processes."

With this answer Aristotle perhaps became the original enunciator of the now commonly accepted "fermentation" theory of tooth decay, which was first put upon a scientific basis by Miller in 1885. In support of this theory we have today indisputable evidence that soft, sticky particles of food, especially carbohydrate food, furnish excellent fare for certain types of strongly acid-forming bacteria, which, if allowed to grow in contact with the teeth, are capable of destroying them. We have in addition plenty of evidence to show that if the mouth is kept scrupulously clean and the teeth as free as possible from such fermentable material, the process of decay can be retarded.

But dental decay cannot be entirely prevented by this means as

most of us know from unfortunate personal experience. In fact, the "fermentation" theory as the sole explanation for the prevalence of tooth decay fails to cover many situations. For example, adjacent teeth in the same mouth are by no means always acted on in the same way by the same organisms. "Why is it," asks one dentist, "that a molar decays and a bicuspid remains sound in the same mouth, acted on by the same bacteria, and lodging carbohydrate material in the interstices between, respectively, their mesial and distal surfaces?" "Such a thing," he adds, "could not happen in a test tube." Why also, we may ask, do the teeth of primitive peoples the world over—Eskimos, New Zealanders, Africans, and North American Indians—deteriorate so rapidly when they are brought under the influence of civilization? Certainly their primitive ideas of mouth hygiene have not been superior to ours. Why, too, are the teeth of some civilized peoples, for example the Highland Scotch, now losing the immunity which they have long enjoyed? Finally, why has there been no decline, but rather an increase in the occurrence of dental decay in spite of the fact that methods for the daily care of the teeth similar to those in use today have been known and advocated by doctors and dentists for the last five hundred years?

It would be impossible here to discuss all of the efforts which have been made to expand the fermentation theory to fit all cases. None of these attempts, however, has met with signal success, largely because causes outside the tooth itself have been looked for. But recent simultaneous study of microscopic structure and the influence of diet on this structure seems to be giving real progress for both animals and human beings.

INTERNAL STRUCTURE OF THE TEETH

That resistance to decay might be determined by forces inside the tooth has been suspected for some time, but has been very difficult to prove since satisfactory methods for studying its internal structure had not been developed. Not until about 1925 was it possible to demonstrate the existence of a circulatory mechanism inside the tooth which allows for its continuous nutrition both during growth and after full growth has been attained, and also for withdrawal of calcium and phosphorus in time of stress. Early attempts to correlate abnormalities of structure with decay also seemed fruitless because such gross abnormalities of structure as could be recognized were not widely distributed and appeared to be in no way responsible for the various degrees of susceptibility of different teeth. Recent microscopic studies, however, especially of the teeth of

rachitic or scorbutic as compared with normal animals, have thrown an altogether new light upon the subject.

The details of these microscopic studies are beyond the scope of this book. A brief description, however, of the structure of normal and more or less defective teeth will be in order.

Broadly speaking, the tooth is made up of three main sections: the outer covering or enamel, the dentine, or ivory, and the pulp. Ideally, the enamel is a hard, brittle, semitransparent substance which to the naked eye has a smooth, lustrous, and whitish appearance. It is non-cellular and is built up of prisms united by a densely calcified intermediate substance. The pulp is a soft tissue composed largely of cells, blood vessels, and nerves, its outer layer being made up of dentine-forming cells called odontoblasts. The dentine, which makes up the largest portion of the tooth and is the most like bone in its composition, is a yellowish white, translucent substance consisting of a non-cellular, homogenous material traversed regularly by branched dentinal tubes, which contain projecting fibers or outgrowths from the dentine-forming cells, together with nerves, some tissue fluid, and other organic matter. In young growing teeth, between the pulp and the already formed dentine there is always a layer of uncalcified matrix, which is penetrated by fibers from the odontoblasts. This is the zone of growth where further calcification is taking place. In a well-calcified tooth this zone is always thin; in an imperfectly calcified tooth, on the other hand, it is wide and irregular and uncalcified areas are left in it as permanent defects in the resulting dentine. These areas are the so-called "interglobular spaces" of defective teeth. Defects may also occur in the enamel varying from slight roughnesses and some discoloration to diffuse pigmentation, pits, and grooves, and even the entire absence of enamel over certain areas. For further histological details the reader is referred to May Mellanby's review of "The Influence of Diet on the Structure of Teeth" in *Physiological Reviews* for October, 1928, from which most of the foregoing material is taken, and also to Dr. Percy Howe's various publications.

MRS. MELLANBY'S WORK ON TEETH OF DOGS

The most extensive published experiments on teeth have been those done in England by Mrs. May Mellanby on the dogs which her husband, Dr. E. Mellanby, was using in his study of rickets. Her fundamental thesis seems to be that the teeth, being part of the bony structure of the body and largely composed of the same material as bones, might be

affected by the same factors as those which control the calcification of bones; and that abnormalities in teeth and bones might be expected to run parallel. The observation of the teeth in rickets or healed rickets would therefore be particularly valuable.

Dogs as experimental animals.—Her experiments, like her husband's, have been very numerous. Up to the time of the latest report 1,400 dogs had been observed and more than 2,000 ground sections of their teeth

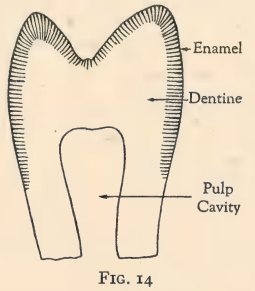


FIG. 14



FIG. 15

FIG. 14.—Diagrammatic drawing of cross-section of human molar tooth.

FIG. 15.—The comparative effect of cod-liver oil and olive oil on the arrangement of the incisors. *Above*, cod-liver oil; *below*, olive oil. (From May Mellanby, *British Dental Journal*, XLIX [1928] 787).

and jaws prepared. In order to secure such a large number of dogs, all sizes, shapes, and varieties, including mongrels, have had to be used.

Naturally it has been no easy task to accommodate the different sizes of dogs in the laboratory, to vary the quantities of food given to suit their individual needs, and otherwise to arrange the experiments so that the results might be strictly comparable with one another. Yet there have been compensations as well, for when comparable results were secured the experimenters were assured of their general application to all members of the dog family at least.

One may wonder why dogs rather than rats or guinea pigs or other animals have been chosen for this work. Unfortunately, rats or guinea pigs, which are so easy to care for in the laboratory, present technical difficulties in the way of investigations upon the teeth. In the first place,

their teeth are too small to work with easily. More important, however, is the fact that their teeth are not readily comparable to those of man, since they form one set of teeth only, which grow continuously throughout life from actively developing pulps.

If results are to be applied to man, the monkey which is more closely related to the human species might appear to be an eminently suitable experimental animal. But such is not the case, since the monkey eats an herbivorous diet which makes comparison with man difficult, and in addition he is reported to be particularly difficult to keep in health under laboratory conditions, however good the diet may be. The dog, therefore, seems eminently suited to this work. He forms two sets of teeth, temporary and permanent, which in their growth and development are readily comparable to those of man, eats a mixed diet, similar to that of man, and he is, moreover, accustomed to living more or less indoors as a member of the family. He therefore adapts himself fairly readily to laboratory routine. People who have tried to raise dogs at home will realize that, especially on the deficient, rickets-producing diets, it is not too easy a matter to keep them free from distemper, bronchopneumonia, and other infection, but by giving them the very best possible care, "the inroads of disease can be kept within reasonable limits."

Experimental procedure.—When testing the effects of any particular variation in diet, puppies from the same litter so far as possible have been used, the experimental diet being begun when the puppies were about five to eight weeks old. Individual experiments have usually been of from three to six months' duration, and have been repeated, as Mrs. Mellanby says, "again and again" so as to eliminate all possible sources of error which might arise through variations in rate of growth, illness, and so forth.

At the end of the experimental period, the animal has usually been killed, the jaw bone dissected out for examination, and one tooth—usually the upper or lower carnassial, a back tooth corresponding to the first molar in man—extracted and analyzed for its calcium content. Another tooth—usually a carnassial also—is extracted for cross-sectioning and microscopic examination.

During all of this work, which has necessarily extended over a period of years, the basal ration, while it remained the same in principle, has nevertheless undergone a moderate amount of evolution. Consisting originally only of white bread and skim milk, it has been gradually modified until in most of the later work the dogs were fed as a foundation diet

a liberal allowance of skim milk, white bread, yeast, orange juice, and meat. Such a diet meets all of the puppy's requirements except that of the fat-soluble vitamins. Definite figures as to the mineral content are not given except that in one of her articles Mrs. Mellanby states that calcium is supplied to the extent of 300–400 mg. a day in the skim milk alone. It should be noted that the food as given has always been soft and "pappy", the bread being soaked in milk and water.

Characteristics of the dogs' teeth.—Examination of the teeth of the very first cases of rickets which Dr. Mellanby was able to produce showed that those dogs which were suffering from severe rickets had also developed very serious defects in the teeth, so serious that they could be detected even by the most casual external examination. The defective teeth were late in erupting and irregularly set in the jaw, the jaw bone itself being spongy and made up of tissue resembling that found at the end of the long bones in rickets (see Fig. 15). The enamel of the teeth was very poor—sometimes so poor that it could be cut with a knife—and the calcium content of the entire tooth was low. For example, one rachitic puppy fed on the basal ration plus 10 cc. linseed oil had 0.154 gm. calcium (computed as calcium oxide) in the tooth selected for extraction, while a healthy dog, fed the same diet, with cod liver oil substituted for the linseed oil had 0.395 gm. calcium oxide in the corresponding tooth.

Microscopic examination of cross-sections of these teeth proved that there was a considerable difference in the two sets. Not only did the teeth of the dog free from rickets look well to the naked eye, but the internal structure, both of enamel and dentine, was found to be good, whereas the rachitic dog's teeth had a poorly constructed enamel and dentine containing many interglobular spaces (see Fig. 16).

Further studies developed the fact that on diets deficient in the calcifying vitamin, the internal structure of the teeth always deviates considerably from the normal, the degree of deviation depending upon the severity of the diet, that is, upon the amount of vitamin D which it contains.

Unfortunately, in spite of these abnormalities of structure, actual decay has not appeared in any large proportion of the dogs' teeth. This seems the more remarkable because the teeth of rachitic children are notoriously defective and because certain other investigators, notably McCollum and his co-workers at Johns Hopkins University, have succeeded in demonstrating a certain amount of decay in the teeth of rachitic rats. Nevertheless, the microscopic defects of structure which the

Mellanbys have been able to produce in dogs' teeth by means of rickets-producing diets, when they are found in children's teeth appear to be a forerunner of decay. Mrs. Mellanby suggests that possibly the dogs' teeth have not decayed because the experiments have not been continued for a sufficient length of time.

The effects of antirachitic treatment.—Practically all types of antirachitic treatment, including cod liver oil and ultraviolet light, have been found to have a favorable effect upon the teeth. While these experiments are too numerous to quote in detail, it may be said in general that not only in each case was the structure of the tooth improved but the calcium content was increased as well. All sources of vitamin D, either natural—for example, cod liver oil or egg yolk—or artificial—irradiated

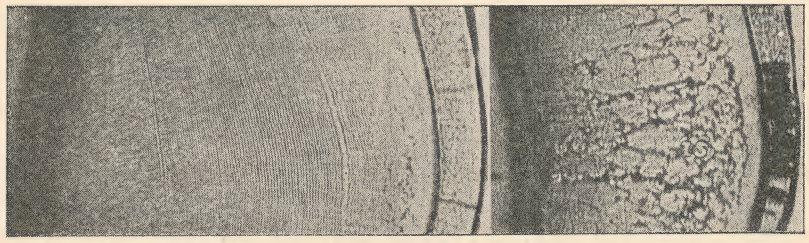


FIG. 16.—The effect of adding egg yolk to a diet deficient in vitamin D; left, egg yolk-enamel and dentine normal; right, control-enamel and dentine very effective. (From May Mellanby, *British Dental Journal*, XLIX [1928], 787.)

olive oil, other irradiated foods, or irradiated sterols—have been fed with excellent results.

Exposure to ultraviolet radiation, as might be expected from its curative effect upon the bones, also exerts a beneficial influence upon the teeth. To illustrate this action, three puppies were fed from the ages of six weeks to six and one-half months on the basal rickets-producing diet. Two of these received 45 to 100 gm. of oatmeal and 10 cc. of olive oil, and the third 45 to 100 gm. of oatmeal and 10 cc. of cod liver oil. During the entire experimental period, one of the animals in the first group was irradiated for twenty to thirty minutes three times a week, at a distance of three feet from the lamp. Of the two puppies on the deficient diet the teeth of the one receiving the ultraviolet light contained more calcium (0.190 gm. calcium oxide) and were better formed than those of the non-irradiated dog (0.154 gm.). In this particular experiment, however, the effect of the irradiation was not equivalent to that of the cod liver oil fed, since the dog receiving the cod liver oil had considerably better teeth

(0.437 gm. of calcium oxide) than either of the other two. Similar results were obtained when other dogs were exposed to sunlight instead of ultraviolet radiation.

The effect of added salts.—Increased quantities of calcium phosphate, on the other hand, either as the inorganic salt or in increased quantities of skim milk, had little if any effect upon the structure or upon the calcium content of the teeth. The addition of as much as 5 gm. of calcium phosphate to a combination of the basal diet and 10 cc. of linseed oil, did not improve the quality of the teeth, nor was doubling the quantity of skim milk fed any more effective.

The anticalcifying effect of cereals.—Dr. Mellanby's rather startling demonstration that diets containing large quantities of cereal, especially oatmeal, and lacking in vitamin D, are particularly productive of rickets will be discussed in a later chapter. It should be said at this point, however, that Mrs. Mellanby has shown that such diets are as detrimental to the teeth as to the bone. That is to say, if the basal diet contains no D, the larger the amount of cereal fed, especially if the cereal be oatmeal, the more severe will be the rickets and the poorer the teeth. If the diet contains adequate amounts of D the teeth will be perfectly formed, no matter how much oatmeal is fed. Mrs. Mellanby believes, however, that the greater the amount of cereal eaten the more vitamin D will be required to offset its anticalcifying effects. For a complete discussion of this point the reader is referred to chapter xi.

Age as a factor in the effect of diet.—During the period of active growth, the teeth seem to reflect very promptly the nature of the diet which is being fed at any particular time. That is to say, if the diet is poor, the dentine which is being formed at that particular time will be poor also. But a change from a poor diet to a good diet will immediately be followed by an improvement in the structure of the later-formed dentine. Thus the same tooth may contain successive layers of poorly constructed and well-constructed substance.

The opposite change from a good to a poor diet may result in the production of a defective dentine if the dog is not too old and the calcification of the teeth is not too nearly complete. This change in the dentine is not so easy to produce, however, and the older the dog the more difficult it is to produce defects. If the puppy is fairly advanced in growth, no defects may appear. For example, one puppy, which was put on the rickets-producing diet at fourteen weeks of age instead of the usual five to

eight weeks, had apparently normal teeth. The enamel was white and shiny, the teeth were regularly arranged, and they contained a normal amount of calcium.

Time of calcification.—The period during which calcification of a dog's teeth takes place is relatively short and yet they do not all calcify at the same time, so that all of the teeth are not equally affected by inadequate diets. The incisors, which are not so seriously affected as some of the other teeth, begin to calcify considerably before birth. The most seriously affected tooth is the carnassial, a large tooth toward the back of the puppy's mouth, which corresponds more or less closely to the first, or "six-year" molar in man. This tooth begins to calcify at or just before birth, and develops very rapidly during the experimental period.

It has been Mrs. Mellanby's experience that it is almost impossible to produce defects in a puppy's teeth by feeding the pregnant mother a rickets-producing diet. After the puppy is weaned, however, defects will appear very rapidly if it is given the same inadequate food. Such an occurrence, no doubt, is due to the well-known fact that the tissues of the mother are sacrificed as far as possible to meet the needs of the young developing in the uterus. The parts of the teeth that are formed before birth, therefore, will be well calcified, even though the mother's own bones and teeth may suffer in consequence. But when the animal becomes independent of the mother for food the results of unsatisfactory diets show up immediately.

For this reason, since the teeth begin to calcify from the top down and from the outside in, there is generally, in the case of the first set of teeth at least, a band of normal dentine just under the enamel. The width of this band varies greatly in different teeth, being widest usually in those teeth which begin calcification the earliest—that is, the incisors—and which, therefore, are more nearly completely calcified at the time of weaning. The rest of the tooth may be more or less hypoplastic, depending upon the puppy's later diet.

Such observations as these emphasize the importance of correct feeding during the period of rapid growth after weaning if the young animal is to have sound, healthy teeth. A poor start, however, although serious is not altogether hopeless, for if vitamin D be added to a faulty diet while the teeth are still growing, they will be strengthened to a certain degree at least.

Work on other animals.—To prove that the effects of lack of vitamin D are not peculiar to dogs' teeth, Mrs. Mellanby has also carried out an

extensive research on rabbits and has done some work on rats, with corresponding results. Two other investigators, Orban in Vienna and Toverud in Norway, also have found that diets lacking in the antirachitic vitamin resulted in very poorly calcified teeth in rats.

STRUCTURE OF HUMAN TEETH

The teeth of children.—Children's teeth in their ideal condition may have a structure, as observed either by the microscope or by the naked eye, much like that of healthy dogs' teeth. The disturbing fact is, however, that most of them actually do have defects similar to those developed in dogs' teeth on a rickets-producing diet. These defects in children, though not in dogs, are often associated with decay, the underdeveloped and poorly calcified teeth decaying in the large majority of cases, and the degree of caries being roughly proportional to the degree of underdevelopment. Teeth which are perfectly constructed are much less subject to decay.

Mrs. Mellanby within the last few years, parallel with her work on dogs, has examined more than one thousand temporary or deciduous teeth from children. These teeth have been obtained from dental clinics and from private sources, some of them having "fallen out" naturally and some having been extracted for various reasons. Considering only those teeth to be "normal" in which the enamel was smooth and little pigmented and the dentine free from "interglobular spaces," in other words perfect in structure, she has divided the remainder into three classes—slightly underdeveloped or "hypoplastic," moderately underdeveloped, and grossly or severely underdeveloped.

The results of this examination are startling. Only 149, or about 14 per cent, of the total 1,036 were soundly constructed. About one-fourth were only slightly hypoplastic, but nearly two-thirds showed moderate or severe hypoplasia. The differences in structure in the different types of teeth were equally striking. The "front teeth" or incisors were relatively well constructed, only a few of them being seriously underdeveloped, but the first and second molars, or "grinders," were very poorly constructed, three-quarters of the first, and nine-tenths of the second molars being classed as moderately or grossly underdeveloped.

No correlation between the children's diet and the structure of the teeth was attempted at the time of this study except that the defects in the teeth from the clinics and from private sources were tabulated separately, the assumption being that the children from the more comfort-

able homes were the better fed. It was found that the teeth from the private sources were as a matter of fact considerably better formed than those from dental clinics. Even among the more well-to-do children, however, only a little over one-fourth of the total teeth were really well formed, and about one-third showed "hypoplasia or severe hypoplasia."

These figures may be somewhat exaggerated owing to the fact that some of the teeth undoubtedly had to be extracted because of their defects. Nevertheless they must be considered fairly representative of actual conditions in children's mouths, since many of the teeth were not extracted but shed in the normal manner.

Permanent teeth.—It is more difficult to obtain a true picture of the structure of the teeth in the average adult mouth, since except in cases of pyorrhea permanent teeth are rarely extracted unless they are defective enough to cause the owner real difficulty. A few of the 266 teeth of adults examined by Mrs. Mellanby were extracted for straightening purposes only, but, as she herself remarks, conditions which produce irregularities in the position of the teeth usually produce defects in structure as well. Under these circumstances the figures derived from the examination of these adult teeth are not so conclusive as those based on the study of the children's teeth, but they are nevertheless very illuminating. All types of teeth were examined, although the majority of them were first molars.

As might be expected from the condition of the temporary teeth, the permanent teeth also were found to be highly defective. Not one of the 266 was normal, that is, perfect, in structure. A few (about 8 per cent) were only slightly hypoplastic, but the great majority were very badly formed. Again, certain types of teeth were found to be better constructed than others. That is to say, the incisors, canines, and pre-molars were considerably better formed than the molars, the second molars being much worse than the first.

The relation between structure and decay.—The general prevalence, both of defective structure and of dental decay, would lead one to suspect a very close relation between the two, especially when it is remembered that those teeth which are the poorest in structure—the molars—are also the most susceptible to decay, and that those which are most nearly perfect—the incisors—are the least so.

That there is indeed such a relationship is definitely shown by Mrs. Mellanby's figures. Those teeth which were normal or nearly normal in structure exhibited comparatively little decay, only a little more than

one-fourth having carious cavities as compared with 85 per cent in the distinctly hypoplastic teeth. The incisors, with their more perfect structure, were also very much freer from decay than the molars, which were almost 100 per cent carious. The size of the cavity and the general extensiveness of decay also appeared to bear a direct relation to the structure of the tooth, the largest cavities and the most extensive destruction occurring in the teeth with the poorest structure. In fact, all things being considered, about nine-tenths of the teeth showed a direct relationship between the original structure of the tooth and its liability to decay. Even the other 10 per cent, which at first glance appear to be exceptions to the general theory, can to a large extent be accounted for, again on the basis of structural conditions inside the tooth.

Formation of secondary dentine.—The explanation for these exceptions is found in the production under certain circumstances of entirely new areas of so-called "secondary" dentine in the completely calcified and full-grown tooth. In dogs the formation of a secondary dentine can be artificially stimulated by rubbing the tooth every few days with a file. In human teeth such dentine appears naturally, if it appears at all, under decayed spots or portions of the tooth which have been worn away by long, hard use. Its production very evidently marks the effort of the tooth to repair the damage and protect the vital tissues of the pulp against bacterial or mechanical invasion.

Like the original substance of the tooth, the secondary dentine may be well or poorly made. When produced experimentally in dogs, its structure depends upon the quality of the diet. If the food contains adequate amounts of vitamin D, the secondary dentine is well calcified. If vitamin D is lacking, the secondary dentine is of poor quality or entirely absent.

The mechanism by means of which the secondary dentine is formed is still a subject of controversy. Certain dentists believe that the calcium which is laid down in it is derived from the saliva rather than from the blood; that is, that it is deposited from the exterior rather than from the interior of the tooth. Even if this be true, the importance of vitamin D is not diminished since Dr. C. L. Pattison, who has co-operated with Mrs. Mellanby in some of her later experiments, has recently shown that the calcium content of children's saliva may be doubled or even trebled by changing from a diet low in vitamin D to one that is adequate in this respect.

In the children's teeth which Mrs. Mellanby examined, more or less secondary dentine was found. In the normally calcified teeth, which nev-

ertheless had decayed, the secondary dentine was nearly always absent or defective in structure. In other words, the tooth was unable to defend itself against decay. Those teeth, on the other hand, which were poorly calcified but free from decay were usually protected by a secondary dentine which was abundant and well calcified.

The majority of the apparent exceptions, then, still support the theory that poor structure is a predisposing cause of tooth decay and indicate that the presence of vitamin D in the diet is essential not only for the original development of the tooth but for its protection later in life.

EFFECT OF VITAMIN D UPON THE PREVENTION OF CARIES IN CHILDREN'S MOUTHS

In order to discover whether vitamin D actually could protect living teeth against decay, Mrs. Mellanby, Dr. C. L. Pattison, medical superintendent of the King Edward VII Hospital, of Sheffield, England, and J. W. Proud, an English dentist, have recently been carrying on a series of investigations of the spread of caries in the mouths of children living on diets containing more or less of the antirachitic factor.

Three distinct studies have been made, all of them upon children under twelve years of age who were patients in the King Edward VII Hospital, suffering from bone tuberculosis. In one study at least and probably in the other two although this is not definitely stated, the children were in bed during the entire experimental period. The wards had a southern exposure and were so arranged that the children were virtually out of doors during the whole twenty-four hours of the day. All had approximately the same amount of sunshine and each child brushed his teeth twice daily with chalk. About 125 children have been studied for periods of from five to eight months each.

Diets used in the three series of experiments varied to some extent, especially in the method of supplying vitamin D. All were based upon the regular hospital diet, which would be considered fairly good from the ordinary nutritional standpoint since it contained an average of 1½ pints of milk, some cod liver oil (2 to 3 drachms), and moderate amounts of fruit and vegetables. Meat was served daily and eggs occasionally. In the first series, the children were divided into three groups, one living on the hospital diet just described, another receiving additional amounts of milk, butter, eggs, and cod liver oil, and the third receiving less milk than the first (only ½ to ¾ pint), very little egg, no cod liver oil, and more cereal, especially oatmeal.

In the second investigation the diets were similar but somewhat better controlled than in the first. Vitamin D was again supplied in varying amounts of whole milk, eggs, and cod liver oil.

Only one group of children was studied in the third experiment. These children received in addition to the ordinary hospital diet slightly different amounts (1 to 4 cc.) of radiostol, a commercially prepared solution of irradiated ergosterol.

The children's teeth were closely inspected and carefully charted at the beginning and end of each study. Among the older children especially, there were about equal numbers of temporary and permanent teeth in the mouth at the start. The permanent teeth appeared to have a considerably worse structure than the deciduous teeth, but of course showed less caries, because they had not been in the mouth so long. In this connection, it is interesting to note that Mrs. Mellanby says that she is now able to judge very accurately from the external appearance of a tooth what its internal structure will be. She has repeatedly checked her first estimate based on inspection in the mouth by later microscopic examination and found the two to agree very closely. In order to give the diets the severest possible test, the children with the worst teeth, that is the most caries, were put on the best diets, and vice versa.

Results in each of the three studies point to the conclusion that increased quantities of vitamin D, whether in the form of milk, eggs, and cod liver oil, or as irradiated ergosterol, have a distinctly beneficial effect upon the teeth. Each time the work was repeated it was found that the spread of caries was less, and the average amount of hardening of the teeth, or arresting of the process of decay, was greater when larger amounts of D were fed.

For the purpose of eliminating any possible variation in susceptibility to decay, due to age, Mrs. Mellanby has selected and tabulated the figures for children under six years of age in each group. These figures are given in Table V. The figures show more plainly than words the benefits of the good diet. Although a complete cure did not result, certainly the spread of decay in the children's mouths was very materially lessened.

The effect of irradiated ergosterol (radiostol) would appear to be somewhat greater than that of the cod liver oil, milk, and egg yolk. However, since the vitamin D content of the latter foods was not definitely known, the only fair conclusion is that irradiated ergosterol is at least as effective as the combination of foods.

The objection may be raised and Mrs. Mellanby herself admits that

her work is subject to the criticism that all estimates of the extent of caries and all decisions as to whether a cavity had "hardened" or "softened" or had actually enlarged in size are based on judgment and opinion alone. For this reason the figures are not so satisfactory as they might otherwise be. But Mrs. Mellanby and her associates have devised a most elaborate system of testing the teeth and of estimating the size of cavities and have made every effort to eliminate the element of personal bias as far as is humanly possible. These three investigators have found that in individual examinations of the same teeth in different rooms, at different times, and unknown to one another, they can check each other very closely, so that it would appear that their results are as reliable as human judgments can be. But in spite of these objections the indications are very clear that vitamin D is an important factor in building up the resistance of the teeth and preventing the spread of caries. It should be noted that in the study as a whole temporary and permanent teeth shared alike in the protection afforded by diets rich in D.

TABLE V

EFFECT OF DIET CONTAINING VARYING AMOUNTS OF VITAMIN D UPON TOOTH DECAY IN CHILDREN

Group	Number of Children in Each Group	Average Number of Teeth per Child Showing Initiation or Increase of Caries	Average* Degree of Increase of Caries per Child	Average* Amount of Hardening or Arrest of Caries per Child
A_3 (radiostol)	21	1.0	1.1	3.9
A_1 and A_2: Milk, eggs, cod liver oil, no cereal	18	1.4	1.7	3.7
B_1 and B_2: Less milk and egg, no cod liver oil, oatmeal	19	5.0	6.0	0.2
C_1 and C_2: Moderate quantity of milk, eggs, and cod liver oil, no oatmeal	20	3.3	4.5	1.2

* Figures in fourth and fifth columns are based on an arbitrary numerical scale adopted by the experimenters but are strictly comparable.

THE TEETH IN SCURVY

Although this book is chiefly concerned with the relation of vitamin D and light to calcium and phosphorus metabolism, no discussion of the experimental production of defects in the teeth or of the cause of dental caries is complete without some mention of the teeth of animals with scurvy, and of the present discussion as to whether lack of vitamin D or vitamin C is of first importance in the prevention of tooth decay.

In 1919, Zilva and Wells, two English physiologists, reported that they had observed profound changes in the teeth of scorbutic guinea pigs, these changes appearing considerably in advance of other symptoms of the disease and while the animals were still in good health. At about the same time Dr. Percy Howe, of the Forsyth Dental Infirmary of Boston, reported similar observations, which have been extended and confirmed by later research in his laboratory on other guinea pigs and on monkeys. The changes taking place in the teeth in scurvy, however, appear to be on the whole quite different from those which occur in rickets.

Deterioration of the pulp.—In scurvy the first of the dental tissues to be affected is the pulp, which according to Zilva and Wells undergoes a "fibroid degeneration" so severe that "no trace of cellular organization is left. Nerves, cells, blood vessels and odontoblasts" (dentine-forming cells) "are no longer recognizable."

In further description of the changes which take place in the pulp, Dr. Howe states that it becomes shriveled and shrinks away from contact with the dentine. The orderly arrangement of the odontoblasts is destroyed, and the fibers connecting them with the dentinal tubes are torn apart. The space between the dentine and the pulp becomes filled with fluid and the dentine itself gradually liquefies and may be extensively or completely destroyed. When the animal is given orange juice, the pulp recovers to some extent although it is incapable of returning to its original size or form. The odontoblasts tend to rearrange themselves in an orderly fashion and resume the function of calcification. The liquid between the pulp and the dentine calcifies, forming a secondary dentine not wholly like the original substance because it has less well-defined structural form, but which might be called "dentinal scar tissue."

These changes in the pulp and the accompanying changes in the dentine, it should be remarked, have been described only in guinea pigs. Dr. Howe, largely because of the number of animals required and the consequent expense involved, has not examined the pulps of his monkey's teeth, nor has he examined human teeth in the same manner. According to Mrs. Mellanby, defects of this type are rarely if ever found in human teeth. This may be so because human diets are seldom as completely deficient in vitamin C as the guinea-pig diets. Should such changes occur in the pulp of human teeth it is easy to realize that the nutrition of the tooth would be seriously interfered with and its resistance to disease thereby lowered.

Appearance of dental caries.—In addition to the deterioration of the

pulp, Dr. Howe has observed that his scorbutic guinea pigs' teeth become very soft, so soft that they can be easily pierced by a very fine instrument, that they bend easily, and that decay appears in a large number of cases. The defects in the bony portion of the tooth and also the tooth decay have been seen in monkeys as well as guinea pigs when they are put on deficient diets, especially those deficient in vitamin C.

Pyorrhea alveolaris.—One of the most spectacular phases of Dr. Howe's research has been the development in the scorbutic animals, both monkeys and guinea pigs, of a condition very closely resembling pyorrhea in man. Not only do the gums become red and spongy and ready to bleed upon the slightest pressure as is expected in scurvy, but the alveolar border of the jaw bone (that portion of the bone which contains the tooth sockets) is absorbed to such an extent that the teeth become loose and may actually drop out if the animal happens to bite very hard either upon its food or upon any other substance. In many instances there is also a copious flow of pus from the tissues surrounding the tooth. When the animal is fed orange juice, however, the gums become healthy once more, the teeth tighten up, and the pus disappears.

Effect upon the teeth of increased quantities of vitamin C in human diets.—Very remarkable cures of pyorrhea in man have been accomplished by feeding large quantities of orange juice and other foods of high antiscorbutic value. At the present time Dr. Milton T. Hanke, of the University of Chicago, in collaboration with the Chicago Dental Research Club, is engaged in an extensive study of the effect of diet upon dental disease, both pyorrhea and dental caries, in human mouths. Dr. Hanke has now examined several hundred patients of all ages, both children and adults, who have been referred to him by the members of the Dental Research Club. He has questioned them in detail about their diet, has investigated their medical history, especially with regard to gastro-intestinal or endocrine disorders, and has determined the concentration of calcium and phosphorus in the blood. The information thus obtained, he feels, has made it possible to judge fairly accurately the adequacy of the previous vitamin intake. A normal blood calcium and phosphorus indicates, he believes, that there is no deficiency of vitamin D.

Of the 114 cases whose records are complete at this date, 17 were free from dental disorders, and 11 of these were eating diets that contained ample vitamins. According to Dr. Hanke's report, "The dietary deficiencies in all of the other cases (in this group) were slight excepting in the case of one boy, age 17, whose diet was markedly deficient in vitamin C but whose mouth was in good condition. This boy is not, however, in good health."

Every case of dental disorder, either caries or pyorrhea, was associated with some dietary deficiency. None, however, was associated with a pure D deficiency. Half of the cases were deficient only in C, and the others deficient in C and D.

The results of the improvement of the diet of these patients have been astonishing. Disappointingly enough, increase in the intake of D, usually in egg yolk or irradiated ergosterol or both, has not in these patients noticeably retarded the process of decay. But very large quantities of vitamin C in orange and lemon juice have brought about almost unbelievably rapid cures of pyorrhea and an apparent complete cessation of decay. The size of the cavities in these cases has been determined by X-ray photographs and in a number of instances there has been no measurable increase, at least over a period of six months.

The quantities of vitamin C which must be used to obtain these remarkable results are however far in excess of what has previously been considered necessary for the average person. The antiscorbutics recommended by Dr. Hanke as the most agreeable and the most effective are orange juice, lemon juice, and lettuce. These, he believes, should be eaten daily in the following amounts: the juice of one lemon mixed with sufficient orange juice to make one pint, plus at least one-fourth head of lettuce. For children from six to ten years of age he recommends one-half of these quantities.

OTHER STUDIES OF THE RELATION OF DIET TO THE SPREAD OF TOOTH DECAY

Other studies of children's teeth, to be reported in the later pages of this chapter, are less specific in their indications as to whether vitamin C or vitamin D is the more important in the prevention of tooth decay. In some cases improvement in the children's teeth may be attributed to the influence of vitamin D, in others to vitamin C, and in still others to either or both.

The teeth of rachitic children.—The influence of the actual disease of rickets upon children's teeth must be considered from two standpoints: first, its effect upon the time of eruption of the first set of teeth; and, second, its effect upon the quality of the teeth as evidenced by their ability to resist decay.

For many years physicians have considered delay in cutting the teeth as a symptom of rickets. Recently Drs. Julius Blum and Jacob Mel-

lion have published the results of a statistical study of the time of the eruption of the teeth in eighty-seven rachitic and sixty-eight non-rachitic infants, residents of a children's home in New York City. The rachitic children were observed several years ago (1920–22) when cod liver oil was not used as a routine method of treatment as it is today.

Although the cases of rickets observed were mild and although the time of eruption of the first tooth varied considerably even among the normal children, nevertheless the rachitic children were distinctly behind the normal ones in their teething schedule. About one-tenth of the normal babies had their first tooth when they were six months old, whereas none of the rachitic children had a tooth at this age. At nine months almost two-thirds of the normal children and only one-fourth of the rachitic children had a first tooth, and at one year all but one of the normal babies and only three-fourths of the rachitic children had a tooth. Teething was delayed until the twelfth to the fifteenth month in eighteen of the infants having rickets, and until the fifteenth to the twenty-first month in four others. The time of eruption of the later teeth was also observed and the authors state that

> the deduction seems to be warranted that not only the first tooth but also the eruption of subsequent teeth is delayed in rickets. Even in the mildest form of rickets at present recognizable, there is a definite delay of dentition in rachitic as compared with normal infants. . . . . This is interesting in showing the systemic nature of the metabolic disturbance of rickets as well as the close relation of teething to the development and ossification of the long bones.

A search through the literature has revealed very little definite data concerning the influence of rickets in early life upon the structure and quality of the permanent teeth, although general statements abound to the effect that the teeth of rachitic children are particularly subject to decay. Dr. B. G. de Vries describes the cases of two eight-year-old children with distinctly hypoplastic permanent teeth, each of whom had a history of early rickets. In one of these children the temporary teeth were badly decayed. Dr. de Vries states that these cases are typical of numerous others which he has seen. "Most frequently," he says, "we find a condition of hypoplasia of these permanent teeth" (the six-year molars and the incisors) "which were being developed at the onset of the disease."

A severe condition of hypoplasia associated with an actual disintegration of the teeth from the biting edges upward has been observed in two children with active rickets by Drs. F. V. Simonton and M. R. Jones,

of the University of California. These two investigators have also been able to reproduce this condition, which they call odontoclasia, in experimental animals (dogs).

It is evident that much more work needs to be done in this field, but such data as have so far been presented point to the conclusion that the teeth of rachitic children suffer fully as much as their bones from the effects of the disease.

The Massachusetts survey.—Evidence of the close relation between the quality of the diet and the quality of the teeth is furnished by a recent survey of the dietary habits and the condition of the teeth of children of elementary school age in two towns in Massachusetts. The towns selected were of very similar social and economic status, the chief distinction between them being that one was and had been for years a dairy town.

Data concerning the diets and the health of the children were obtained through home visits and medical and dental examinations. The diets were scored on a scale of 100 points, according to the amount of milk, cooked vegetables, fruit, and raw vegetables, whole grain cereals, meat, and eggs which they contained. Twenty-four of the one hundred points were assigned to milk.

The diets of the children in the two towns proved to be very similar on the whole, with the one very important exception of the amount of milk drunk. In Town S, the dairy town, 64 per cent of the children drank a quart of milk or more daily, but in Town C only 16 per cent of the children drank that much. Chiefly because of this difference in milk-drinking a larger proportion of generally satisfactory (high-score) diets was found in Town S than in Town C. The percentage of diets in both towns which attained scores of 70 or above and of 50 or above are shown in Table VI.

The difference in the condition of the teeth of the children in the two towns is most impressive. In Town S, the milk-drinking town, 35 per cent of the children had no carious permanent teeth, either filled or unfilled, and only 11 per cent had five or more carious teeth. But in Town C, where less milk was drunk, only 17 per cent of the children had permanent teeth which had never had any decay in them, and 22 per cent had five or more decayed teeth.

Since the six-year molars are so prone to decay, the contrasting figures for these teeth are particularly interesting. In Town S, 33 per cent of the children had all four of these molars free from caries, and 18 per

cent had all four of them carious or extracted, while in Town C only 13 per cent of the children had all four molars free from caries and 46 per cent had all four carious or extracted. The sharp contrast between the condition of the teeth of the children in the two towns and its relation to the quality of the diet in each case is clearly brought out by the figures set down in Table VI.

It should be said here that dental attention was about equal in the two towns, about one-fourth of the children in each town not having had such care. In view of the similarity in dietary habits other than milk-drinking, and in view of the similar amounts of dental care, the author of the report believes that the superior teeth of the children in Town S are

TABLE VI

RELATION OF DIET TO CONDITION OF TEETH OF CHILDREN IN TWO TOWNS IN MASSACHUSETTS

	Town C, per Cent	Town S, per Cent
Diets:		
With score of 70 or better	15	24
With score of 50 or better	64	76
Children having 1 qt. of milk or more	16	64
Children having:		
No carious permanent teeth, filled or unfilled	17	35
1 to 4 carious teeth	61	54
5 or more carious teeth	22	11
All 4 molars (six-year) free from caries	13	33
All 4 molars (six-year) carious or extracted	46	18

to be explained on the basis of their larger milk consumption. "Since the town has been a dairy one for years, the children have not only profited directly by their own milk intake but have doubtless also indirectly reaped the benefits of the milk consumption of their mothers during pregnancy."

It is impossible to say which of the elements in the milk has been the determining factor in the development of the stronger and more resistant teeth. Certainly the quantity of calcium and of phosphorus which it adds to the diet must be important in this connection. If much of it was taken raw, as is quite possible in a milk-producing community, it may have added appreciable amounts of vitamin C. Most probably, however, its beneficial influence is to be explained on the basis of its mineral and vitamin D content.

The University of Iowa study.—Another study of the effect of diet

upon the teeth is that made by Drs. J. D. Boyd and C. L. Drain, of the State University of Iowa, College of Medicine.

In the course of routine dental examinations at the University Hospital, it was noticed that an unusual number of children were showing "arrested" caries, that is, a gradual hardening of the areas surrounding decayed spots in the teeth, and that decay was decreasing instead of increasing. Such an occurrence is so unusual among children that an investigation of the medical history of these cases was begun. It was discovered that without exception all of the children whose teeth were improving were diabetics whose diets had been carefully and closely supervised for six months or more. The diabetes itself could not account for the arrest of caries, for the teeth were in an active state of decay when the children first came to the hospital.

With the aid of insulin these diabetic children had been furnished all of the essentials of a complete diet, including sufficient energy for full activity. The diet differed from that of the well child in that it contained relatively large quantities of fat, bulky vegetables and fruit, and small quantities of carbohydrates, such as sugar, bread, and other cereals. The diabetic children included in the present report received diets made up largely of milk, cream, butter, eggs, cod liver oil, meat, bulky vegetables, and fruit. Such a diet is high in all the mineral salts and in all the known vitamins, probably much higher than that of the average well child. Certainly it contains an abundance of vitamin D and also of vitamin C, either or both of which may have played a part in the protection of the children's teeth.

The Rochester, Minnesota, study.—At Rochester, Minnesota, Dr. Louise Kappes, of the Mayo Clinic, has compared the dietary and medical history of two groups of public-school children, one with almost perfect teeth and the other with marked dental caries. Seventy-five children, ranging in age from five to thirteen years, were included in each group, information concerning them being obtained by carefully questioning the mothers. By this means fairly accurate information was obtained concerning the child's diet during the first year of life and during the later years, the time of eruption, condition, and daily care of his teeth, the amount of outdoor play that he had had, and the illnesses from which he had suffered. The mothers were also questioned as to their own diet and health during pregnancy, including the degree of dental trouble and the amount of sunshine and outdoor exercise which they had had. The gen-

eral condition of the teeth of both parents was ascertained by questions or, where possible, by inspection.

On the whole the data obtained from the two groups are very similar, the most significant difference being the larger amount of fruits and vegetables eaten by the children with the good teeth. Surprisingly enough, the children with the poor teeth actually drank more milk than those with the good teeth. In the poor tooth group, however, the diets containing much milk also contained much carbohydrate (cereal, potato, sweets, and candy) and little vegetable and fruit. The author of the study therefore concludes that milk is not as effective as fruits and vegetables in protecting the teeth against decay.

The Sioux Indians of South Dakota.—Studies of the skull of the primitive American Indian show that his teeth were comparatively free from decay. Yet, according to a recent investigation of present-day conditions among the Sioux Indians of South Dakota, made by Jessie Stene and Lydia Roberts, decayed teeth are now so prevalent as to be evident even to a casual observer. The early diets at their best were probably fairly adequate and consisted largely of meat, including all parts of the animal, especially internal organs and bone marrow, with liberal supplies of wild turnips, whole corn, and wild berries. The present-day Indian lives largely upon meat as long as the ration issued by the government lasts, and upon "grease" bread, made from white flour, and coffee for the remainder of the time. Fruits and vegetables form an uncertain and variable part of the food intake, even during the spring and summer. Butter and eggs are not much used, and milk also has a very minor place in the dietary. The result is a diet which is generally deficient but particularly so in calcium and the calcifying vitamin. This diet, together with the change from the natural outdoor life to one of indoor housing on the reservations, undoubtedly is leaving its mark upon the teeth.

Summary.—We cannot apparently at the present time fix the responsibility for the health of the teeth upon any one element in the diet. Possibly we shall never be able to do so. But it can be said without hesitation that the most common dental disorders, tooth decay and pyorrhea, are primarily dietary deficiency diseases, which can be in large part, if not entirely, prevented by a diet that contains generous quantities of the tooth-building materials, calcium, phosphorus, and vitamin D, and also of the protective vitamin, vitamin C.

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CHAPTER VI

ULTRAVIOLET LIGHT

In previous chapters frequent references have been made to the fact that sunlight will cure rickets or, more specifically, that ultraviolet light has marked effect upon calcium and phosphorus metabolism. For a better understanding of these facts and better control of the valuable effects of light, the nutritionist or physician has need to review certain long-known facts of the physics of light, and to keep in touch with new research.

SOME SIGNIFICANT POINTS IN THE PHYSICS OF LIGHT

First, some elementary physics. For details on many of these points, the reader is referred to such books as Mayer's *Clinical Application of Sunlight and Artificial Radiation,* or to Laurens' excellent briefer summary, "The Physiological Effects of Radiation," in *Physiological Reviews* for 1928.

The spectrum.—Sunlight passing through a quartz prism is broken up into the familiar color spectrum, made up of radiations of different wave-lengths. Only part of the spectrum is visible. The visible part, ranging from red to violet, consists of radiations measuring from about 800 mμ[1] at the red end to about 390 mμ at the violet. Longer than 800 mμ are the infra-red rays, which are invisible, but which may be recognized by their heating effects when a blackened thermometer bulb is placed at their end of the spectrum—rays not to be considered in this discussion.

At the other end of the spectrum, shorter than 390 mμ, are the invisible ultraviolet rays, which are recognized especially by their chemical action upon a photographic plate and are sometimes called chemical or actinic rays. The shortest of these which reach the earth from the sun,that is, which escape being absorbed by the earth's atmosphere are 290 mμ, but shorter radiations down to 185 mμ are obtained from a mercury arc in quartz (see Fig. 17).

For comparison with these figures, it should be stated briefly here, although developed more fully later, that radiations of long wave-length are valueless in curing rickets, only those of 302 mμ or shorter having much

[1] A millimicron, or mμ, is one-millionth of a millimeter; an angstrom unit is one-tenth of a millimicron, or one ten-millionth of a millimeter.

effect. It is rather surprising that such an important part of the animal economy as bone formation and the other aspects of calcium and phosphorus metabolism should be dependent upon such a small section of the sun's light. The whole solar spectrum is, of course, of value to mankind, and therapeutic uses of sunlight may rest upon other parts; but in rickets the limiting factor is the ultraviolet light.

In Table VII the reader will find a number of important figures on

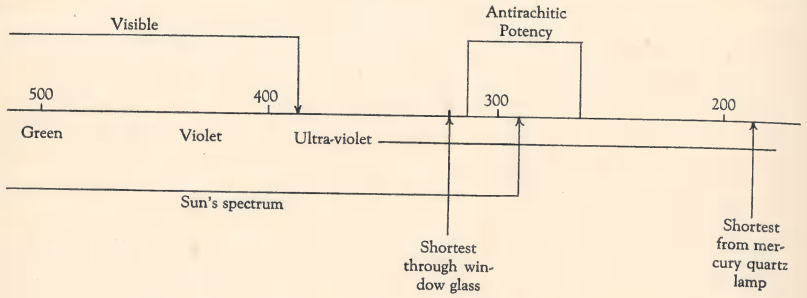


FIG. 17.—Scheme of significant wave-lengths of spectrum

the wave-lengths of different light, which will be convenient to refer to in reading this chapter.

TABLE VII

SIGNIFICANT FIGURES OF WAVE-LENGTHS OF LIGHT

	Millimicrons
Visible light	770–390
Ultraviolet	390–185
Wave-lengths with greatest antirachitic potency	302 or lower
Longest wave-length with antirachitic potency	313
Shortest wave-length passing through window glass	320
Shortest wave-length in summer sunlight	290
Shortest wave-length in May sunlight in Chicago	299
Shortest wave-length in December sunlight in Chicago	305
Shortest wave-length from mercury-quartz lamp	185

The intensity of light.—The question of the length of the light-waves, however, is only part of the problem. To know the value of a given source of light, we must know also its intensity. This is a perfectly familiar and commonplace notion with sunlight as a whole but one which has sometimes been ignored in studying the effects of ultraviolet radiations. A light with weak ultraviolet has, of course, less antirachitic potency than

one with intense ultraviolet even though the lengths of the light-waves may be the same. The spectral distribution, the wave-length, has been measured more frequently than the intensity of the different parts. Accurate measurement of intensity is not simple, but, roughly speaking, the intensity of the ultraviolet, even more than of the visible portion of sunlight, varies greatly with the hour of the day, the season, the altitude, the dust or clouds or smoke of the atmosphere. The intensity of the ultraviolet light from a lamp varies with the distance, with the electric current sent in, and often with the amount of use that the lamp has had.

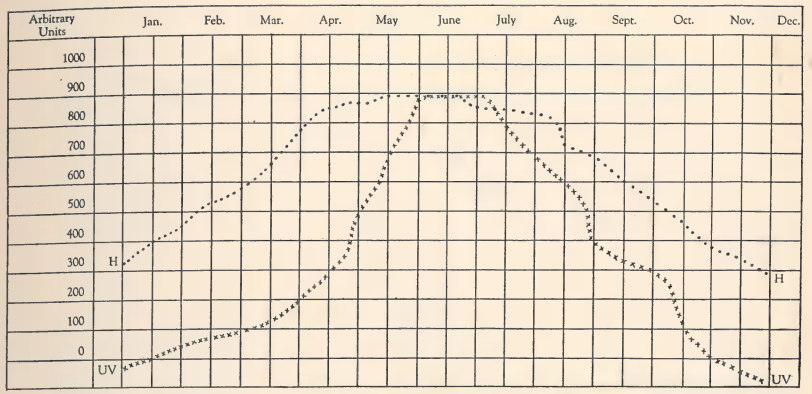


FIG. 18.—Seasonal variations of the sun's spectrum: *H*, solar heat; *UV*, ultraviolet. (From Hess and Lundagen, *Journal of the American Medical Association*, LXXIX [1922], 2211.)

Methods of measurement.—The physicist determines the distribution of the rays from a source of light by observation of the lines on a photographic plate which has been exposed to the spectrum under definite conditions. He determines the intensity of the different rays in terms of ergs or calories per square centimeter per minute with the use of a suitable thermopile and galvanometer—a method requiring expensive apparatus and special skill. Details of the methods may be found in various scientific papers of the United States Bureau of Standards, written by Dr. W. W. Coblentz and his co-workers.

Two much simpler methods have recently been devised which are very useful in finding roughly the intensity of the ultraviolet light. These are so simple and require so little time and equipment as to be usable by all people working seriously with ultraviolet therapy and will probably do

much to lessen the present uncertainties of dosage. They make use of chemical reactions brought about by light of the short wave-lengths.

One of the methods depends upon the fact that zinc sulphide is darkened by ultraviolet light but not by visible light. More definitely, it darkens only with wave-lengths shorter than 350 mμ and has its maximum sensitivity at 310 mμ. The number of minutes required to darken a paste of zinc sulphide to a definite shade may, therefore, be taken as a rough but highly useful measure of ultraviolet in sunlight or other light. It is Dr. Janet H. Clark, of Johns Hopkins University, who has developed this method. She recommends a special C.P. zinc sulphide ground to a paste with saturated lead acetate solution. The paste is pressed flat under a piece of quartz and exposed to the light in a box with blackened sides to protect it from stray radiation. The time necessary to darken the paste to a certain shade is taken as "one ZnS unit of ultraviolet energy." In direct sunlight at noon in March, it takes about two minutes to give one unit. Dr. Clark first used for the tests a light sensitive paint called lithopone, which is a mixture containing barium sulphate and zinc sulphide. She has since substituted the pure zinc sulphide as an improvement, but "lithopone units," based on her original procedure, are sometimes spoken of in the literature.

The other simple method rests upon the fact that a solution of oxalic acid, especially in the presence of a uranium salt, is decomposed fairly rapidly by ultraviolet light, but is practically unaffected by visible light. Tonney and his co-workers, in the Chicago Department of Health, found that this method, already devised by Anderson and Robinson to standardize quartz mercury vapor lamps, best served their purpose for sunlight, being "sufficiently sensitive to indicate for practical purposes the differences of ultraviolet light intensity for the hourly range of the day, for the season of the year, and for localities of different latitude." It will be given in some detail here as it is probably the simplest and most useful of available methods for determining the relative intensities of the physiologically significant ultraviolet of the sun. The observations made with it in and near Chicago will be discussed later on page 81.

The solution of 6.3 gm. of pure oxalic acid and 4.27 gm. of uranyl sulphate per liter of distilled water is kept in a dark bottle away from strong light while not in use. The only apparatus needed is a rectangular fused quartz cell (obtainable from the Hanovia Chemical and Manufacturing Company, Newark, N.J.) with an area on two sides of 3.35 cm. by

10 cm., and a cross thickness of not less than 1.65 cm. This thickness is sufficient for the absorption by the solution of all the ultraviolet light.

The cell walls are completely covered with opaque paper except for an area of 10 sq.cm. on the lower part of one face, through which the exposure is made, and 25 cc. of the oxalic acid solution is put in the cell, which is then placed in the direct sunshine so that its open face is exactly at right angles to the sun's rays. It is exposed for a definite period, usually an hour, its position being changed every fifteen minutes to keep the correct angle.

After the exposure, the solution is rinsed into a flask with 2 cellfuls of water, 2 or 3 cc. of concentrated sulphuric acid is added, the whole is heated to boiling and titrated with potassium permanganate. The latter solution is made to contain 3.16 gm. $KMnO_4$ per liter and is conveniently standardized to be exactly equivalent to the oxalic acid solution.

The number of cubic centimeters of the oxalic acid solution decomposed, multiplied by 0.63, gives the milligrams of oxalic acid decomposed per square centimeter of exposed surface. Duplicate determinations may be expected to agree within 0.06 mg. or less. The maximum value found for sunlight by Tonney and his co-workers was 7.12 mg. per hour. This reading is, therefore, taken as 100 per cent and all others calculated accordingly.

These authors have also made very interesting and valuable correlations between this method and sunburn. The "erythema reaction" of untanned skin was definitely obtained whenever the oxalic acid value was at least half of the maximum, 3.52–3.72 mg. At practically all readings above this value erythema occurred, and at practically all below it was absent. Erythema and pigmentation of skin following exposure to sunshine are variously stated to be due to radiations lying between 302 and 297 mμ or between 320 and 300 mμ. The correlation, therefore, shows that the rays which bring about the oxalic acid decomposition are about the same as these, or at least include these. More exact information of the wave-lengths active in this chemical change is lacking, except that only invisible rays are involved.

Next points to be considered.—So far we have presented the conception of light as made up of radiations of different wave-lengths with a variation from one light source to another, both in the radiations present and in their intensities. The next points to be considered are, first, what are the specific rays which affect calcium and phosphorus metabolism; and, second, how do sunlight and other sources of light vary in their content of these antirachitic rays?

THE RAYS POTENT IN RICKETS

Antirachitic potency has again and again in this book been referred to the ultraviolet rays in general, but recent investigators have shown that a sharper statement can be made—that some parts of the ultraviolet are of greater value than others. The relative value of the different parts is of great practical importance to many a winter baby in latitudes like that of the northern United States.

Hess and Weinstock, in 1923, obtained a tentative answer to the question as to the rays potent in rickets when they found that ultraviolet waves to be of value "must have a length not longer than 302 or possibly 313 millimicrons." More recently Hess, with another co-worker, Anderson, has obtained more definite results and in an unusual manner.

The source of light which they used was a mercury vapor quartz lamp, which it will be remembered, gives rays of much shorter wavelength than does sunlight. By means of two special glass and bromine or chlorine filters, Hess cut off for one set of experiments all radiations longer and shorter than those from 290 to 366 mμ, and for a second set of experiments all longer and shorter than from 250 to 280 mμ. Thus, for one experiment he had radiation similar to the ultraviolet of summer sunlight, and for the second, ultraviolet obtainable only from artificial sources. Rats receiving both these groups of radiations recovered from rickets, but, rather surprisingly, the shorter, or, we might say, the "unnatural" rays were the more effective. The very short ultraviolet rays thus have more intense antirachitic power than the shortest of those from the sun.

Still more definite results were obtained by Hess and Anderson by isolating a single line or group of lines from the ultraviolet spectrum. By an ingenious arrangement, the light from the mercury quartz lamp was passed through a series of quartz lenses to make it sufficiently intense, through quartz prisms to form the spectrum, and then through very narrow slits so as to obtain a single individual line of the spectrum. The separate lines thus obtained for three different experiments were 313, 302, and 280 mμ. These were caused to fall, not upon rats, but upon different samples of cholesterol which were afterward fed to rats. (See chapter ix for further discussion of the potency of irradiated cholesterol and ergosterol and the identification of the rays which activate it with those which cure rachitic rats.) The cholesterol exposed to waves of 313 mμ had only slight antirachitic effect, but that exposed to waves of 280 and 302 mμ had marked potency. The results do not permit distinguishing between the strength of these two samples.

Thus 313 mμ seems to be the upper limit of the antirachitic field and decidedly feeble. The region of 302 mμ, which is by no means always in sunlight and of 280 mμ which is never there, are more potent than the commoner parts of the spectrum.

Two English investigators have recently defined the field still further by establishing what might be considered a lower limit of potency. They irradiated ergosterol in three regions of the spectrum and determined its antirachitic potency for rats. The ergosterol receiving only rays longer

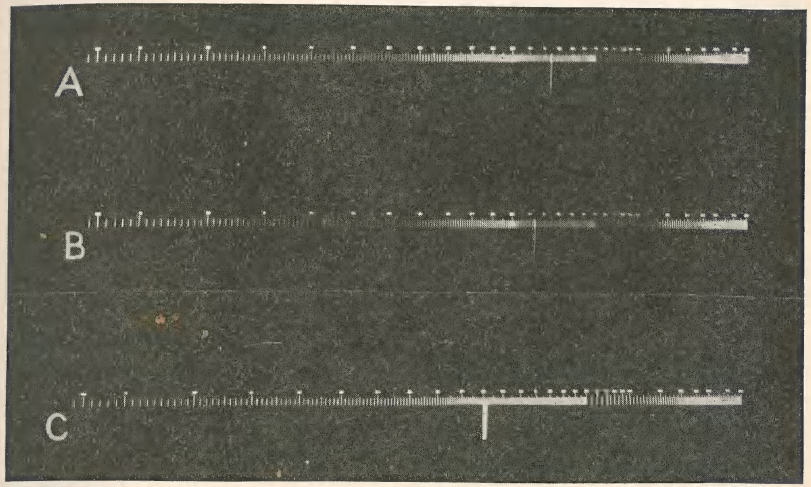


FIG. 19.—Monochromatic ultraviolet waves: *A*, 313 mμ; *B*, 302 mμ; *C*, 280 mμ. (From Hess, *Journal of the American Medical Association*, LXXXIX [1927], 1224.)

than 313 mμ did not prevent rickets (a confirmation of Hess' work), that receiving rays of 313–265 mμ was highly potent, and that with rays below 265 mμ had decidedly less effect, so that 265 mμ may be regarded as not far from the lower edge of the field (Griffith and Spence).

It is plain that knowledge is far from complete as to the antirachitic potency of different parts of the ultraviolet spectrum. We can imagine a curve of the potent rays beginning at 313 mμ with only slight power, rising to 302 mμ and 280 mμ, which are highly potent, and falling in the region of 265 mμ; but whether the peak of the curves comes before 302 mμ or after 280 mμ, or even whether there is a peak or a broad plateau, we do not know. And to complicate the limitations of our knowledge, there is the factor of the intensity of the rays. It is easy to imagine, though defi-

nite measurements are lacking, that intense rays of, say, 313 mμ might be more potent than feeble rays of 302 mμ. The physicist and biologist still have a tremendous field to explore together.

VARIATIONS IN THE ULTRAVIOLET OF THE SUNSHINE

We must now bring together the somewhat limited information available on the occurrence of these short rays in ordinary sunshine and their variation under different conditions.

Effects of altitude and reflection.—It is common knowledge that the light of mountain tops has more ultraviolet than that of the lowlands, since the skin burns and tans more readily there and the sun's glare is harder on the eyes. In the Canadian Rockies, the railroad sells its patrons eyeglasses designed to protect the eyes from the short rays. These shorter wave-lengths from the sun are much more readily absorbed by the earth's atmosphere than are the longer, and so only in part do they penetrate to sea-level. Measurements made at different altitudes—near sea-level, at an intermediate point, and on a high mountain (about 260, 5,850, and 10,000 feet)—gave the ratio of the intensities of the ultraviolet as 40, 61, and 90, more than twice as much at the higher altitude as at the low (quoted from Mayer).

Reflection from snow may almost double the light intensity. Snow with slightly frozen surface reflects about 90 per cent of the light falling on it, new snow 74 per cent, and green meadows only 6 per cent. It is not surprising that mountain-climbing on glaciers may produce violent sunburn, that "snow blindness" is not uncommon in the Arctic, nor that much of the early work with light therapy was done in Swiss sanitariums. Water, too, is an excellent reflector of the ultraviolet, and hence the easy tanning at the seashore in spite of the low altitude.

Latitude.—In the tropics where the sun's rays are more direct than in the temperate zones, the intensity of the ultraviolet is usually greater. However, haze or cloudiness or dust often brings the ultraviolet well down to that in other parts of the globe. Laurens quotes Knipping, an investigator who publishes in a journal of tropical hygiene, as reporting that in the British and Dutch Indies near the coast the humidity is so high and the dust so prevalent that the maximum intensity of the ultraviolet light is not so great as on a June midday on the North Sea coast. On the whole, however, the tropical and semitropical light has greater antirachitic potency than that of temperate zones, a fact borne out by the much smaller amount of rickets and its lessened severity. In New Orleans, severe rickets is extremely rare, but a mild form of the disease does prevail to the extent of about 45 per cent of the children aged three years or less.

Even in the Canal Zone mild rickets is found. Colonel Roger Brooke, an army surgeon, examined one hundred white children, practically all there were in the Canal Zone, and also one hundred negro children who were admitted to the hospital for troubles other than rickets. Of the white children, five showed mild but unquestionable clinical signs of rickets and five others questionable signs. When examined by X-ray, there were thirty-three cases of definite or doubtful or healed rickets. The negro children, examined for clinical signs only, had a somewhat higher proportion of cases and more severe signs, even to bowing of the legs in three instances. While this is far, far less than the amount found by a similar survey in New Haven, Connecticut (see page 206), it is enough to prove that rickets does exist in Panama. Colonel Brooke believes its occurrence is due in part to the long, rainy season when the clouds and high humidity obstruct the ultraviolet rays, and in part to the excessive fear of tropical sunlight held by many white women, especially newcomers, who would consider it unjustifiable, if not criminal, to let their infants bask in the sun.

Colonel Brooke, however, quotes another physician from Panama as writing, "I have yet to see my first case of rickets in the West Indian negro child," and a colonial health official in Trinidad as stating that he has not met with a case in twenty-four years. The tropical ultraviolet light in these regions is plainly strong enough to prevent rickets or almost to prevent it.

The ideal conditions of ultraviolet light, according to Colonel Brooke, are found in Arizona, New Mexico, and other dry, sunny portions of the United States. Here the sunlight is intense, the atmosphere is free from smoke, the humidity is low, and the number of cloudy days in a year very few. Moreover, the temperature is high enough during the winter months for people to be outdoors all day long and not bundled up with wraps. Rickets almost never develops in these localities.

The distribution of rickets near the Arctic Circle is commented on in chapter xiv, and on page 88 below.

Season of the year and time of day.—Since the sun at the zenith is separated from us by less of the earth's atmosphere than when it is near the horizon, we should expect more ultraviolet light at noon than in the early morning or late afternoon, and also more in the summer than in the winter. The differences have been found to be very marked, both in the intensity of the ultraviolet and in the minimum wave-lengths that get

through to us. Most of the earlier work on this point was done in Switzerland. There the ultraviolet intensity in summer has been found to be twenty times as great as in winter; also the shortest wave-length at one place varied from about 295 mμ during the noon hours to only 307 mμ in the late afternoon.

Interesting and important as these Swiss observations are, they will not be quoted in detail here but the reader referred for accounts of them to the books by Mayer, Luckiesh, and others. Instead will be reported recent investigations in Boston, Toronto, Washington, D.C., Chicago, New York, and Boulder, Colorado, which have supplied us with figures for the marked variations in the antirachitic potency of the sunlight at different seasons and at different hours of the day in this country. Though these observations do give considerable idea of conditions near at home, there is still need for much more data, a complete survey of the whole country. It is also desirable that the measurements in different places should be made by the same and strictly scientific methods, so that they will be comparable one with another. The results given in the following paragraphs were obtained differently—by physical, chemical, or biological methods not yet well correlated, so that they cannot be accurately compared. They are an interesting beginning, rather than the final word.

SPECIAL INVESTIGATIONS IN THIS COUNTRY

The Chicago investigations.—Dr. Bundesen, of the Department of Health, and Dr. Lemon and others, of the University of Chicago, have collected some very significant figures. Under the supervision of the members of the Department of Physics, automatic, all-day photographs of the solar spectrum were secured over many months. Particularly interesting here are the data on the shortest detectable wave-lengths which got through to the University campus. During December, 1926, and January, 1927, the short wave-length limit ranged from 3,150 to 3,030 angstrom units, and was of extremely low intensity. In March and April the limit was decidedly lower, down to 3,000 A, and in May it was 2,990 A. This, of course, is of special interest in connection with Hess' figures of 3,130 A for the longest line with even slight antirachitic potency, and his 3,020 A for the line with marked power.

Thus, apparently, winter sunlight in Chicago, even in the University neighborhood, can be of little help in preventing rickets. In the words of the investigators, "Comparatively little ultraviolet radiation of known physiologic significance appears in the sun's spectrum during the winter months in Chicago."

The harm that may be done by city smoke was also plainly shown, for the shortest wave-length in the morning of a very clear day in February was 3,030 A, and in the early afternoon, when the sun fell on the spectrograph through the smoke pall from the stock-yards manufacturing district, it was 3,090 A, and the reduction expressed in intensity was much greater even than the change of 60 angstrom units would imply. It has been estimated that the smoke pall in great cities may rob the city dweller of fully three-quarters of the ultraviolet rays he might enjoy, and that down in the depth of the city street canyons, the diminution is particularly marked. One of this year's bulletins from the Chicago commissioner of health says:

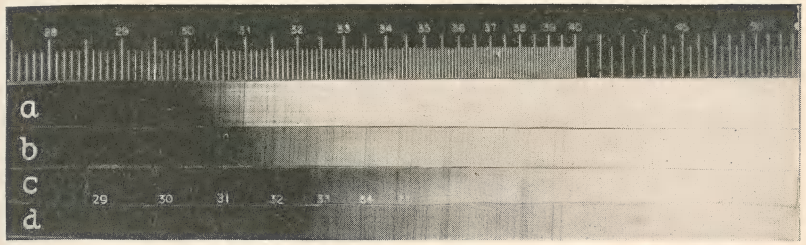


FIG. 20.—Absorption of ultraviolet rays in Chicago at different times and by smoke: *a*, 11 A.M., April 10, 1927, wind northeast, very clear; *b*, 10:30 A.M., February 19, wind northeast, very clear; *c*, 3 P.M., February 19, wind northeast, very clear, but sun seen through smoke from the stock-yards district; *d*, 2:45 P.M., February 23, wind southwest, clear, sun seen through smoke. Short wave-length limit: *a*, 2,995; *b*, 3,030; *c*, 3,090; *d*, 3,090. (From Bundesen *et al.*, *Journal of the American Medical Association*, LXXXIX [1927], 187.)

> The Department of Health, which has been making observations since early last winter, finds that only half of the sunlight with its curative ultra-violet rays which we find on the tops of the buildings reaches the surface of the streets. This is explained by the fact that much of the smoke and foreign particles lie low between the tops of buildings and the street, effectively screening out the light.

These Chicago observations have very recently (July, 1929) been supplemented by others obtained in Baltimore, Maryland, where the health department has also been studying the smoke problem. Here it was found that the intensity of ultraviolet light, as measured by Clark's lithopone paint method, was 50 per cent greater in the country where there was little dust and smoke than in the center of the city where there was much. That coal smoke was the chief offender in the exclusion of

the ultraviolet was shown by the fact that the intensity of the rays varied inversely with the amount of soft coal used. In seasons when more

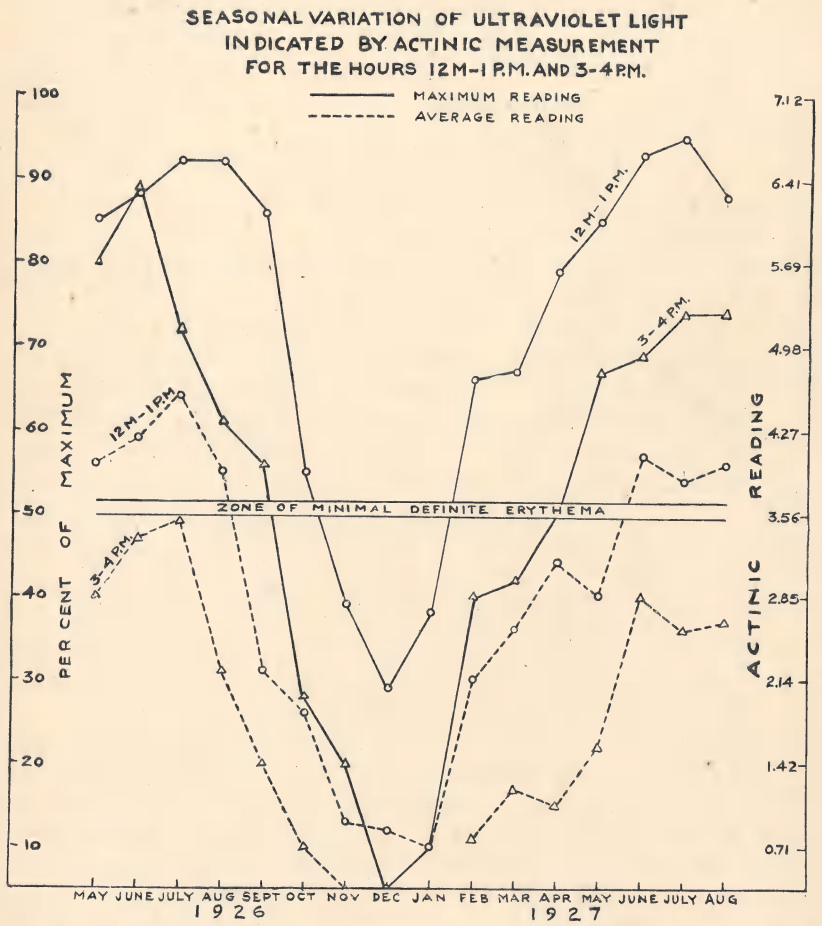


FIG. 21.—Seasonal variation of ultraviolet light in Chicago indicated by actinic measurement. (From Tonney, Somers, and Marti, *Journal of Preventive Medicine*, II [1928], 493.)

hard coal, and less soft coal, was burned the sunlight contained a larger proportion of the ultraviolet. More definite proof of the obstructive properties of coal soot was afforded by experiments in which light was passed through dust from fuller's earth, street sweepings, and lampblack. Fully

fifty per cent more of the ultraviolet light was absorbed by the lampblack than by the street sweepings (Shrader, Coblentz and Korff).

Against the decrease due to the sun's variation mankind is powerless except as he may change his outdoor habits, but the absorption of the ultraviolet rays by the soot and smoke and dust of cities he can control.

Another Chicago investigation, made by means of the decomposition of oxalic acid and the erythema effect, has already been referred to in the discussion of methods. Results obtained in the clear air of the Navy Pier and the nearby Indiana Dunes help to justify the foregoing conclusions for Chicago sunlight. The average actinic readings were highest in the summer months, from May to August, with the peak coming in the early part of July, and the hour of maximum actinic effect being with few exceptions from 12 to 1 P.M., with 11 to 12 A.M. and 1 to 2 P.M. not far different. Closely correlated with these analytical data are the results in the production of erythema in untanned skin. Sunburn occurred almost invariably with one-hour exposure in those hours when the actinic value was between 3.52 and 3.72 mg. of oxalic acid, or higher. These hours came in June between 9 A.M. and 4 P.M., in October between 10:30 A.M. and 2 P.M., and not at all in November, December, and January (Tonney and others).

These chemical and physiological studies strengthen the conclusion of the physicist that winter sunlight in Chicago contains very few of the shorter ultraviolet rays.

Boulder.—From Colorado has recently come a report of the variation in intensity of the ultraviolet at different hours of a June day. The darkening of zinc sulphide paste, according to Dr. Janet Clark's procedure, was the method used and results are reported in zinc sulphide or "lithopone units"—"the reciprocal of the time necessary to darken lithopone paste to a reflection factor of 50 per cent." At 6 A.M. this value was 0.1 and at 11:30 A.M. (the highest point) it was more than thirteen times as great, or 1.33. From about 10 A.M. to 3, there was a general high plateau when the sunlight had much ultraviolet, but before and after these hours, the intensity fell off fast (Earp). It is disappointing that these figures cannot be compared directly with those from Chicago. All that can be said is that the hourly fluctuation is similar in the two places. Plainly a walk during one's noon hour is of greater value than a walk before or after work.

Toronto.—In Toronto, Tisdall and Brown have shown the seasonal variation in the ultraviolet by testing its antirachitic effect on rats rather

than by physical and chemical measurements. Through the spring and summer, from April through August, the sunlight had marked antirachitic potency, approximately eight times as much as in the winter—November, December, and January. A sharp increase occurred about February 15 and a sharp decrease about October 15. Yet even in the winter the sunlight had some slight effect on the rats. In other words, while the results in general were like those derived from the physical measurements in Chicago, the value of the winter sunshine seemed somewhat greater.

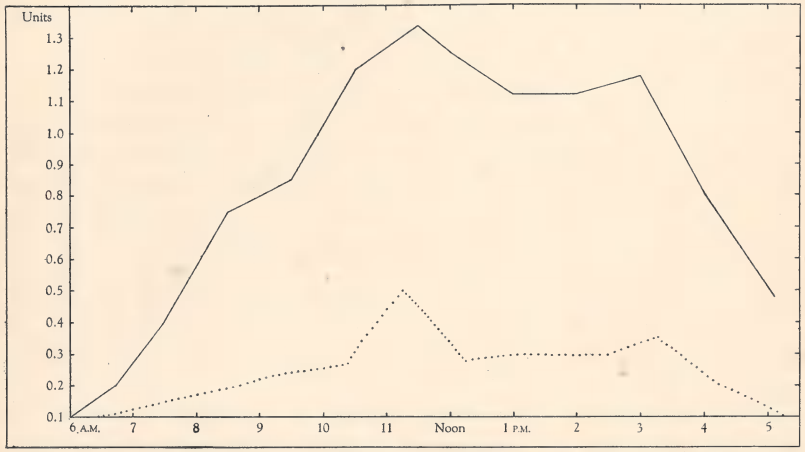


FIG. 22.—Intensity of ultraviolet radiation in the sunshine and skyshine, respectively, at Boulder, Colorado, during the day of June, 30 1928: solid line, sunshine (thirteen observations); broken line, skyshine (twelve observations). (From Earp, *Journal of the American Medical Association*, XCII [1929], 312.)

Washington, D.C.—In Washington, too, rat experiments were used as criterion of the antirachitic potency of the light. During December, 1927, and January, February, and March, 1928, Captain William D. Fleming, of the Army Medical School, exposed two groups of rats to light from the southern sky. The cage of one group was glazed with ordinary window glass that would cut off any ultraviolet light which might be present, and of the other with vitaglass, a glass somewhat permeable to ultraviolet (see page 93). Both groups were fed Steenbock's rachitogenic ration.

As the experiment progressed, there were marked differences in the general appearance and behavior of the two groups. Those behind the vitaglass were larger, sleeker, and much more active, "playing with each other and moving with rapid gait and with many leaps and bounds";

while the controls "were content to lie quietly, usually huddled in groups, and, especially towards the last, moving with limbs flexed and with uncertain gait." One of the females in the ultraviolet group gave birth to a litter of nine young, and others were found pregnant on autopsy, a condition not observed among the controls. Roentgenograms of the tibial heads and other bones of both live and dead rats showed decided rickets in the control group and absence of it in the other.

Thus in the outskirts of Washington, with an atmosphere "uniformly free from smoke," the winter sunlight was entirely adequate for the prevention of rickets in rats to which it was available all day long.

Boston.—Similar results were obtained in Boston during the winter of 1927. From January 1 to March 2, groups of chickens, used as the experimental animals, were kept on an inadequate diet on which they might develop "leg weakness" (a disease like rickets). In the groups receiving the sunlight through the ordinary laboratory windows or only the diffuse daylight away from the windows, almost all showed marked signs of the disease. Those with fifteen minutes daily exposure to a mercury vapor arc were completely free from rickets, and those receiving the sunlight through three window-glass substitutes were almost free from it. The point for us at this time is, again, that the Boston winter sunshine had real antirachitic potency for these animals.[2]

New York City.—Here, too, the winter sunshine has been found to have antirachitic potency for animals placed in south windows behind ultraviolet transmitting glass. Dr. Eddy, of Columbia University, obtained positive results with rats even in the middle of winter—January 18 to February 16, 1928. He also showed later that exposure of the animals for only three or four hours, between 11 A.M. and 3:30 P.M., was just as satisfactory as all day long—an observation well in line with other measurements of short wave-lengths at different times of day.

New York and Boston observations on babies.—Results reported on babies several years ago were not so favorable as these recent ones with rats, possibly in part because the exposures were limited to the short times that the children could be exposed in the cold to the direct sunshine without the protection of special glasses. Dr. Alfred F. Hess, who has done much work both with babies and animals in New York City, wrote as follows in 1925:

[2] This work is included in the *Report on Window Glass Substitutes* of the Council on Physical Therapy of the American Medical Association, *Journal of the American Medical Association*, LXXXVIII (1927), 1562.



FIG. 23.—Babies receiving treatment with sunlight through Corning glass and vitaglass windows. (From Wyman, *Boston Medical and Surgical Journal*, CXCVII [1927], 379).

For the last few years, I have been attempting to prevent and to cure rickets during the winter by means of heliotherapy. The infants have been exposed to the sun for as long a period and to as great a degree as was feasible in this climate. The results have not been all that might be desired. Although some benefit was brought about by this treatment, I found that it can not be relied on to prevent or to cure rickets. There are so many days in winter when there is little or no sunshine or when the sun is overcast at midday—the period on which we depend for the effective radiations—that the total number of hours of exposure is necessarily restricted.

TABLE VIII

TREATMENT OF RACHITIC CHILDREN BY WINTER SUNSHINE

EFFECT OF BOSTON WINTER SUNSHINE ON RACHITIC INFANTS*

RACE	GLASS USED	DURATION OF EXPERIMENT	TOTAL SUNSHINE		BLOOD FINDINGS				X-RAY REPORT
					Date	Ca	P	Ca × P	
			Hrs.	Min.		Mg.	Mg.	Mg.	
Negro...	Quartz	12–17–25 to 2–10–26	136	40	12–18–25 2–14–26	10.8 11.2	3.1 4.9	33.4 54.8	Healing
Negro...	Quartz	1–18–27 to 4–27–27	159	35	1–12–27 4–25–27	9.0 10.7	3.4 5.6	30.6 59.9	Healing
White...	Quartz	2–11–26 to 3–27–26	110	40	2–11–26	6.4 12.0	8.1 6.25	51.8 75.0	Healing
Negro...	Corning	2–28–27 to 4–23–27	123	0	2–23–27 4–25–27	9.7 9.5	3.8 4.4	36.8 41.9	Healing
White...	Corning	2–15–27 to 4–22–27	110	45	2–14–27 4–12–27	8.3 10.8	4.6 4.8	38.4 51.8	Convalescence steady
White...	Corning	2–10–27 to 4–21–27	91	40	2–14–27 4–25–27	6.5 9.9	4.9 5.5	32.0 54.4	Healing
Negro...	Cathedral vitaglass	1–12–27 to 4–11–27	147	50	1–12–27 4–11–27	8.5 9.9	2.7 2.25	22.9 22.2	Little evidence of healing
Negro...	Vitaglass Changed to Corning	2–28–27 to 4–11–27	84	35	2–12–27 4–11–27	10.0 10.0	3.8 2.58	38.0 25.8	No healing
		4–12–27 to 4–25–27	25	40	4–25–27	10.2	2.9	29.5	More deposition of calcium
White...	Ordinary window	4–8–26 to 5–5–26	46	40	4–8–26 5–5–26	12.3 9.8	4.26 4.65	52.4 44.6	No healing
	Changed to quartz	5–5–26 to 5–25–26	14	35	5–25–26	10.5	6.95	72.9	Healing

* Data from Dr. E. T. Wyman, *Boston Medical and Surgical Journal*, CXCVII (1927), 376.

Recently reports of successes have come both from New York and Boston. Dr. Wyman, in Boston, placed rachitic babies in their cribs all day long, in the winter, directly in front of windows made of clear quartz, Corning glass, or vitaglass. The babies were kept undressed and the cubicles heated enough to maintain a temperature of 80°. The diet was kept the same as that which the babies were receiving on admission to this hospital, and on which they had developed the rickets.

The four babies receiving the winter sunshine through the quartz glass and the three through the Corning glass all showed definite evi-

dences of recovery. The vitaglass was disappointing, but the two babies tested were both very black negroes. The details of Dr. Wyman's experiment are given in Table VIII, both as an illustration of the antirachitic power of the winter sunshine in Boston and its transmission by the special glasses which are further described on page 92, and also of the changes brought about in the infant by the light.

In New York, Drs. G. W. Caldwell and R. H. Dennett gave infants and children sun baths of two or three hours daily throughout the winter in front of vitaglass windows, not as a substitute for ultraviolet lamp irradiation in the cure of disease but as a prophylactic measure. Of the thirty-five cases, 80 per cent showed an increase in blood calcium or blood phosphates or both, and the lack of increase in the remaining seven cases could easily be explained by some determined pathological condition. "There are ample ultraviolet rays," they conclude, "in the antirachitic range in this latitude during the winter to be of definite value to those receiving them through this type of window glass when exposures are made in the direct path of the sun's rays."

SKYSHINE

Fortunately, especially for city-dwellers, much of whose sunshine is cut off by tall buildings, the ultraviolet is not limited to the direct sunlight. "Skyshine" from the northern sky on a bright, clear day may give much, occasionally even as much as the direct sun, but here, too, experimental results are somewhat contradictory. It must be remembered also that heavy clouds cut down the potency of skyshine as well as of direct sunshine.

The measurements at Boulder, Colorado, given in Figure 22, showed very much less ultraviolet in the skyshine at all hours of the day. Yet in Toronto when measured by rat experiments, the skyshine sometimes had from half to two-thirds as much potency as the direct sunshine. In New York City, rats near a window open to the northern sky were not protected from rickets in December, and but incompletely protected in May.

The most recent report on the subject comes from Captain Fleming, in Washington, D.C., who describes some interesting spring and summer experiments, extending over one hundred days from April to July. He transferred the cages which he had used for his sunshine experiments to the north side of a northeast corner room and placed them on a bench in such a position that they projected part way out of the open window, but the direct sun never fell on them. The twenty-five rats in the cage surrounded by ordinary window glass developed rickets as expected. The twenty-six rats in the cage surrounded by the glass permeable to the ultraviolet showed normal calcification in every respect and good growth to an average weight of 144 gm. at the end of the experiment in contrast to the 117 gm. of the controls. In other words, the light from the north sky from April to July had enough ultraviolet for complete protection. Fleming's concluding remarks are:

> The degree of protection against rickets offered by skyshine . . . . is a surprise to the writer. It appears that the minimal amount of ultraviolet light necessary to produce normal ossification in the absence of other sources of the protective factor is very small and is in great excess in direct sunlight and in excess to but slightly less a degree in skyshine.

It must be remembered that these Washington experiments were carried out during the season of almost maximum solar ultraviolet light. It looks as if one might do pretty well, given enough out-of-doors hours in summer, without much direct sunlight or the summer tan, but that in the winter direct sunshine is highly desirable.

THE SUN'S ALTITUDE AS THE LIMITING FACTOR

Weak ultraviolet below 35 degrees.—It is the altitude of the sun, that is, in our northern latitudes, its distance from the southern horizon, that makes these differences between summer and winter. It is altitude also, of course, that makes the difference even in the summer time between noon and morning or afternoon. Tisdall and Brown, in Toronto, have proved these facts by an ingenious series of rat experiments, exposing the different cages for two-hour periods at different hours of the day and noting meantime the maximum altitude of the sun. Only when the sun's altitude was 35 degrees or more did the light have much antirachitic effect. This altitude is not attained at all in Toronto in November, December, January, and half of February (see Fig. 24); but from the middle of May to the middle of July it extends from eight or a quarter past in the morning to almost half past four in the afternoon, with much higher altitude between these hours. It is no wonder, therefore, that noon time and summer have the greatest antirachitic effect.

Tisdall and Brown make interesting correlation of their 35-degree observations and the geographical distribution of rickets, and come to the conclusion that rickets is uncommon or very mild in those places where the minimum seasonal altitude of the sun is above about 35 degrees, and

is encountered in severe form where the sun's altitude is below 35 degrees for some months of the year. They write,

Rickets today occurs largely in Europe and North America, between the latitudes of 40 and 60 degrees. The minimum seasonal altitude of the sun at 40 degrees north latitude is 26 degrees. In Glasgow, Scotland, the minimum seasonal altitude of the sun is 11 degrees and for six months of the year the altitude is below 35 degrees. In London, England, the minimum altitude is 16 and below 35 for five months of the year. In Boston, the minimum altitude is 23

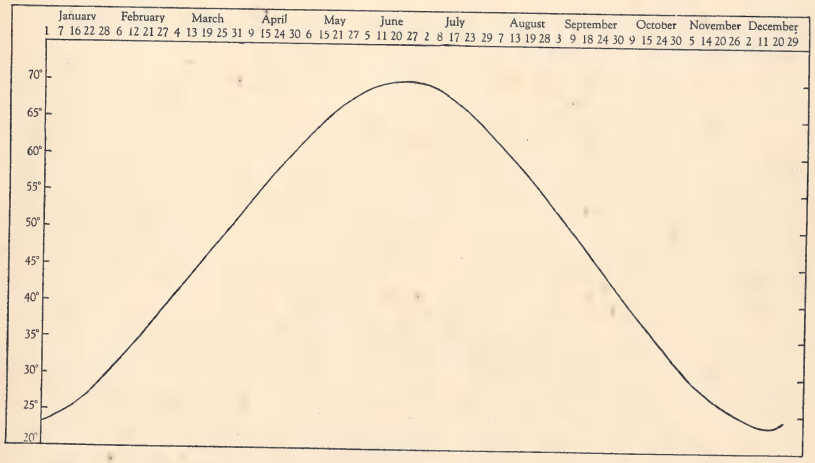


FIG. 24.—Maximum daily altitude of the sun throughout the year at the latitude of Toronto. (From Tisdall and Brown, *Journal of the American Medical Association*, XCII [1929], 863.)

and below 35 for four months of the year, while in Baltimore, the minimum altitude is 27 and below 35 for three months of the year.

For New Orleans, the minimum is 37 degrees and for Jamaica 50.

Iceland and the Faroe Islands.—Yet there is interesting evidence that even when the sun stays below 35 degrees it may have antirachitic potency if other conditions are near to the ideal. In the *British Journal of Actinotherapy,* December, 1928, there is an account of the German Scientific Expedition to Iceland to study the health of the inhabitants with particular regard to the effect of solar radiation. Iceland is practically free from rickets, and the usual explanation of this immunity has been the plentiful fish diet and the large amount of cod livers consumed by the inhabitants. However, in the Faroe Islands, only 75 miles south of Iceland and about 250 miles north of Scotland, the inhabitants eat practically the same amount of fish, and yet 40 per cent of the breast-fed children and 65 per cent of the artificially fed are stated to have rickets.

The Faroe Islands lie completely in the Gulf Stream and are usually covered with a mist, the tops of the mountains only being visible. Iceland, on the other hand, is only slightly touched by the Gulf Stream, and is therefore much freer from fog and mist and enjoys many more hours both of direct sunshine and of the skyshine which goes on far into the evening. Evidently the difference in the amount of ultraviolet light has made the difference in the occurrence of rickets, even on the vitamin D rich diet of the two localities.

GENERAL CONCLUSIONS

These scattered investigations, it is plain, have yielded rather contradictory results. Winter sunshine contains enough of the ultraviolet in New York, Toronto, and Washington to prevent rickets in rats, and in Boston to prevent "leg weakness" in chickens. New York and Boston babies also gain from it *when they get enough of it.*

From the biological experiments, therefore, one would expect the winter sunshine in these four cities to have a fair amount of the radiations shorter than 313 mμ, maybe even down toward 302 mμ. But physical measurements in Chicago showed that radiations as short as 302 mμ were never present in December and January, and those as short even as 313 mμ were frequently lacking, or if present were always faint. It is unlikely that the winter light on the University of Chicago campus differs so much from that in the other cities unless there is a difference due to city smoke. More probably the animals with their much longer exposures could take advantage of the very small amounts of slightly potent rays much better than the babies could. Finding enough antirachitic value for animals does not prove that human beings, with all their clothing and their short exposures to light, can get much help.

Of course, the fundamental difficulty in drawing definite conclusions from this work is that we have no clear-cut knowledge as to how much ultraviolet a human being really needs, and especially as to how the needs of rats and of babies compare. The rat experiments show much, but not enough for more than tentative conclusions with human beings. Much more research is needed to supplement the encouraging advances of the last few years. Already great advantages are being gained from the present progress.

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CHAPTER VII

FURTHER POINTS ON MAN'S USE OF THE ULTRAVIOLET LIGHT

WINDOW GLASS AND ITS SUBSTITUTES

The window glass which civilization has developed unfortunately cuts off much of the ultraviolet light which falls upon it and all of antirachitic potency. The shortest wave-length which gets through is about 320 or sometimes 310 mμ; hardly shorter, that is, than the 313 mμ, which is the longest with antirachitic potency. Numerous examples have been published, several of which have just been cited, and many others are the common experience of clinical and laboratory workers, in which rickets has developed when the only light received came through window glass and in which it has been cured or prevented by direct sunlight or other sources of ultraviolet light.

In the last few years, since these facts have been thoroughly understood, efforts have been made to develop window-glass substitutes which are permeable to the short rays. At present the subject is in a somewhat controversial state. Some of the results seem highly encouraging, but there appears to be a possibility of exploitation of the new materials in places where they will not really be useful.

Four of these materials were reported upon favorably in 1927 by the Council on Physical Therapy of the American Medical Association. Vitaglass, invented by Dr. F. E. Lamplough, of England, which has since been much investigated and advertised, comes in two kinds, one being smooth and in appearance like ordinary window glass and the other or "cathedral" glass being rough and translucent. Corning glass (corex) made by the well-known glass works in Corning, New York, is also a true glass, looking like window glass. The composition of these is in part a trade secret, but it is known that avoidance of contamination with iron is one of the chief points in the manufacturing process. Celoglass, another material tested by the Council on Physical Therapy, is composed of a wire-mesh screen filled with an apparently celluloidinous material, and flexoglass is a thin, fairly loosely woven cloth treated with a paraffin-like substance. The two latter cost less than ordinary window glass, the others more. The non-glass materials are recommended particularly for animal houses or

chicken coops to give protection from the weather during the winter and still permit entrance of the ultraviolet light. They may crumble on rough treatment.

Biological tests.—Some of these glasses, particularly vitaglass, were successfully used in the animal experiments on the ultraviolet of winter sunshine which were discussed in some detail in the last chapter. The vitaglass let through enough ultraviolet light in winter in Washington, D.C., New York, Boston, and Toronto to protect rats or chickens from rickets—a rather striking biological proof of its penetrability. The chickens behind vitaglass and celoglass gained in weight quite as rapidly as those receiving direct artificial ultraviolet; the flexoglass group did not grow quite so satisfactorily, but better than those getting the sunlight only through ordinary window glass. Children also in New York were helped by winter sunshine through vitaglass and in Boston by winter sunshine through Corning glass.

Spectroscopic tests.—The Council on Physical Therapy, in addition to the experiments on the chickens, measured the transmission of some of these glasses for different parts of the spectrum. Their results were quite striking. Corning glass, which had not been received in time to be included in the biological tests, was shown up as the best in the physical measurements. Ordinary window glass, Corning glass, and vitaglass all transmitted about the same high percentage of the fairly long rays down to 350 mμ. But when the transmission of the shorter, potent rays was measured marked differences appeared. At about 315–310 mμ the window glass transmitted practically nothing, the vitaglass about 45 per cent of the incident rays, and the Corning glass about 80 per cent.

The United States Bureau of Standards has since published additional figures for the percentage transmission of a number of different glasses at 302 mμ. New material from a forthcoming article kindly supplied by Dr. George K. Burgess, the director, is included in Table IX. The results in general are similar to earlier reports from the Bureau and other workers—several of the glasses transmit considerable of the short rays which common window glass does not. New glasses and improvements in old are being constantly made, so that Dr. Coblentz, of the Bureau, in earlier reports is careful to give the date of his observations. He also says elsewhere, "No doubt in a few years, new ultra-violet transmitting glasses will be a common article of commerce, costing little more than common window glass."

Photographs of the spectrum from a mercury arc, which extends far

into the short ultraviolet and of the same spectrum passed through vitaglass and ordinary window glass, are given in Figure 25. These show graphically the transmissibility of the vitaglass.

Solarization.—The "uncomfortable discovery" was soon made in investigating the new glasses that their permeability decreased markedly with use. This decrease, however, seems to progress to a certain point and then stop. With vitaglass, for example, the Bureau of Standards reported

TABLE IX

PERCENTAGE TRANSMISSION OF VARIOUS GLASSES AT 302 Mμ*

(WHEN NEW AND AFTER PHOTOCHEMICAL STABILIZATION BY EXPOSURE AT A DISTANCE OF 15 CM. FROM A QUARTZ MERCURY ARC FOR TEN HOURS)

TRADE NAME	NUMBER OF SAMPLES TESTED	AVERAGE THICKNESS, Mm.	AVERAGE PERCENTAGE TRANSMISSION	
			New	After Exposure
Quartz glass	1	4.7	92	92
Corex D	15	2.3	61	59
Neuglas	12	2.3	63	49
Uviol-Jena	14	2.3	58	43
Helioglass (Vioray)†	24	2.3	58	40
Sunlit	9	2.3	65	39
Vitaglass	19	2.3	48	23
Cel-o-glass‡	5	0.1§	30	.....
Quartz-lite	16	1.9	0.5	0.5‖
Common window glass	14	3.3	0.0	0.0

* From Bureau of Standards letter, revised to July 19, 1929.

† Vioray is the foreign trade-name of helioglass.

‡ This consists of a fine wire screen whose interstices are covered with cellulose acetate. The value of 30 per cent includes practically all the rays diffusely transmitted.

§ About 0.1 mm.

‖ About 0.2 per cent for t=2.3 mm.

a decrease from an average transmission of 47 per cent when new to 35 per cent after 123 hours of exposure to the sun and to 25 per cent after complete degeneration by the mercury arc. That is, considerable ultraviolet light does get through even after long use (Fig. 26).

Dirt on the glass is also an important consideration. Captain Fleming submitted to the Bureau of Standards for test, pieces of the vitaglass cage which had been used all winter for his rats.

The glass was tested both before and after cleaning off the film of dirt which had accumulated on it while in the cage. This film was mostly on the inner surface of the glass, the outside having been washed by rain and snow and having been cleaned once midway in the experiment. The inside of the

glass was not cleaned throughout the experiment and the film of dirt was so slight that it was not until the glass was removed for testing that it was seen that the inner surface was soiled.

The measurements were made of the transmission of the highly potent light of 302 mμ. One piece of the glass let 17.4 per cent of this through when dirty and 28.1 per cent when clean; for another slightly thinner piece the figures were 24.2 and 39.9 per cent. In other words, the slight film of dirt did cut off a good deal of the light, and yet enough had penetrated to prevent rickets in the rats.

Practical usefulness of special glasses.—Physical measurements and animal experiments thus both show that certain of these window-glass

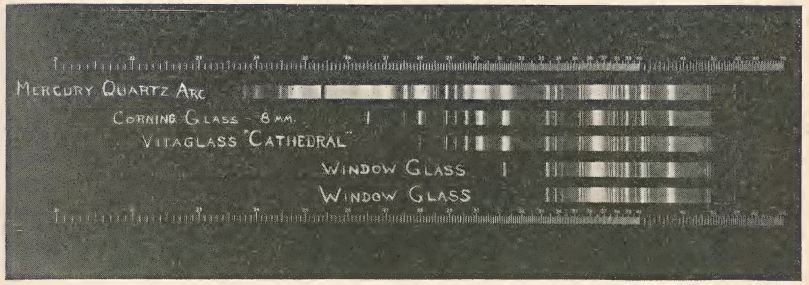


FIG. 25.—Spectrogram showing relative transparency of Corning glass, vitaglass, "cathedral" and window glass. (From Wyman *et al.*, *American Journal of Diseases of Children*, XXXVII [1929], 476.)

substitutes are definitely superior to ordinary window glass. What of their use, then, in homes, schools, office buildings, and hospitals? Are they worth while in spite of their considerably higher cost? These points are still much under debate.

First, it is obvious that no glass can transmit light that does not reach it, so that, judging from the Chicago figures, in smoky cities in winter the use of permeable glass is, to speak conservatively, still in the experimental stage. Next, probably the only people to derive any benefit from living in a room glazed with it are those who sit near the windows, in the direct line of the sun. But with these limitations in mind, it is probably safe to say that the best of such glasses, if intelligently used, may be of real value. For example, they may well be used in solariums where patients can lie directly under the sunny window; also in winter nurseries, especially during the late winter and early spring, when the sun's ultraviolet light has

begun to increase and the weather is still too bad for much outdoor exposure.

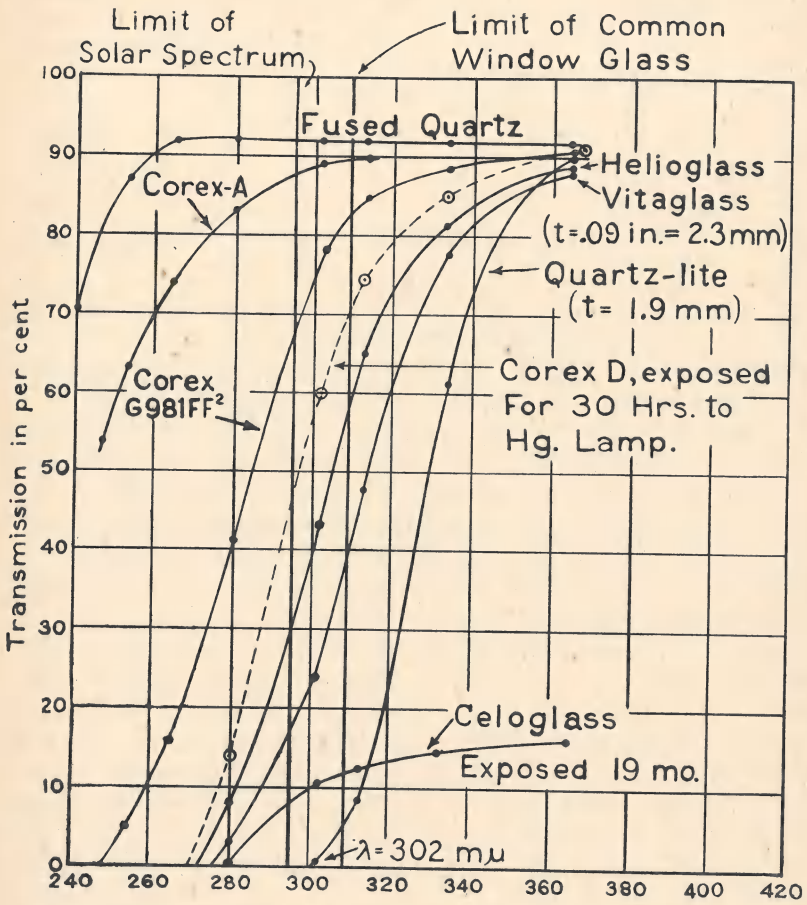


FIG. 26.—Ultraviolet spectral transmission of various window glasses after exposure to the sun for twelve months. Thickness, t=0.09 inch=2.3 mm. (From U.S. Bureau of Standards.)

Captain Fleming came to the conclusion that "the construction of a solarium glazed with a glass permeable to ultraviolet light would therefore appear practical in this locality" (the Army Medical Center in Washington).

Dr. Janet H. Clark, writing of one of the best of the glasses, which

transmits from 50 to 60 per cent of the solar radiation between 290 and 320 mμ, when it is new and about 30 per cent after it has aged, says further: "If it is used in a solarium there is no doubt that a patient exposed to the direct rays of the sun under it would get about as much ultra-violet radiation in three hours as he would get in one hour in the open sunshine, provided the intensity of the sunlight remained the same."

In schoolrooms and office buildings, however, their usefulness is probably slight. Using her zinc sulphide method, Dr. Clark has recently measured the intensity of the ultraviolet light passing into the interior of the room. In March, at noon, according to her observations, it takes about two minutes to give one unit in direct sunlight and ten minutes in the north skylight, from a hemisphere of northern sky. At five meters from a north window through the ultraviolet transmitting glass, from fifteen to twenty *hours* is required; that is, two minutes outdoors in the noon sun gives as much ultraviolet irradiation as fifteen or twenty hours in the middle of the schoolroom. Or, as Dr. Clark says, "Any child going out for recess or any stenographer going out to lunch will get more ultra-violet radiation than she could get all day behind a window of ultra-violet-transmitting glass. . . . . It would be cheaper and more efficient to send the individuals concerned out into the sunshine for a few minutes every day at noon."

Finally, Dr. Eddy of Columbia University writes:

> My own feeling is that schools and office buildings would invest their money more efficiently [than for special windows] by equipping solaria, preferably with sky lighting and sex segregated, so that the needy cases could lie exposed for certain periods of the day to the full effect of the sun, with as little clothing as possible. I do see a place in homes and apartments for these glasses to permit mothers to save some hours of perambulation with the baby or chaperonage of small children.

Other opinions from numerous authorities as to the usefulness of ultraviolet transmitting glass are interestingly summarized in the April, 1929, *Scientific American*.

It is not irrelevant to report that the great Shedd Aquarium, now under construction in Grant Park, Chicago, is installing 1,500 square feet of skylight made of wire cathedral vitaglass, and that the Lincoln Park Zoo uses vitaglass in its new monkey house. (Information supplied by Vitaglass Corporation.)

Hopeful though the outlook for these glasses may be, anyone who installs them in home windows or skylights or in office or school must do

so with the realization that there is still a large element of experimentation in their use.

CLOTHING AND ULTRAVIOLET LIGHT

Does any of the ultraviolet light pass through ordinary clothing? Experience tells us, of course, that much of it does not, since it is only the exposed parts of the body which "burn" in the sun. However, the question of whether or not small amounts of light are transmitted through cloth is of considerable practical importance, whether one wishes to protect the skin from too much sunshine, as in the tropics, or whether one wishes to be sure of securing an adequate supply.

In the attempt to answer this question, a variety of methods, both biological and physical, have been used. Rats on a rickets-producing diet have been irradiated through screens of different fabrics, and the degree of protection observed. In the same manner, cottonseed oil has been irradiated through different materials and the resulting quantity of vitamin D measured by rat-feeding experiments. A somewhat different method of attack has been used at Kansas State Agricultural College, where they have determined the relative lengths of time required to burn the human skin or to produce an effect on light-sensitive paper, either by direct irradiation or by irradiation through small squares of the cloth. Finally, the United States Bureau of Standards has become interested in this problem and has recently published the results of a series of exact physical measurements of the percentage of ultraviolet light transmitted by a number of different fabrics.

The effect of weave.—As might be expected, the results obtained by all these methods are strikingly similar. First of all, it is of course agreed that the quantity of light passing through a piece of cloth depends upon the looseness or the closeness of the weave. By the simple but clever device of passing light through white cloth, and then through that same cloth after it had been dyed black, definite figures for the actual quantity of light transmitted by the spaces in the weave and by the fibers themselves have been obtained. Using this method, which they themselves developed, Dr. Coblentz and his associates at the Bureau of Standards have found that open-weave fabrics such as voile or georgette crepe will transmit from 55 to 65 per cent of the ultraviolet light received, and that 40 to 55 per cent of the light passes through the openings of the cloth. On the other hand, a closely woven fabric, such as duck or cotton broadcloth, will transmit an average of about 10 to 20 per cent of light, of

which only from 1 to 4 per cent passes through the spaces of the weave. Thus light passes chiefly through the openings but also a small part may pass through the fibers themselves.

Color and thickness.—The color of the fiber and the weight and thickness of the cloth are also important factors in the transmission of light. So slight a color as the yellow tinge of old silk, or the yellowish tan of un-

TABLE X

INFLUENCE OF DYEING ON TRANSMISSION OF LIGHT BY FIBERS

Fabric	Color	Ultraviolet Light Transmitted through Thread, per Cent
Rayon:		
Twill	White	12.9
Twill	Yellow	1.7
Twill	Gold	0.7
Plain knit	White	19.5
Plain knit	Cream	12.3
Plain knit	Dark cream	10.4
Plain knit	Light peach	9.1
Plain knit	Light yellow	5.2
Plain knit	Yellow	1.9
Cotton:		
Balloon	Bleached	20.9
Balloon	Natural	4.7
Linen:		
Airplane	White	12.4
Airplane	Natural	4.3
Silk:		
Crepe (unweighted)	White	17.6
Taffeta (unweighted)	White (yellowed with age)	5.0
Crepe (weighted)	White (yellowed with age)	7.6
Crepe, flat	Reddish orange	9.2

bleached cotton or linen, will cut down the transmission of light materially; dyeing will reduce it to almost nothing. Table X, which consists of data selected from the Bureau of Standards figures, illustrates the reduction in the amount of light transmitted by the fiber as it is dyed in progressively deeper shades.

The heavier the yarn and the thicker the cloth, the less light is transmitted, as is shown by Table XI, also selected from the Bureau of Standards figures.

The kind of fiber.—Biological tests, "burning" tests, and physical measurements all combine to indicate that there are some real differences

in the absorption or transmission of light by the various fibers—cotton, linen, wool, silk, and artificial silk. These differences, however, are slight. Cotton, linen, and artificial silk appear to transmit a greater proportion of the ultraviolet light than do silk or wool. It is difficult to give definite figures on this point, because differences in transmission due to weight and thickness of the fiber often serve to cover up the differences due to the kind of fiber used. Silk, when not yellowed with age, may have a transmission equal to many samples of cotton (about 18 per cent), and some samples of wool may compare favorably with the silk. Silk, however, seems to have a somewhat lower, and wool a decidedly lower, average

TABLE XI

EFFECT OF WEIGHT OF CLOTH ON TRANSMISSION OF ULTRAVIOLET LIGHT THROUGH FIBERS

Fabric	Ultraviolet Transmitted through Thread, per Cent	Weight, Oz. per Sq. Yd.	Fabric	Ultraviolet Transmitted through Thread, per Cent	Weight, Oz. per Sq. Yd.
Linen:			Cotton:		
Handkerchief...	16.1	2.2	Nainsook.....	20.0	2.0
Airplane.....	12.4	3.8	Nainsook.....	15.2	4.5
Napkin.....	7.1	4.4	Shirting.....	19.7	2.0
Towel:			Shirting.....	8.5	3.8
Huckaback..	6.7	5.0	Handkerchief...	9.8	4.3
Huckaback..	3.1	7.8	Handkerchief...	6.6	5.8
			Duck.....	7.6	7.0

transmission than has cotton or artificial silk. Also the proportion of ultraviolet light, when compared with the visible light transmitted by the fabric, is found to be very much lower for wool than for silk or for cotton. The ratio is about 44 per cent, in fact, for wool as compared with 60 to 65 per cent for silk and 65 to 80 per cent for cotton.

The ash content of the fiber.—A partial explanation of the difference in transmission by different fibers is found in an experiment recently reported by Harriet Morgan, of the Utah Agricultural Experiment Station. In this study rats were fed cottonseed oil irradiated through artificial silk (viscose), cotton, and wool materials which had been specially woven so as to be as nearly as possible of the same weight and the same amount of interspace. In spite of these precautions, differences in transmission did occur, which could apparently best be explained on the basis of the percentage of ash contained in the fiber, the artificial silk having the least

ash and the highest transmission. "This fact," says the author, "strongly suggests that the porosity of the fiber is a significant factor which influences the ultraviolet-ray transmissibility of clothing materials."

Summary.—From all the foregoing data it would appear that, in order to obtain as much of the ultraviolet light as will pass through clothing, thin, loosely woven fabrics made of cotton, linen, or artificial silk should be worn; and to protect against sunburn a closely woven fabric, possibly of silk, seems best. Dr. Coblentz advances the following as a very tentative suggestion for wear in the tropics:

> In conclusion, it is relevant to refer to these data in connection with the question of shielding the body from ultra-violet and visible solar radiation, which is an important problem in the Tropics. . . . . For protecting the body from the ultra-violet rays transmitted through the outer clothing(which should be white in order to have a high reflecting power), the inner garment may be made of thin, closely woven yarn, of wool or cotton, dyed (red or khaki) with a substance that absorbs the ultra-violet.

In the temperate zones, especially in the winter time, ordinary dress probably allows very little ultraviolet light to penetrate to the skin. Recent German experiments with light-sensitive paper have shown, however, that modern women's dress is much more satisfactory in this regard, since it does permit the continuous access of some of the light-waves to the skin, than men's closely woven and lined clothing, which allows no light whatever to penetrate it. The author expresses surprise that recently obtained knowledge of the action of light-rays on the skin has had no influence on men's clothing.

ARTIFICIAL SOURCES OF ULTRAVIOLET LIGHT

With the uncertainties of sunshine, especially in our smoky cities in winter, artificial sources of ultraviolet light are highly desirable and have already been frequently referred to. In order to obtain an appreciable amount of ultraviolet radiation, it is necessary to heat the radiating substance to a high temperature, 3,000 C. (5,400 F.) or higher. (The temperature of the surface of the sun is about 5,500 C.) Since metals such as tungsten evaporate very rapidly at high temperatures, sources of ultraviolet radiation are practically confined to electric arcs. Two kinds of lamps are therefore most employed, the mercury vapor arc in quartz and the carbon arc with or without added metals. One of these lamps, the mercury vapor quartz, is shown in Figure 27.

Physical measurements.—Both of these kinds of lamps give off short-

er radiations than are contained in sunlight, and the short radiations are much more intense; that is, the lamps give far more powerful ultraviolet rays than does sunshine. Sharp comparison of them with sunlight is not easy, however, especially for the mercury arc, which emits a discontinuous spectrum, in contrast to the sun's continuous spectrum. In addition, the intensity of the rays from both lamps varies with the strength of electric current employed.

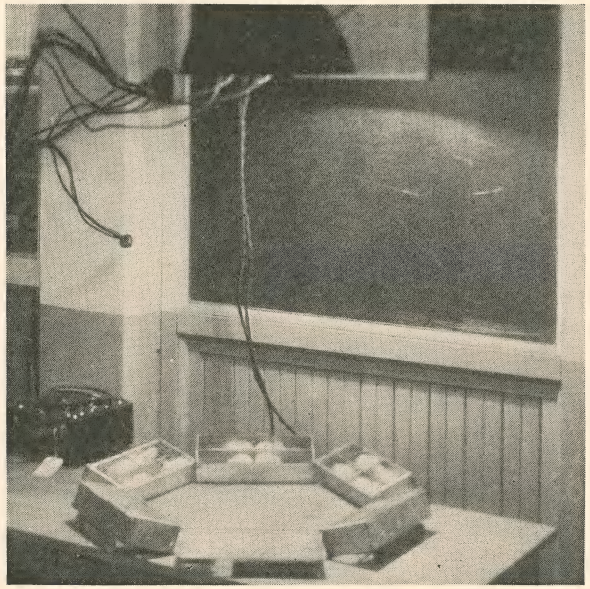


FIG. 27.—Method of irradiating animals. (From Wyman *et al.*, *American Journal of Diseases of Children*, XXXVII [1929], 475.)

The shortest wave-length from the quartz mercury vapor lamp is 185 mμ, from the white flame carbon 218 mμ, and for sunlight 290 mμ. (It will be remembered that radiations with antirachitic potency range roughly from 313 to 265 mμ.) The intensity of several lamps in different parts of the ultraviolet has been measured in ergs per second per square millimeter of area at 40 inches, by Goodman and Anderson. A few of their figures, condensed, are given in Table XII. They show clearly that the mercury quartz arc has high intensity in the very short radiations, considerably higher than the carbon arc, and also that increasing the voltage and amperage increases the short-wave intensities.

Other data showing in different terms this same high intensity of the ultraviolet rays from the lamps have been obtained by Dr. Coblentz, of

TABLE XII

ULTRAVIOLET UNITS IN ERGS PER SECOND PER SQUARE MILLIMETER OF AREA AT FORTY INCHES

Type of Arc Lamp	Arc Voltage	Arc Amperage	Arc Length	400 to 320 Mμ	320 to 290 Mμ	290 Mμ and Shorter
Quartz mercury (used 200 hours)	75	3.4	55	11.0	8.6	4.0
Quartz mercury (three-electrode type, alternating current)	150	5	120	9.4	11.3	6.3
White flame, therapeutic carbon A	35	17.0	15	7.8	1.1	0.4
Therapeutic carbon B, blue flame, "iron"	35	16.0	13	6.6	2.2	1.4

the Bureau of Standards (Table XIII). They are expressed as the percentages of the total radiation in different parts of the spectrum, the percentage in 1,700–2,900 angstrom units being 0 for sunlight, 1–4 for the carbon arc, and 17 for the quartz mercury arc.

TABLE XIII

SPECTRAL DISTRIBUTION (COBLENTZ)

(ANGSTROM UNITS)

	1,700–2,900, per Cent	2,900–4,360, per Cent	1,700–4,360, per Cent	4,300–14,000, per Cent
Sun:				
Sea-level	0	55	55	45
Carbon arc:				
Pure carbon	4	40	44	56
Impregnated carbon	1	15	16	84
Impregnated "violet flame"	.....	58	.....	42
Quartz mercury arc:				
Used 250 hours	17	45	52	38
New	.....	.....	66	34

Powerful incandescent lamps may also give a fair amount of ultraviolet light. A 300-watt Mazda lamp, even with an ordinary glass bulb, showed a short wave-length limit of 298 mμ and with a vitaglass bulb 280 mμ (Bundesen *et al*), but they are not comparable in power with the mercury and carbon arcs. Others tested by Coblentz "did not emit an ap-

preciable amount of ultraviolet of wave-lengths less than 310 millimicrons."

Many so-called ultraviolet or "sun" lamps are now on the market, their promoters bombarding the prospective buyer with a variety of claims. The good ones are highly useful if used rightly and highly dangerous if used wrongly. E. E. Free, in a vivid article in *Harper's Magazine* for February, 1929, writes: "Fortunately, many of the alleged sun lamps and ray lamps of dozens of kinds and titles now being hurried out on the American market will damage nothing but the purchaser's pocketbook. This is especially true of the cheapest ones." One laboratory, in New York, in testing scores of such lamps found none for less than ten dollars "able to emit enough real ultraviolet to damage a mouse."

In spite of possible fraud, the better of these lamps seem destined to stay and to be widely used.

USEFULNESS AND DANGER OF THE ULTRAVIOLET LIGHT

Therapeutic use of these lamps.—All through this book the great usefulness of these lamps has been and will be mentioned. Both the mercury in quartz and the carbon arcs are of value in curing or preventing rickets in children and in animals, and they influence bone formation, blood calcium and phosphorus, and calcium and phosphorus metabolism in general. They also have numerous other influences—bactericidal, on the blood cells, possibly as preventive of colds, etc.—that need not be discussed here. The physician has a powerful aid in them, far more powerful than in sunshine, and one that he is increasingly using.

They are also dangerous. They furnish an abnormal environment for the inhabitant of the earth, with shorter and more intense ultraviolet rays than his body is adapted to. Bad burns may be caused by too long exposure, much worse than the worst sunburn. The eyes may be seriously and permanently injured if they are not protected—a fact well known to motion-picture actors who look too long at the bright arc lamps. Other possible dangers are not well understood; employment of artificial ultraviolet rays is still new and still very uncertain in many of its aspects.

The usual method of treatment with the lamps for a human being, child or adult, is to cover the eyes with dark glasses or a dark cloth and irradiate the nude body, front and back each, for half a minute only the first day, gradually increasing the time up to from ten to twenty minutes. Sometimes exposures are given weekly, sometimes oftener. The lamp is kept at a constant distance, usually about a meter. Exposure to the carbon arc can be longer than to the mercury quartz. The strong but not unpleasant odor noted around the lamps is due to ozone formed from the oxygen of the air by the short light-waves.

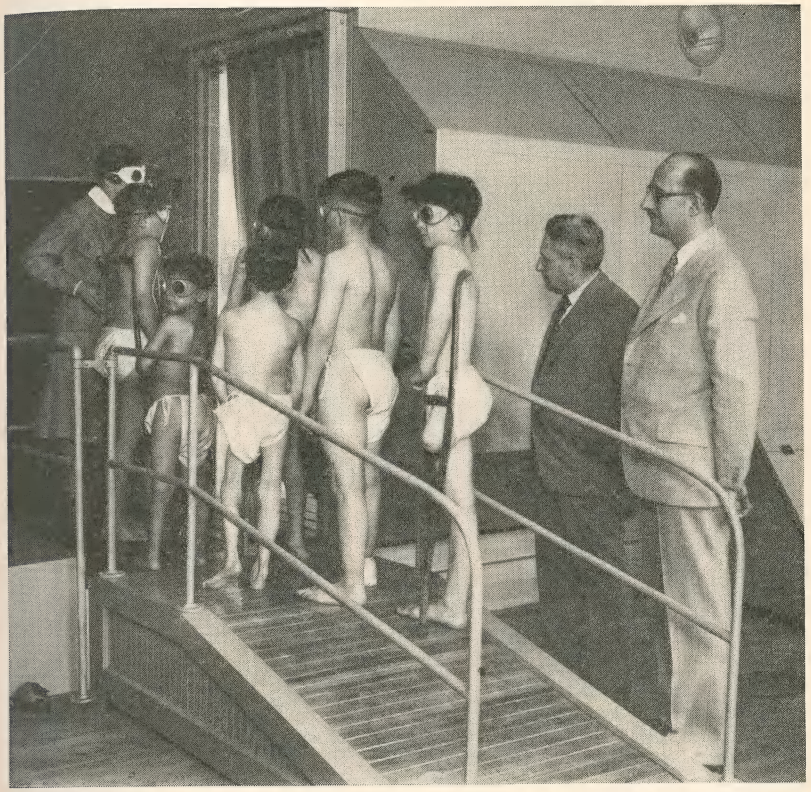


FIG. 28.—Photograph of the exterior of the ultraviolet-ray apparatus installed at the Spaulding School, showing children ready to be sent through the cabinet on the moving platform. (Pacific and Atlantic Photos, Inc.)

Experiment in the University Co-operative Nursery School.—At the University of Chicago, in the Co-operative Nursery School, two mercury vapor quartz lamps are being used. They are arranged with a small pen-like space between, so that six children at the same time may stand under them and at a definite distance from the light. The teacher gives exercises or games to each little naked group, carefully watching the time of the few minutes' exposure, and the children regard the performance as

great fun. The mothers, teachers, and physician in charge are all much pleased with the results, which seem to be not only tanned bodies but increased good spirits and general improvement in vigor. Previous irradiation experiments at the school have involved treatment of one child at a

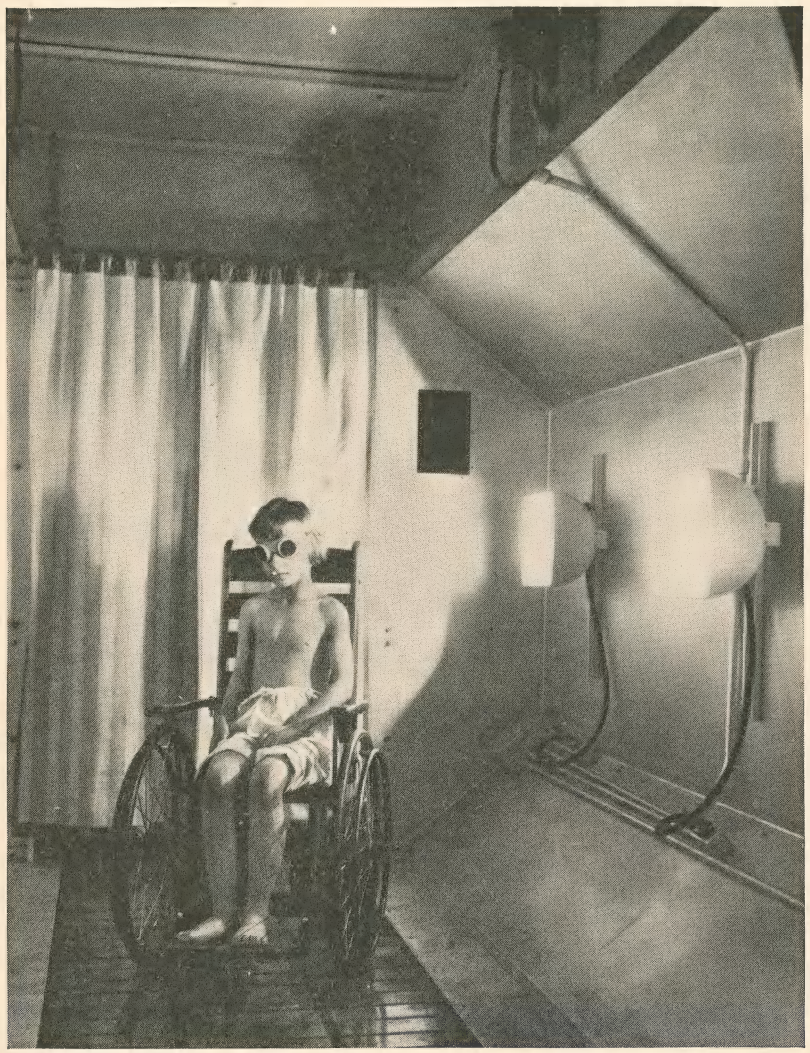


FIG. 29.—Crippled child receiving treatment in the ultraviolet-ray apparatus at the Spaulding School. (Pacific and Atlantic Photos, Inc.)

time, with no better results, less fun for the children, and much more labor from the adults.

Experiment in a school for crippled children.—Another dramatic experiment with ultraviolet irradiation has recently been reported in the newspapers. In the Spaulding School for Crippled Children, Chicago, there has been installed an apparatus designed by Dr. Benjamin Goldberg, director of the Municipal Tuberculosis Sanitarium, which is said to be the world's largest mercury quartz lamp. The *Chicago Tribune* (June 18, 1929) says:

> The chief feature of the contrivance is an automatically moving platform that carries the children through at a rate designed to give each small group the prescribed dosage of ultraviolet rays. Six large mercury quartz lamps are ranged three on each side, giving radiation to every part of the body.
>
> Each of the small patients wears a minimum of clothing for his daily sunshine bath and colored goggles to protect his eyes from the glare of the lamps. For the first treatments, given two weeks ago, the platform moved the children through at a high rate of speed. As they became accustomed to the artificial rays, which are extremely powerful and will cause a sunburn within the space of a minute, the speed was reduced and the doses made longer.
>
> Small backs, chests, and legs that were a pasty white only two weeks ago are taking on a healthy tone, and the new game of a daily sun bath is extremely popular.
>
> These children, because of their deformities and physical handicaps, are brought to school in buses. They have not the chance an ordinary child has for sunshine. The giant lamp is designed to provide the element they have been lacking.

It is too soon to report results from this experiment, which is given here merely as an illustration of what is being done.

Pigmentation.—Burning and tanning usually follow treatment with the lamps, but the color of the tan is not exactly the same as that from the sun. Tanning seems to be a protective action of the skin and is quite different in different individuals. Some physicians have thought that it was a hindrance to ultraviolet light therapy, but more, apparently, regard it as an indication of the effectiveness of the treatment. Patients with marked pigmentation, according to Mayer's experience, improve more rapidly than those who lack pigmentation. Yet rachitic children can be cured without browning the skin, so that tanning is not necessary for healing. After the skin has begun to tan, light treatments can be continued longer without danger of burning.

The red-yellow rays are the only ones which penetrate at all far into

the tissues. It is their penetration which causes the rosy color of the ear when the sun shines through it, or the reddish glare seen through the cheek from a bright electric lamp held in the mouth. Neither these rays nor any others that can pass through window glass cause pigmentation. That is brought about by rays from about 320 to 300 mμ, which reach as far into the skin as the basal layer of the epidermis where the melanin (brown coloring matter) is formed and are absorbed there. The shorter ultraviolet ray is probably absorbed by the outer layer of the skin, the pigment especially preventing penetration of light which would otherwise have harmful effect.

That negro children and dark-skinned children in general are more prone to rickets than fairer races is probably owing to the absorption of the curative rays by the pigment of the skin. It has recently been definitely shown that white human skin is more permeable to ultraviolet irradiations than negro skin (Macht *et al*), yet negro babies *are* cured of rickets by light treatment, showing that when the radiant energy is intense enough it is not completely shut off by the pigment.

Psychic influences.—The psychic influences and the general effects upon the nervous system must not be passed over in discussing the effects of irradiation. We are all conscious of the favorable influence of sunlight on bodily and mental well-being. Two of the important authorities on irradiation may be quoted in this connection.

> Striking results have also been reported following irradiation with mercury and carbon lamps . . . . a feeling of exhilaration expressing itself in the joy of work and living, Hausmann feeling as if he had been on a mountain trip. The effects of an overdose of radiation, well known and personally familiar to most of us, are accompanied by feelings of unrest, more or less vague apprehensions, sleeplessness, etc. In many these symptoms appear long before the erythema.[1]
>
> It is well known that after general irradiation of the entire body most people feel invigorated, and are in a better frame of mind. Fatigue, irritability and depression are overcome.[2]

Mayer[3] also quotes observations on a group of children suffering from debility, anorexia, and listlessness without any visible cause. After irradiation with the mercury quartz lamp for three-quarters of an hour, five

[1] Laurens, "The Physiological Effects of Radiation," *Physiological Reviews,* VIII (1928).

[2] Mayer, *Clinical Application of Sunlight and Artificial Radiation.* Baltimore: Williams & Wilkins Co., 1926, p. 111.

[3] *Ibid.,* p. 136.

days a week, for a month, there was a complete transformation in the condition of each child. Appetite, cheerfulness, and desire to play returned. Musculature and especially the skin improved.

The cautious *Journal of the American Medical Association* editorially warns against quackery and the "tendency to draw unwarranted generalizations from a restricted group of facts," and then says: "After irradiation, general improvement of health has been observed in many cases. It may be attended by increase in appetite, gain in weight, improved sleep, or less well defined signs."

Controversial aspects of the question.—Undoubtedly too many claims are being made for ultraviolet therapy, and enthusiasm rather than scientific fact is sometimes governing the use of the lamp. Even careful judgments tend to both sides of the question. The annual report of the British Medical Research Council, for 1927–28, published in March, 1929, contains a "searching" (and adverse) criticism of the uses of ultraviolet rays in the treatment and prophylaxis of disease other than rickets. On the other hand, report after report of carefully controlled experiment seems favorable. Caution is still necessary; much of the use is still highly experimental, but a useful method does seem available.

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CHAPTER VIII

DISTRIBUTION OF VITAMIN D

COD LIVER OIL

So far the assumption has been tacitly made that cod liver oil is *par excellence* the natural source of the antirachitic vitamin. While this is true only with certain reservations, the importance of the oil can hardly be overemphasized, both for practical use and laboratory research. As already stated in chapter ii, it had been used for many years in the treatment of rickets with fluctuating amount of medical respectability, before the discovery was made that rickets actually is a deficiency disease due to the lack of a substance occurring in the oil. Then came the knowledge of the distinction between this substance of antirachitic potency and the already known vitamin A, and following and parallel with this discovery a vast amount of information, still incomplete, of the functions of this vitamin in the body.

Growth in use of the oil.—Not often does nutrition research have so marked an effect on a business as it has had on the cod-liver-oil industry. In the six years from 1922 to 1927 our imports of cod liver oil and cod oil together have more than doubled, as shown by these figures from the Bureau of Foreign and Domestic Commerce of the United States Department of Commerce.

TABLE XIV

COD OIL AND COD LIVER OIL STATISTICS OF IMPORTS INTO THE UNITED STATES

Year	Gallons	Year	Gallons
1922	1,809,478	1925	2,975,510
1923	2,316,562	1926	4,347,024
1924	2,846,588	1927	4,495,375

"Cod oil" is the name given to oil from rotted livers which is now seldom used in medicine, but in the technical arts, especially tanning. If the figures were given for cod liver oil alone instead of combined with the cod oil, they would be far more startling, for fishermen now tend to boil down the livers promptly for medicinal oil instead of sending them to importers for the production of cod oil. The *Commerce Yearbook* for 1928 says, "Medicinal oil production has increased greatly, and the advance in its price has lessened the supply of common cod oil for tanning."

The United States imports almost all its cod liver oil from Norway (the leading source), Newfoundland, and the United Kingdom, and even a little from Japan.

Some points on chemical composition.—The chief components of cod liver oil are the same as those of other fats and oils and especially other fish oils—olein, myristin, palmitin, and stearin, and the highly unsaturated and less well-known clupanodonin and docosapentenoin, to which the fishy smell is partly due, and others. Bills, chemist with Mead Johnson and Company, lists a number of acids "the existence of which is reasonably well established" and others "less well established," showing that the composition has not been thoroughly investigated, probably because in the past chemists were not much interested in the oil and now their interest is in its vitamin content.

In consideration of the available information on the make-up of the oil and its similarity to other oils, it is not surprising that the common-sense view of its value used to be that it was merely especially easily assimilated. Theories of fatty acids with special chemotherapeutic properties have not been substantiated.

The part that is being investigated today is the non-fatty or unsaponifiable portion, which makes only about 1 per cent of the whole, but which contains both vitamins A and D. According to Bills, this unsaponifiable fraction is about half the solid alcohol cholesterol, and half pigment, vitamins, hydrocarbons, complex alcohols, and unidentified matter. Details of the chemistry of the solid alcohols and vitamin D are given in chapter ix.

MEASUREMENT OF ANTIRACHITIC POTENCY

Since it is the vitamin potency of cod liver oil that we are particularly interested in, we much need a quantitative method for determining the vitamin content. Some day probably we shall be able to say that a given sample of the oil contains such a percentage of A and of D. Before then we can be fairly well satisfied by the selection of an arbitrary unit of vitamin potency, such as has already been done for vitamin A, and statements of the number of units contained in different oils.

The unit which we should like for D would be something of this order: the amount of vitamin D which when fed to rachitic rats will cure them in so many days. The variables involved in this seemingly simple statement are very numerous. Among the points to be decided are these: Which of the rachitogenic diets shall be adopted as standard? What shall be the criterion for rickets and healing of rickets—blood composition or bone composition or mineral retention, or the line test or what? Shall rickets be produced in the rats and then cured, or shall its prevention be the measure of potency? An elaborate comparison of a number of methods recently made in McCollum's laboratory at Johns Hopkins led to the conclusion that there are still many uncertainties and irregularities in these points. Adoption of a unit therefore seemed premature, and a check on research rather than a help.

This emphatically does *not* mean that we must go without knowing whether a given oil is high or low in D. It means that an investigator or group of investigators will have their own methods and will report the "relative potency" of their samples. Sometimes, however, close comparison of one's worker's results with another's cannot be satisfactorily made.

Bills's method.—The method developed by Bills in the Research Laboratory of Mead Johnson and Company is particularly clear-cut. He gives very definite directions for feeding the diet (McCollum's 3143) for eighteen (or a few more) days after weaning and then feeding the test preparation for exactly five days, taking care to use only rats that eat satisfactorily and do not lose weight. The line test is his criterion of healing. He distinguishes four degrees of healing by one to four plus signs. The "minimum curative dose" is the amount of the oil required to produce definite but not extensive healing.

As a standard he takes the average activity of Newfoundland medicinal cod liver oil. On the average this produces distinct (2+) healing at a level of one-fourth of 1 per cent of the diet. He calls this standard 100 and compares other oils on this scale. Some of his results are given below.

Coward's suggestion.—Coward in England has just made an interesting suggestion which is too new as yet to have received general acceptance. It is that the unit of antirachitic potency shall be defined as the amount of activity contained in 0.0001 mg. of irradiated ergosterol. A specially prepared irradiated ergosterol has been adopted as a standard for assay of the vitamin.

The new official unit.—Just as this book is going to press (August 31, 1929), comes the announcement of the acceptance of a unit by the Council on Pharmacy and Chemistry of the American Medical Association. One "rat unit of vitamin D" is "that amount of vitamin D which, when uniformly distributed into the standard vitamin D deficient diet—ration 2965, Jour. Biol. Chem. 64:263, 1925—will produce a narrow and continuous line of calcium deposits on the metaphyses of the distal end of the radii and ulnae of standard rachitic rats." That is, the

line test and Steenbock's rachitogenic diet are henceforth the standard. A "potent cod liver oil" contains one of these rat units in every 75 mg. This step of adopting a unit has been taken particularly for measuring the potency of samples of irradiated ergosterol, now to be officially known as "viosterol" (see chapter ix).

DIFFERENCES IN COD LIVER OIL

Tests on commercial oils.—Outside the laboratory we have no way of being sure whether or not a given commercial oil is highly potent. Relying upon the good reputation of the drug house, however, seems to be safe. Adams and McCollum, after testing eighteen samples and finding considerable difference in potency, concluded that the size of the usual dose for children and the length of time the oil is taken supply "a sufficient factor of safety." It is "probable that any of the better grades of oil upon the market afford protection."

However, the eighteen samples (designated by number only, not by trade names) fell into three groups as to potency—relatively high, moderate, and relatively low. Those "relatively high" gave a 3+ or 4+ line test when making up 0.125 per cent of the diet; one of those "relatively low" gave only a plus line test for twice this amount (0.25 per cent). The "factor of safety" may be adequate and yet one has a desire to know whether and how these markedly different oils are on the market. Also one wishes information as to whether the oil of a given firm is fairly constant in potency.

More specific information concerning four different high-grade cod liver oils marketed in England has been reported by Coward, who measured their antirachitic potency in terms of her unit of the activity of 0.0001 mg. of a standard preparation of irradiated ergosterol. The best oil contained 150 units per gram, and the poorest 50 units, while the other two samples gave intermediate values of from 70 to 80, and 100 units respectively. Probably even the poorest of these oils would be adequate to protect a baby from rickets, but again one would like to be certain of the potency of any particular oil used.

Antirachitic potency in relation to the volume of oil in the liver.—Hess, and Bills and Honeywell have recently combined forces for an investigation that may well have great influence in the commercial production of cod liver oil as well as on scientific knowledge. Ordinarily, they remind the reader, cod liver oil is obtained at the height of the fishing season in the spring or summer, when the livers are large and fat and yield the greatest amount of oil. In Newfoundland the liver then weighs about one-fourteenth as much as the entire fish and contains about 50 per cent of oil. At other seasons when the livers are lean and small or "poor," it has been taken for granted that they are unsuitable for the extraction of a high-grade oil.

The investigators had at their disposal a large number of cod at the hatchery of the Bureau of Fisheries, Woods Hole, Massachusetts. During the winter months the cod there are kept in a large tank and fed very little, so that the fish used were practically in a starved condition. As a result the livers were very small and their oil content was very low, so low that to obtain samples the oil had to be extracted with ether.

Yet these oils were extraordinarily potent. By Bills's method, using a scale with high-grade medicinal oil as 100, the poorest of them assayed at 150, most of them above 1,000, and the best at 20,000—two hundred times as strong as the usual good material. This oil was very dark in color. In general, the less oil in the liver the greater the potency. "For a fish of a given size, antirachitic potency varies inversely with the amount of fat or oil in the liver."

It seems surprising that the antirachitic factor should remain in the liver while the fat itself is consumed. Apparently the fat is oxidized away in the daily metabolism of the fish when the diet is low, but the antirachitic substance resists oxidation, remains behind, and becomes concentrated in the greatly impoverished liver. When the liver fattens again, its content of the vitamin increases but the oil never approaches the high potencies reported in this study.

Does the cod synthesize vitamin D?—A certain answer to this question has not been secured but probably the answer is "yes." Two years before the study just reported, Bills published data showing almost surely that the cod cannot get nearly the full amount of D in its liver from its main food, a little fish called "caplin" which has very little of the vitamin in it. To investigate the problem further he kept other fish, freshwater catfish, in darkened aquariums and fed them on trimmed raw veal muscle, the ether extract of which had shown no antirachitic activity by rat test. After nine weeks on this diet, ten of the fish were killed and their oil was found to assay essentially the same as that of the controls at the beginning of the experiment. The continued potency, Bills argues, could be the result of either synthesis or storage. But later on after the fish had grown more and fat deposits increased, the oil was still of normal

or slightly increased potency, though they could not have obtained the increase from their food.

Neither, apparently, do fish elaborate the vitamin through the influence of ultraviolet light. These catfish were kept in the dark. Others irradiated with a 220-volt uviarc for five minutes every other day for six weeks under 20 cm. of water were adversely affected so that three died and others became subnormally active, and their oil showed no increase in potency.

Bills therefore suggests "that the substance, or group of substances, known as vitamin D may be synthesized by fish."

Vitamins A and D in cod liver oils not parallel.—We tend to think that the two vitamins of cod liver oil must be in the same proportion in different samples, but we have no justification for such expectation. In fact, English investigators who have recently taken the trouble to study the point have found that some which are relatively rich in A are poor in D, and others rich in D are poor in A.

OTHER FISH OILS

Cod liver oil, as already suggested, is not the only active fish oil. The most active substance so far investigated, aside from the extraordinarily potent liver oils of the starving cod, is that from the puffer fish liver. First observed by Hess and Weinstock in 1926, it assays fifteen times as powerful as medicinal cod liver oil—fifteen hundred on Bills's scale. Bills has also tested a number of others. For example, the oil from a sample of goosefish liver from Boston is the same as cod liver oil, 100; shark liver, Newfoundland, is 75; haddock liver (five samples) is 10.

Not only the liver but the body oils of certain fishes are active. Four samples of herring from Newfoundland and four samples of sardines from California gave oils with a potency of 100. As the fat-content of herring averages 7.1 per cent of the edible portion and one might readily eat the flesh of one-half to one pound of the fish, the 9 to 18 gm. of oil furnished will give a good dose of vitamin D. Sardines have about the same percentage of fat, and so they also can compete with cod liver oil. Salmon body fat, too, is potent—one-fifth as potent as cod liver oil. A sample of the blubber oil of an adult female seal is only slightly antirachitic (3 on Bills's scale) and that of the newborn seal not at all.

Burbot, "the nearest fresh-water relative of the cod," is found extensively in all our large inland waters, such as the Great Lakes and the streams leading into them, but it is seldom used for human food. It is

rather considered a nuisance and a waste product by fishermen. Though the fish weighs only about three pounds, the liver is very large, sometimes weighing up to half a pound, with a percentage of oil varying from 36 to 56. Clow and Marlatt, of the home economics department of the University of Wisconsin, have just reported a comparison of the antirachitic potency of this oil with Mead Johnson cod liver oil. They found the burbot liver oil eight times as active as the other. Remembering the possible variability proved for cod liver oil, they conclude conservatively: "At least, we probably can assume that burbot liver oil may be classed with cod liver oil as an excellent source of the antirachitic vitamin."

Whether or not these various newly found sources of vitamin D affect the cod-liver-oil industry remains to be seen.

EGG YOLK

Proof of potency.—The second most potent source of vitamin D, after these fish oils, is egg yolk. Back in 1923, soon after the clear-cut differentiation of the antirachitic factor, Hess both cured and prevented rickets in rats by giving them egg yolk in addition to their rickets-producing diet. Egg white had no effect. Even more striking was his prophylactic treatment of twelve infants. In an attempt to forestall the development of rickets through the winter months, which his experience had taught him to expect in the great majority of bottle-fed babies, he added the yolk of one raw egg to their regular formulas. In most cases the addition was made in December. In March there was no rickets observable either by roentgen ray or by clinical signs, and the blood phosphates instead of going through the seasonal ebb noticed the year before, stayed up to the summer value. Incidentally it might be said that Hess gives egg yolk to bottle-fed babies as early as five weeks, sometimes giving only half a yolk.

About the same time some of the Johns Hopkins investigators cured seven colored children of rickets, in most cases severe, by adding one or two eggs daily to their diet of milk and cereal. Cure is usually a more difficult thing to accomplish than prevention and therefore an even more marked proof of the antirachitic potency of the egg. The results on rats were also confirmed.

Variations in eggs.—However, egg yolk is not an unvarying food. The diet of the hens and the amount of ultraviolet light which they receive both make a great difference in the vitamin D of the egg. For example, in Kansas, hens were divided into four pens, receiving, respective-

ly, sunlight in the yard and also thirty minutes' treatment with the quartz mercury vapor lamp, sunlight through glass and the same lamp treatment, sunlight in the yard alone, and sunlight through glass alone. Then their eggs were fed in addition to a basal rickets-producing diet to growing chicks. It will be remembered that chicks are satisfactory animals to use to study vitamin D, since they easily develop a disease similar to rickets.

The eggs produced without ultraviolet light (sunlight through glass) did not prevent rickets; those with considerable ultraviolet prevented it completely; and those with less (no lamp) allowed the development of slight rickets. These facts have been confirmed by Hart, Steenbock, and their co-workers, who increased the antirachitic potency of eggs tenfold by irradiation of the hens. Ultraviolet light falling on the hens, in other words, produces vitamin D in their eggs.

Cod liver oil, too, improves the eggs, for in Ohio hens kept indoors and fed a basal ration fortified by the addition of a small amount of cod liver oil (2 per cent of the ration) produced eggs which were five times as potent as those on the basal food alone, and other hens that had access to a luxurious blue-grass range gave eggs ten times as active as those from hens with the same basal ration but no direct sunlight and no grass.

Accurate comparison between the antirachitic potency of egg yolk, improved or unimproved, and cod liver oil has not been made so far as the authors know.

Fortunately, the nutrition of the public and the business of the poultryman seem to gain together, for ultraviolet light not only improves the quality of the eggs but increases the egg production greatly and the hatchability of the eggs. In an experiment at the University of Wisconsin a dozen hens without light treatment produced seventy-three eggs in a month and a similar dozen with ten minutes' irradiation daily, 173. The ordinary eggs showed a hatchability of 28.5 per cent, the others 63 per cent, both improvements of great monetary advantage.

These facts are back of the effort to further the use in henhouses of glasses permeable to the ultraviolet rays, and to install ultraviolet lamps under which the hens can run in groups for a few minutes a day during the winter months when egg production from untreated hens is at a minimum.

The suggestion has been made that poultrymen and consumers alike should recognize that the conception that "an egg is an egg" is a mistaken one, and that "an inadequate ration may yield impoverished eggs as well as animals." Eggs could well be graded on their vitamin content

(judged by the ration and management of the layers) as well as on appearance, size, freshness, etc., and such eggs might be demanded especially by hospitals and for infant feeding.

The richness of eggs in vitamin D is merely one of many reasons for their dietary value. Physicians and nutritionists are realizing that the excellent educational campaign for increasing the use of milk could well be supplemented by a similar one for eggs, to the great advantage of babies, children, and adults. The dairy industry is making use of its chance for educating the public; the egg industry apparently has not yet realized its possibly even greater opportunity.

COW'S MILK AND BUTTER

Butterfat, although a good source of vitamin A, contains relatively little of the antirachitic factor. In the samples examined by one group of investigators, the butter showed only one two hundred fiftieth as much antirachitic potency as the particular samples of cod liver oil tested, although the ratio of vitamin A in the two was 1:20 (Jones, Steenbock and Nelson).

Other samples of spring and summer butter assayed by Coward contained only 0.8 to 1.0 unit of vitamin D per gram, as compared with 50 to 150 units for cod liver oil. London milk, examined by the same investigator in the late fall (November, 1927) contained practically no vitamin D, but in the following summer it had a value of 0.2 unit per gram. The summer milk therefore contained approximately 50 units per cup or 200 units per quart, a small, but appreciable, quantity.

The quantity of vitamin D in cow's milk, and consequently in the butterfat, probably varies to some extent with the cow's ration. Particularly interesting is recent work in England (Golding and Zilva) showing that stall-fed cows on a good, practical ration, including silage, gave milk with a fair amount of vitamin D, whether or not cod liver oil was taken in such moderate quantities as two ounces daily. More cod liver oil, six or eight ounces, increased the antirachitic potency of the butter decidedly but decreased the percentage of butterfat in the milk. A poor winter ration, without silage or hay, poorer than would ordinarily be fed, resulted in a butter practically free from D.

The influence of sunlight for the cow, or even intense irradiation with artificially produced ultraviolet light, on the antirachitic potency of the milk is still an unsettled question. According to the University of Wisconsin investigators, irradiation made so slight an increase in the vitamin

D of the milk as to have "no practical significance from the standpoint of good milk production." On the other hand, two other groups of investigators report, one that the milk of cows irradiated with a quartz mercury lamp is markedly antirachitic as compared with that of non-irradiated cows (Gowen *et al*), and the other that when a cow on vitamin-free fodder is irradiated the milk has a doubtful clinical benefit when administered to rachitic infants, but is strongly antirachitic when fed to rats. In the rat experiments, the milk from these irradiated cows proved to be superior even to the milk of cows fed normally.

Goats, however, react differently in this respect, for the Wisconsin investigators found that irradiation practically doubled the antirachitic value of their milk. The reason for this difference in the behavior of the two animals is not clear. Differences in body area with respect to volume of milk produced may account for it. Other possibilities may be differences in thickness of the hide or secretory function of the skin or translocation of activated compounds.

HUMAN MILK

In view of the fact that rickets until recently probably has occurred in from one-third to one-half of breast-fed infants in the temperate zone (Laurens), a low antirachitic potency of human milk would be expected in laboratory experiments. However, since the incidence of rickets is lower in breast-fed than in bottle-fed babies, human milk would be expected to compare favorably with cow's milk in its antirachitic activity. Rather surprising, therefore, are Outhouse and Macy's recent laboratory observations. With very careful rat technique, making sure that the calcium-phosphorus ratio of the diet was always between 4 or 5 to 1, they compared the antirachitic potency of cow's milk with woman's milk, using for the latter mixed samples from the wet nurse bureau. They confirmed the presence of a moderate amount of D in cow's milk, but found that it is entirely lacking in human milk. Other investigators have found a very slight antirachitic potency in human milk, but less than in cow's milk (Hess and Weinstock).

Observations attempting to connect the diet of the mother and rickets in the babies are somewhat contradictory and difficult of interpretation. However, a recent study of a group of colored babies at Johns Hopkins Hospital does indicate that when cod liver oil is given to a mother a certain amount of the antirachitic vitamin passes into the milk. In this study, forty-seven infants were observed, the mothers of nine of whom

had no cod liver oil, while the remaining thirty-eight had been taking three teaspoons of cod liver oil daily from the birth of the baby until it was six months old. No cod liver oil was given to any of the babies. Although there were individual cases showing wide variation in the extent of rickets regardless of the cod liver oil, the average extent of rickets as judged both by X-ray and the calcium-phosphorus content of the blood serum varied inversely with the amount of cod liver oil taken by the mothers (Weech).

Irradiation of the mother, too, has been found to give encouraging results. A woman whose milk had been very low in vitamin D was irradiated for a month with a quartz mercury lamp. The antirachitic potency was decidedly increased as shown by the increased serum phosphate and marked calcification of the epiphyses of experimental rats to which the milk was fed (Hess and Weinstock). But interesting and important though these results are, the best way to protect a baby seems to be to give the cod liver oil or the irradiation to the baby direct, rather than to the mother (see page 191).

SOME FOODS WITHOUT VITAMIN D

Vegetables.—Vegetable foods, even the green vegetables so rich in vitamin A, are ordinarily lacking in D. Hess reports in an early article that neither spinach, green or yellow lettuce, nor green wheat added in large quantity to a rickets-producing diet could cure or prevent rickets in rats. An extract of dried spinach is even used in animal experiments when a source of vitamin A entirely free from D is desired. Other investigators since then have been able to demonstrate very slight antirachitic properties in cabbage and in fresh spinach, especially that grown in the open during the summer months. Without a doubt, however, the idea prevalent before the distinction had been drawn between A and D, that vegetables had marked antirachitic potency, has to be abandoned. In view of the facts reported in the next chapter on antirachitic activation of foods by exposure to ultraviolet light, it seems somewhat surprising that vegetables grown in the sunshine should have little or none. The explanation may lie partly in the relatively small amount of ultraviolet light in the sunshine and partly in its slight penetrating ability, "so that plants, unprovided as they are with any system for the translocation of lipoids, can not be affected to a high degree."

Yet the old adage to "make hay while the sun shines" seems to have at least slight dietary significance, for, according to Steenbock and Hart,

clover hay dried in the sun, without exposure to excessive weathering, had considerable antirachitic potency, while hay dried in the dark, though a fine green color, had none.

Vegetable fats, too, are not antirachitic. Bills has shown the lack in cottonseed, linseed, maize (from white maize), olive, peanut, and cocoanut oils, and hydrogenated cod liver oil. Occasional samples of cocoanut oil have been found to have potency, probably, according to Steenbock and Black, because they have been made from sun-dried copra. Commercial oleo and veal fat extracted with ether were also tested by Bills, with negative results.

LIMITED DISTRIBUTION OF D

Vitamin D is thus much the most limited in distribution of all the known vitamins, cod liver oil, other fish oils, egg yolk, and butterfat to a slight extent being practically the only naturally occurring sources so far discovered. It is plain that many children must grow up, and many men and women live from day to day with very little vitamin D in their food.

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CHAPTER IX

IRRADIATED FOODS AND IRRADIATED ERGOSTEROL

IRRADIATED FOODS

As long ago as 1924 the striking observation was made almost simultaneously by Hess and by Steenbock and Nelson that many foods could be made antirachitic by irradiation with ultraviolet light. Some of the first successes in this line have already been referred to in earlier chapters: Hess' demonstration that his irradiated cottonseed and linseed oils were as potent as cod liver oil to cure rickets in rats; Steenbock's similar showing with his whole irradiated diet; and, particularly significant, Steenbock and Daniels' proof that even non-rachitic babies could have their calcium retention increased by feeding irradiated olive oil instead of ordinary olive oil. Daniels' later article is even more striking than this earlier work. As has already been quoted in discussing the good effects of antirachitic treatment on calcium and phosphorus balances of normal babies (chapter iv), she found her irradiated milk and her irradiated olive oil both more effective than cod liver oil. The reason for this superiority she is unable to explain. She suggests that the milk and the oil, which were irradiated in her laboratory under constant conditions, were very uniform and also that perhaps not a large enough dose of cod liver oil was fed. Our interest here is less in comparison with cod liver oil than in the fact of the high potency for children of these two irradiated foods.

The foods which have been successfully irradiated include a long list: numerous oils and fats—olive, cottonseed, linseed, corn, and cocoanut oils, lard, oleomargarine, and butter, but not mineral oil; cereal products—refined wheat flour, whole wheat flour, shredded wheat, cream of wheat, oatmeal, cornmeal, cornstarch; meat; milk, whole or dry; various vegetables; orange juice. The potency of egg yolk was increased from ten to twenty times. Sugar is almost the only natural food for which attempted irradiation has been unsuccessful; rancid oils, too, cannot be activated, apparently because the activatible substance is destroyed during the development of the rancidity.

Irradiated milk.—Naturally enough, milk is one of the foods whose irradiation has been especially studied, not alone by Daniels but by

numerous others. If this common food, with only moderate antirachitic potency, could be made a real preventive of rickets, its possibilities for good would seem to be much increased.

Numerous experiments besides Daniels' have been described in which irradiated milk has been fed with success both to animals and children. For example, in Baltimore, eight young children with active severe rickets, when put on a diet of orange juice, cereal, and irradiated milk, showed marked or complete healing in four weeks. The serum phosphate increased to approximately normal, and there was marked increase in the calcium and phosphorus retained by the two children on whom balance experiments were made. Hess, also, and Cowell, in England, have successfully experimented with irradiated milk, and recently a German investigator reports treating about sixty rachitic children with fresh, fluid milk which had been exposed to ultraviolet rays in an atmosphere of carbon dioxide so that it had no unpleasant taste or odor. Of the twenty-four reported in detail, ranging in age from 3 months to 2½ years, all were cured or much improved by giving them from 300 to 600 cc. daily for from four to five weeks. For eighteen premature infants as small a quantity as from 10 to 25 gm. daily served successfully as prophylactic against rickets. The cost of the treatment was about one-tenth that of direct irradiation of the children.

On the other hand, some children that were given all the milk in their feeding formula in the form of irradiated, powdered whole milk did better than others with only 25 per cent of their milk irradiated, the first group showing almost complete protection from any sign of rickets, the second showing only fairly good results (De Sanctis *et al*). With not only the human variable but the variable in method of treatment of the milk, such slight contradiction in results is to be expected.

Hess and his co-workers in a recent number of the *Journal of the American Medical Association* (August 31, 1929), writes:

> We have had no clinical experience with irradiated fluid milk, which is being dispensed in some of the large communities of Europe, notably Frankfort and Basel Irradiated dried milk has, from the outset, seemed to be a valuable preparation. It has a definite antirachitic property which is not lost by ageing, nor is its content of vitamins A and C essentially diminished during the course of activation. This product is of moderate potency and is suited for preventive rather than for curative purposes; it is not adequate in itself to protect premature infants.

These are only a few of the satisfactory experiments reported on children. Yet a recent German paper, which has been much quoted, entitled, "Toxicity of Foods after Exposure to Ultraviolet Rays," gives rather incomplete data showing pathological changes in blood, spleen, kidneys, and myocardium of mice and guinea pigs fed irradiated milk and other irradiated foods. The results are so contrary to those of other investigators that one tends to be hesitant in accepting them, though of course they make one cautious about overconfidence. The possibility of harm from overdosage of irradiated ergosterol is discussed later.

Other foods.—Few experiments on children have been carried out with irradiated foods other than milk. In the author's laboratory at present, balance experiments are in progress with two young children, a girl of two and a boy of four, using ordinary and irradiated Quaker oats as important constituents of the diet, but too few results have so far been secured to report.

TABLE XV

ASH OF BONES OF RATS FED NON-IRRADIATED AND IRRADIATED CEREALS

Cereal	Non-Irradiated	Irradiated
Farina	29.4	51.6
Muffets	43.2	52.7
Pettijohn's	30.9	49.2
Quaker oats	36.0	51.6
Macaroni	32.9	48.0

Dr. Steenbock has courteously given the authors the data in Table XV on the ash of the fat-free bones of rats fed irradiated and non-irradiated cereals for five weeks. The figures, which are averages of analyses on four animals, in each case plainly show the potency of the irradiation.

It must be remembered in transferring the results of these animal experiments to human feeding, that the diet of the animals may contain a much larger proportion of the irradiated food than the diet of a child usually can. Steenbock gets his very striking results on the increase of the bone-ash of rats by incorporating in the rations 76 per cent of the different cereals—irradiated or non-irradiated. When Bacharach and Jephcott distinguished samples of cereal irradiated 5, 15, and 30 seconds from one another and from non-irradiated by means of the lowering of the fecal pH (see chapter iv, page 40), they made the cereal 25 per cent of the rat's diet. A young child eating even a generous quantity of cereal will probably make it not more than 10 or 15 per cent of the total solids

consumed, so that effects as striking as those with animals are hardly to be expected.

Methods of activating milk and other foods.—For milk, possibly even more than for other foods, the conditions of activation may make great differences in the product. Too long irradiation develops a disagreeable taste and odor, variously described as fishiness or rancidity. Twenty minutes will do this, or even in some cases five. There is considerable evidence that the change really is due to rancidity and resembles that produced in commercial fats and oils by exposure to light and heat and oxidation. Positive test for nitrites in the milk has also been secured. Long irradiation may also have the harmful effect of destroying vitamin A, so that gain of one vitamin may be overbalanced by loss of another.

It has been thought that atmospheric oxygen hastened the objectionable actions, so irradiation has been carried on in carbon dioxide and in nitrogen, but now it seems more probable that the ozone generated by the short radiations of light does the harm and that adequate ventilation during the process lessens it.

Short exposure, however, with its diminished danger of unpleasant change seems to be entirely successful. Supplee and Dow report that by thirty seconds to three and one-half minutes' radiation a milk can be produced with enough antirachitic potency to cure rachitic rats and decidedly increase the ash in their bones and to prevent the development of rickets. Oils and other foods reported from laboratories have generally been exposed for longer times than milk—usually thirty minutes.

The process consists of exposing the material in a thin layer, often not more than an eighth of an inch, at a distance usually of about two feet, to the quartz mercury vapor lamp, the food sometimes being passed slowly under the lamp or series of lamps. The carbon arc has also been used as the source of ultraviolet.

The stability of the activation.—Apparently the antirachitic activity thus developed in foods is fairly permanent. Tests made on activated olive oil, kept for months after irradiation in a stoppered bottle in the dark, showed its value unchanged; and irradiated dried milk kept for six months in a cupboard under ordinary conditions had lost but little of its potency, and even after a year it had deteriorated only moderately. Some irradiated spinach and lettuce were just as active after cooking as before. Even the violent chemical procedure of boiling with alcoholic alkali, as in saponification of an irradiated oil, does not destroy the active substance.

The potency *is* lost when exposure to ultraviolet radiation is carried

out too long. Activated olive oil lost its activity after seventeen hours' exposure to ultraviolet light, and so even did cod liver oil.

THE WISCONSIN PATENTS

The commercial situation for these irradiated foods is very unusual. Dr. Steenbock at the University of Wisconsin has patented the process of irradiating foods and medicinals by ultraviolet light, but he has assigned his patent to an organization formed for the purpose of receiving it—the Wisconsin Alumni Research Foundation. The Foundation may license manufacturers desiring to use the process and control their procedure, their product, and even their advertising. An illustration of the control is Steenbock's laboratory report (see page 127) on five irradiated products. Profits from the licenses go to the Foundation, not to Steenbock himself, and the profits promise to be large. Rights to manufacture under the patent have already been sold to the Quaker Oats Company, who have two of their irradiated cereals on the market, to the Fleischmann Company, who are selling irradiated yeast, and also to other companies in the United States, England, and Germany.

WHAT WILL FOOD ACTIVATION DO FOR THE GENERAL HEALTH?

What these irradiated foods will accomplish for public health is difficult to foretell. The possible value seems very great. With the limited natural distribution of vitamin D and the limited sunshine of northern winters, a cheap, palatable, readily available food with antirachitic potency may be an important contribution to national health. "Taking your daily dose of sunshine as you eat," as one of the popular writers has it, is very appealing and may be very valuable. Commercial enterprise, however, may exploit to a foolish extent an agency valuable in moderation and unnecessarily bring up the cost of food by an added more or less expensive process. (The Quaker Oats Company sells irradiated cereal with no advance in price over the non-irradiated.) An important possible though not probable disadvantage will shortly be brought out more in detail in the section on irradiated ergosterol—there is real danger in excessive doses of this antirachitic factor. It is conceivable that a child of anxious parents, given cod liver oil and light treatments and irradiated food, might come to serious harm.

The future will thus have to tell more definitely the value of these irradiated foods. It looks now as if wisely and conservatively used, they are a valuable discovery.

IRRADIATED ERGOSTEROL AND THE CHEMISTRY OF VITAMIN D

The question naturally arises as to the chemical composition of vitamin D. What is the substance in cod liver oil or in activated foods which gives them their antirachitic potency? The definite answer has not yet been obtained but a rather surprising amount of information pointing toward it is already in hand. The main discoveries in connection with it brought the Nobel Prize to the German investigator Windaus and the honor of academic priority to Hess.

Unsaponifiable fraction the potent part of fats.—First of all the vitamin is not a fat, but when cod liver oil is saponified by boiling with sodium or potassium hydroxide, the small unsaponifiable fraction which may be extracted from the soap by ether is found to possess all the antirachitic potency of the original oil. It is as effective in promoting calcium assimilation as shown by improvement, for example, in the calcium balance of animals as equivalent amounts of the cod liver oil from which it came. The unsaponifiable portion of inactive fats and oils, like the oils themselves, is inactive except when the oil has been made active by irradiation.

Composition of the unsaponifiable fraction.—The unsaponifiable fraction of oils and fats has long been known to consist largely of sterols (solid alcohols), chief among which are cholesterol in animal fats and phytosterol in vegetable oils. Cholesterol, the best known, occurs also in the brain, skin, and blood—in fact in very small amounts in every cell of the body. A third sterol, ergosterol, very similar in composition to cholesterol but more unsaturated, can be extracted in relatively large quantities from fungi, yeast, and mushrooms, and especially from ergot. Its formula is $C_{27}H_{42}O$, while that of cholesterol is $C_{27}H_{46}O$. Until very recently ergosterol was thought not to be present in animal cells and to have no biological significance, but current experimental work is showing the facts of its distribution to be quite otherwise.

Cholesterol or ergosterol as the provitamin.—Since cholesterol is the chief component of the active unsaponifiable fraction of cod liver oil, it was logical to discover whether cholesterol from other sources which were themselves inactive could be activated by ultraviolet radiation. In 1925, Hess and Weinstock, and Steenbock and his co-workers both reported that the purest cholesterol then obtainable when treated with ultraviolet light developed marked antirachitic potency. The hypothesis was therefore tentatively brought forth that cholesterol might be the parent substance from which vitamin D is formed by ultraviolet light.

But this hypothesis was short lived, for further purification of cholesterol has since given a product which on irradiation either does not develop antirachitic potency at all or develops it to a very slight extent. (Bills and Honeywell find that such very pure cholesterol does bring about slight healing of rickets when reirradiated and fed in quantities thirty times as great as the original active "pure" cholesterol, an effect which they believe due not to a small amount of persisting impurity but to the very weak activability of the sterol itself.)

Meanwhile, before the experiments on this highly purified cholesterol had given such definitely negative results, work begun on the little known ergosterol had shown it to possess the remarkable property of acquiring antirachitic potency on irradiation to an extent two thousand times as great as cholesterol, and also had proved it to be the contaminant of the ordinary "pure" cholesterol. The extraordinary activity of irradiated ergosterol has been demonstrated by numerous investigations on rachitic rats, on puppies, and even on children. Its beneficial effect upon blood calcium and phosphorus levels, upon the retention of calcium and phosphorus, and upon the calcification of the bones are immediate and spectacular. Amounts as minute as 0.0002 mg. are sufficient to give a positive line test in rachitic rats or, in terms of other workers, samples have been obtained a million times as active as average cod liver oil.

Light absorption observations.—Much of the advance in knowledge about the activation of ergosterol and cholesterol has been made by a method heretofore little used by biochemists—the study of their absorption of light.

Solutions of many chemical compounds have the property of absorbing light of definite wave-lengths, so that their "absorption spectrum" is as characteristic of them as any of their other physical properties, such as melting-point or optical activity. To obtain the absorption spectrum the investigator has first a light source containing ultraviolet radiations; second, a quartz prism through which the light passes to form the spectrum; then the solution to be tested contained in a quartz vessel through which the spectrum is passed; and finally a sensitive photographic plate upon which the spectrum is recorded. If the liquid in the quartz vessel is one which does not absorb light, such as pure alcohol, the photograph gives the continuous spectrum from the light; but if it is a solution of ordinary cholesterol or of ergosterol, certain definite bands appear as dark spaces in the spectral photograph, showing that light of these wave-lengths is absorbed by the solution.

It was found early that the absorption bands observed in ordinary pure cholesterol diminish in intensity on repeated purification and finally disappear. The purest cholesterol in 3 per cent solution does not show selective absorption. Pure ergosterol, however, shows intense absorption bands with maximums at exactly the same points as those for ordinary cholesterol—293.5, 282, and 270 mμ, and also a faint but distinct line at 260 mμ.[1]

Bills and Honeywell, working with MacNair, of the Bureau of Standards, found that a solution containing 0.0030 per cent of ergosterol gave slightly less intense absorption than a 3 per cent cholesterol solution, and one with 0.0040 per cent ergosterol slightly more intense. They therefore could compute that their cholesterol contained 0.12 per cent ergosterol. Interestingly enough, they obtained exactly the same result by a method chiefly chemical—following the decomposition of the ergosterol by potassium permanganate—so that they had corroboration of their spectroscopic procedure (see Fig. 30).

So much for a clear-cut difference between cholesterol and ergosterol. Ergosterol can absorb certain light energy, and cholesterol[2] cannot. Ergosterol develops antirachitic potency on irradiation, and cholesterol does not. What are the changes brought about by this light energy?

Changes taking place when ergosterol is irradiated.—Knowledge on this point is still far from complete, but by parallel spectroscopic, biological, and chemical methods, progress is being made. First, a report of a biological and spectroscopic investigation by Bills and his co-workers. By carefully controlled irradiation and their feeding methods already described, they found that in 7½ minutes' irradiation their ergosterol had attained a potency of 150,000 on this scale (average cod liver oil being 100), in 15 minutes 225,000, and in 22½ minutes 250,000. On further irradiation the potency went down sharply: in 30 minutes to 200,000, in 2 hours to 50,000, and in 3 hours it had almost vanished. That is, the tremendously active vitamin D is first formed from ergosterol and then decomposed (see Fig. 31).

Change in the absorption bands of the ergosterol did not come quite

[1] It is particularly interesting that the light-waves which ergosterol absorbs and which activate it are so close to those which have so far been proved especially active in the cure of rickets by direct irridation of the animal—302 and 265 mμ.

[2] Bills, Honeywell, and MacNair found that a strong solution of their purest cholesterol does show faint absorption bands when the light is passed through a deep layer of it, bands different from those of ergosterol and far less intense. This is in accord with the very faint antirachitic potency of the cholesterol.

so soon as change in the antirachitic potency. When the potency was at its height, the absorption was almost the same as for the original non-

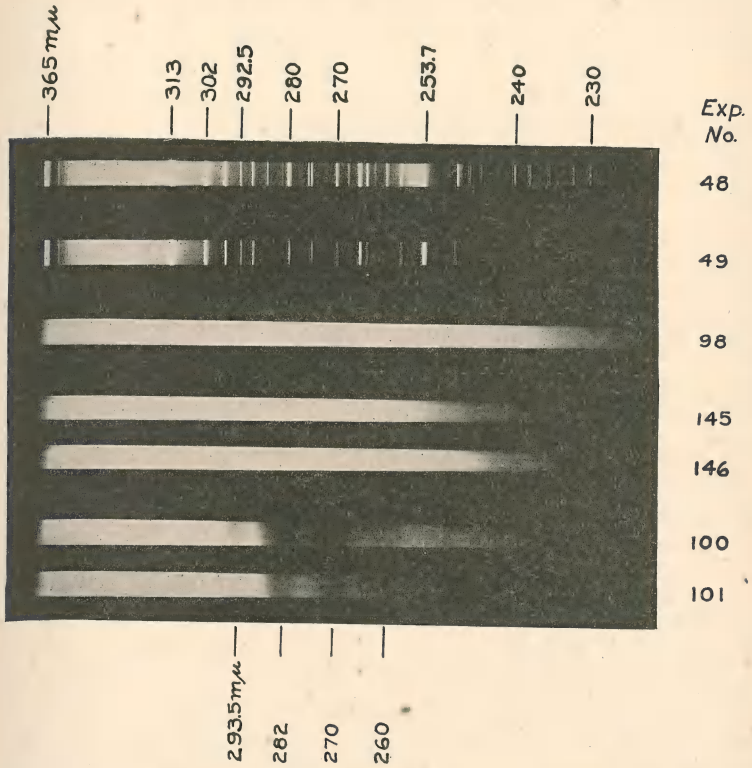


FIG. 30.—Seven absorption spectra of cholesterol and ergosterol, selected from 200 exposures:

Exposure 48: Mercury arc through 2.0 cm. of ether.

Exposure 49: Same through 2.0 cm. of 3.0 per cent solution of ordinary cholesterol (Cholesterol A).

Exposure 98: Special discharge tube through 2.0 cm. of ether.

Exposure 145: Same through 2.0 cm. of 3.0 per cent solution of cholesterol purified by charcoal (Cholesterol B).

Exposure 146: Same through 2.0 cm. of 3.0 per cent solution of cholesterol purified by bromine (Cholesterols C, D, E, or Windaus).

Exposure 100: Same through 2.0 cm. of 0.0040 per cent solution of ergosterol.

Exposure 101: Same through 2.0 cm. of 3.0 per cent solution of ordinary cholesterol (Cholesterol A). (From Bills, Honeywell, and MacNair, *Journal of Biological Chemistry*, LXXVI [1928], 261).

irradiated ergosterol, showing that considerable of the unchanged ergosterol was still present, and possibly that vitamin D has much the same absorption spectrum as ergosterol. On continued irradiation, as the potency declines, the ergosterol bands diminish in intensity and finally dis-

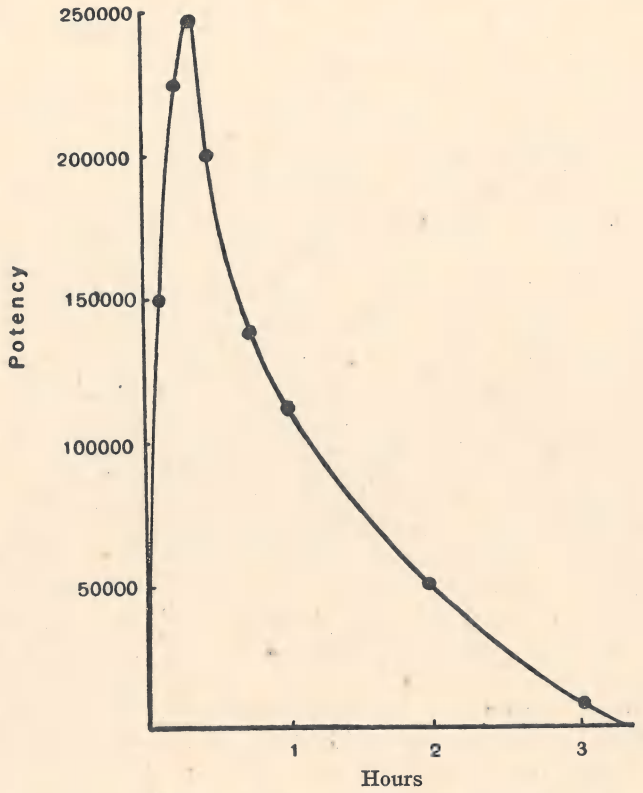


FIG. 31.—Effect of irradiation on the antirachitic potency of ergosterol. (From Bills, Honeywell, and Cox, *Journal of Biological Chemistry*, LXXX [1928], 560.)

appear, and meantime a new band comes at 248 mμ. This new band must be due to the formation of a new substance, not vitamin D, for its appearance coincides with the destruction of antirachitic potency. Finally, on keeping up the irradiation for 15 hours, this line at 248 mμ also goes. The story, therefore, as Bills sees it, is that irradiation of ergosterol produces at least two substances, the unstable vitamin D and another less unstable, antirachitically inactive substance which may come more slowly from the ergosterol or may be a decomposition product of D.

A beginning has also been made in following the chemical changes on irradiation. Ergosterol, like cholesterol, has the property of forming an insoluble substance with digitonin. With non-irradiated ergosterol the precipitation is complete and the filtrate contains only traces of material. With the irradiated, however, precipitation is not complete and the filtrate gives on evaporation a transparent, glassy, hard solid, much more soluble in alcohol than ergosterol and having an entirely different melting-point and different absorption of light. It has all the antirachitic power of the irradiated ergosterol; it is, or much more probably it contains, the vitamin D (Webster and Bourdillon).

The biophysicist is interested in the amounts of light energy required to form vitamin D from ergosterol. Investigators at the University of Wisconsin by experiment and computation have come to conclusions that will be given only briefly here. To make enough vitamin D for a minimum biological line test on a rat requires 700–1,000 ergs. This value is constant for radiations of a number of different wave-lengths—256, 265, 280, and 293 mμ. From this energy measurement, making use of Einstein's law of photochemistry, it is possible to compute the number of molecules of vitamin D formed, 10×10^{13}; and from this by Avogadro's number and the assumption that the molecular weight of vitamin D is essentially the same as that of cholesterol, the minimum weight of vitamin necessary for a positive line test, or 6×10^{-8} grams, may be estimated. Coward, by use of irradiated ergosterol of maximal potency, considers that she has confirmed this prophecy as to the minimum quantity of D for a positive line test.

Distribution of ergosterol.—This sterol, as already stated, is found in largest quantities in ergot and in yeast, but it also seems to occur wherever cholesterol is found. All samples of cholesterol so far tested for ergosterol have contained it in small amount—from cod liver oil, brain, spinal cord, gallstones, skin, blood. It has been detected in the eggs, brain, liver, spleen, and ovaries of the lower forms of animal life, and it has been isolated from beef blood in almost pure form, and even from human blood it has been separated and identified by its characteristic absorption bands. Phytosterol, too, the sterol common in plants, is accompanied by ergosterol. It appears to be the most widely distributed of all sterols.

Recrystallized sterol from red blood cells containing ergosterol or some closely related sterol has been tested on rats for antirachitic potency at the University of Stockholm. Irradiated, it showed much activity, but

even without irradiation it had some effect—quite startling indication of the presence of vitamin D in the animal's circulation.

Further information about the distribution of ergosterol is highly desirable, and especially quantitative information. We are probably justified in assuming that the extent to which any food can be irradiated depends at least in large part upon the amount of ergosterol it contains. We can feel fairly sure, for example, that oils with their relatively high proportion of sterols can be more strongly activated than cereals with their smaller quantity, but our knowledge is very far from accurate.

Color reactions of irradiated ergosterol.—In addition to the changed absorption spectrum and the failure to precipitate completely with digitonin, irradiated ergosterol shows certain other reactions which the non-irradiated does not. For example, irradiated ergosterol gives a violet color with fuchsin-H_2SO_4 reagent, while the non-irradiated does not, and it will also reduce ammoniacal silver oxide to a stable colloidal silver solution while the non-irradiated will not. It also gives a red color on boiling with aniline hydrochloride as do oils which contain vitamin D, and as also do certain unsaturated ketones. These reactions suggest that irradiation has transformed the original substance into an aldehyde or an unsaturated ketone; that vitamin D may itself be a ketone, or else that a ketone is produced with the vitamin on irradiation of ergosterol.

Effect of changes of temperature on vitamin D.—Vitamin D appears to be fairly resistant to heat and cold if dissolved in a neutral medium. An exposure of one hour to temperature down to —60° C. does not destroy it and heating for 1½ hours at 130° hardly affects it. There is slight destruction if heated to 140–145° for 1½ hours, and almost complete destruction if heated for the same length of time at 165–170°. It is, however, destroyed much more rapidly if heated in either acid or alkaline solution. In this case heating for one hour at 100° is sufficient to destroy it if the acid or alkali is of tenth-normal strength.

The unique position of ergosterol.—Several other sterols are known which are associated with ergosterol in yeast or ergot as well as a number of other compounds closely related chemically to cholesterol or ergosterol. It was a point of interest to find whether any of them behaves like ergosterol. No one of them so far tested has been found to have absorption bands in the ultraviolet and, as would be expected from this fact, no one has been given antirachitic potency by irradiation. This work has strengthened the theory that ergosterol is unique, is in fact the parent substance of vitamin D.

IRRADIATED ERGOSTEROL FOR CHILDREN

The discovery of the remarkable power of irradiated ergosterol to cure rats with rickets was promptly followed by tests of its power to cure rachitic children, and from many clinics where it has been used come glowing accounts of the rapidity and reliability of its action. Dr. Alfred Hess has called irradiated ergosterol "one of the most remarkable of specifics," and other physicians have pronounced it the "therapeutic agent of choice" both for rickets and tetany.

An important reason for the enthusiasm for irradiated ergosterol lies in the fact that because of its tremendous potency the dose needed is very small, usually from 1 to 4 mg. daily. For a dose of this size only 2½ to ten drops of a 1 per cent solution of irradiated ergosterol in oil are needed. Such a dose has been calculated to be the equivalent of from 14 to 56 teaspoons, or more than 1 cup, of a good grade of cod liver oil![3]

The practical advantages of giving maximum quantities of vitamin D with minimum quantities of oil are apparent, especially for children whose digestive systems are weak and who therefore cannot tolerate large quantities of fat. Such children, if they have rickets, often cannot take as much cod liver oil as they need to cure them and healing takes place very slowly, if at all. They improve very quickly, however, on irradiated ergosterol. A number of cases of this kind have been described within the last year, several of them by Hess and Lewis, who report a rapid disappearance of the signs of rickets after two or three weeks on irradiated ergosterol, when 3 teaspoons of cod liver oil given daily for five weeks had previously proved ineffective.

Even the normal infant, especially if he is growing rapidly, may benefit by the use of this new compound, since occasionally the standard dose of cod liver oil—1 teaspoon three times a day—fails to protect him from at least a mild degree of rickets. More than 3 teaspoons of oil a day is usually not considered wise for any baby and, according to Hess, not more than from 6 to 8 teaspoons can be given under any circumstances. Therefore, a more concentrated form of the vitamin is needed for prevention as well as for the cure of rickets.

A second advantage of irradiated ergosterol over other forms of antirachitic treatment is the speed with which results are obtained. During

[3] These figures are based on work with the early, unstandardized preparations of irradiated ergosterol. "Viosterol," the new, standardized product is much less concentrated, the prophylactic dose of from 8 to 10 drops being the equivalent of about 3 to 5 teaspoons of cod liver oil (see p. 146).

the last two years numerous instances of remarkably rapid cures have been described. At the Hospital for Joint Diseases in New York, Doctors Sobel and Claman have for a number of months been treating a selected group of children with a commercial preparation of irradiated ergosterol (vigantol). In some instances they describe the effects to be "not only prompt but . . . . dramatic" as when they found it not uncommon for a marked case of craniotabes (softening of the bones of the skull) to be cleared up in two weeks. Very rapid calcification of the ends of the long bones, often beginning in two weeks and becoming marked in four, also occurred in cases of active rickets, and the inorganic phosphorus of the blood which was low to start became normal in from a week to ten days. Such remarkably rapid healing has never been obtained with any other method of treatment.

Infantile tetany also yields promptly to dosage with irradiated ergosterol. Doctors Bakwin and Bakwin, of New York City, have compared the time required to obtain results with irradiated ergosterol, ultraviolet radiation, and cod liver oil, and have come to the conclusion that irradiated ergosterol is much to be preferred. Cod liver oil, in comparison, is "slow" and "inconstant"; in one case convulsions occurred nine days after the oil was begun, and in others the blood calcium returned to normal only after sixteen or more days of treatment. With ultraviolet light the blood calcium rose to normal levels in fourteen days, but with irradiated ergosterol the calcium became normal in an average of seven days. The clinical symptoms disappeared at once, convulsions being present in only one case out of fifteen after the first day.

Many other instances of spectacular results obtained with this new compound might be quoted. Hess in 1928 summed up these studies with the following statement: "In all cases this new therapeutic agent has been found to be reliable in the prevention as well as in the cure of rickets . . . . its action has been remarkably rapid, all signs of rickets disappearing more quickly than has been accomplished heretofore with cod liver oil, its concentrates, or with direct irradiation."

After another year's experience with this substance, he now writes (August 31, 1929):

> Beginning in October (1928), a large group of infants was given . . . . irradiated ergosterol in various amounts, ranging from minimal doses to what might be considered generous amounts. . . . . Our results were well defined and can be summarized in a few words. . . . . Full term infants were protected from rickets, almost in every instance, except when the smaller amounts were given. . . . . In an occasional case, mild beading of the ribs, craniotabes or bowing of the legs developed. Of course the spectacular healing, for example, of craniotabes, which was brought about by large amounts of irradiated ergosterol cannot be expected when much smaller amounts are given. In spite of partial failures, irradiated ergosterol must be regarded as one of the most remarkable of specifics. In therapeutics there is no such thing as an absolute or infallible specific; all fail to a certain extent occasionally.
>
> It will be noted that emphasis has been laid on the success of treatment in infants that were born at full term. It is highly important that this distinction should be borne in mind, for it will be found, not infrequently, that preparations of irradiated ergosterol given in adequate doses will fail to protect rapidly growing premature infants. As will be brought out in the discussion of dosage, such babies require very large amounts of irradiated ergosterol, and even when this precaution is observed it may be found that rickets has not been entirely prevented.

DANGERS OF IRRADIATED ERGOSTEROL

Enthusiasm for irradiated ergosterol must, however, be tempered with caution, since, like many other potent drugs, large doses of it may be distinctly dangerous. In this respect it may be compared with the internal secretions of glands, such as the thyroid or the pancreas, which in minute quantities are absolutely essential for normal physiological activity but which in large quantities function as violent poisons. The comparison becomes the more vivid if we assume, as is entirely possible, that vitamin D promotes calcification in the body through the stimulation of the parathyroid glands (see page 201).

Fatal effects of very large doses.—One of the earliest investigations designed to demonstrate the effects of large doses of vitamin D was that of Kreitmair and Moll, two workers in the research laboratories of a large chemical and drug manufacturing firm in Germany. In the course of this investigation it developed that exceedingly large doses, at least ten thousand times the minimal protective dose, caused a rapid loss of weight, followed by death within a short space of time, not only in white mice and rats, but also in guinea pigs, rabbits, cats, and dogs. All of these animals presented the same picture of definite and severe disease—loss of appetite, rapid loss of weight, severe emaciation, and decided decrease in vigor. They often developed a diarrhea, and the hair became rough and shaggy. Death followed in varying lengths of time for different animals, from an average of ten days for the rabbit to thirty-six days for the guinea pig.

Pathological changes in the tissues.—After death enormous deposits

of calcium were found in the walls of the blood vessels and of the vital organs, heart, stomach, and kidney, evidence that calcification had been stimulated to the point where the mineral was deposited in any and all tissues which would receive it, whether or not it was needed or even useful there.

These experiments have been repeated and similar results obtained by a number of other investigators, notably Drs. Smith and Elvove, of the United States Public Health Service, Dr. I. J. Klein, of the Jewish Hospital of Brooklyn, by a group of experimenters working in Spain, and by L. J. Harris, Thomas Moore, and C. P. Stewart, in England.

Blood calcium and phosphorus.—In only a few of these studies have the figures for blood calcium and phosphorus been determined. Whenever such determinations have been made, a striking rise in blood calcium or phosphorus or both has been observed. Klein reports a 50 per cent increase in the serum calcium of his rats although the phosphorus remained practically unchanged, while Harris and his associates observed a 25 per cent rise in the blood calcium and a 50 per cent increase in the inorganic phosphorus. The urine in the latter animals also was "literally saturated" with calcium salts. Evidently there had been a marked overflow of calcium from the blood into the urine, but in spite of this, and in spite of the huge deposition of calcium in the tissues, the concentration of calcium in the blood still remained far above normal.

Calcium content of the skeleton.—Apparently the high concentration of calcium and phosphorus in the blood is maintained at the expense of the deposits of these minerals in the bones, for Hess reports that the bones of rats after fourteen days of excessive dosage with irradiated ergosterol contained only 48 per cent of ash as compared with 52 per cent in the bones of normal controls. He also quotes Hottinger who found that very large amounts of irradiated ergosterol, when given to puppies, led to negative instead of positive balances of calcium and phosphorus.

Effects of size of dose.—The toxic effects of excessive doses of vitamin D appear to be in direct proportion to the size of the dose. Early work in Germany showed that when 2 mg. of irradiated ergosterol was fed daily to a group of white mice, sickness and death occurred within a very short time, in some cases within a space of six days. On 1 mg. a day the mice became sick but lived somewhat longer. Half a milligram daily produced only a loss of weight without further illness, while 0.2 mg. was taken without any apparent ill effects.

More recently Harris and Moore have made similar observations. It has been their experience that irradiated ergosterol fed as 0.00001 per cent of the diet will protect their rats from rickets. When the irradiated ergosterol is increased to 0.1 per cent of the diet, one hundred thousand times the minimal protective dose, there is an immediate and rapid loss of weight, calcium is deposited in the tissues in enormous quantities, and death follows quickly. Intermediate doses are followed by proportionate effects. With irradiated ergosterol at 0.025 per cent of the diet, the animals fail to grow, but do not actually lose weight, and there is a considerable lengthening of the period before they finally succumb. At 0.001 per cent, growth is not quite so good as at 0.00001 per cent, but there are no symptoms of poisoning.

Influence of age of animal.—Harris and his associates, unlike the majority of workers in this field, have with a few exceptions used young and growing animals (rats and rabbits), instead of adults. Invariably the same pathological changes have been seen in the young animals as were reported in the older ones. In the few instances in which Harris and his colleagues have themselves used older animals, the only difference in reaction which could be noticed was a difference in time, the older animals being more resistant and surviving for a longer time than the younger ones.

Possibilities of recovery.—If the excessive doses of irradiated ergosterol are discontinued, the animals usually make a rapid and complete recovery. Appetite is regained, growth at the normal rate is resumed, and the abnormal calcium deposits very largely disappear.

Effect of solvent and possible by-products of irradiation.—Toxic effects similar to those produced by irradiated ergosterol have sometimes been observed when very large doses of irradiated food, especially milk, have been fed to animals, and the suggestion has been made that the toxicity might be due, not to vitamin D, but to nitrates or other substances developed as by-products of the irradiation of the material itself, or of the substance in which it is dissolved.

As evidence against this theory, Harris and his associates submit first of all the fact that no matter how a sample of ergosterol may be irradiated, whether dry, in an atmosphere of nitrogen in a quartz flask, or in solution in alcohol, or dissolved in oil, it still exhibits the same toxic properties when given in excess. At the International Physiological Congress in the summer of 1929, Bills reported marked differences in *potency*, depending upon the solvent in which the ergosterol is dissolved for irradiation. His new curves showing this are given in Figure 32. The differences

in toxicity observed by other investigators may therefore be due to variations in potency of the irradiated ergosterol rather than to any by-products which might be formed.

Further and more convincing evidence that it is the vitamin D itself that is dangerous is the fact that overirradiated ergosterol in which practically all of the vitamin has been destroyed no longer produces any undesirable effects. To establish this point, Harris and Moore took some of

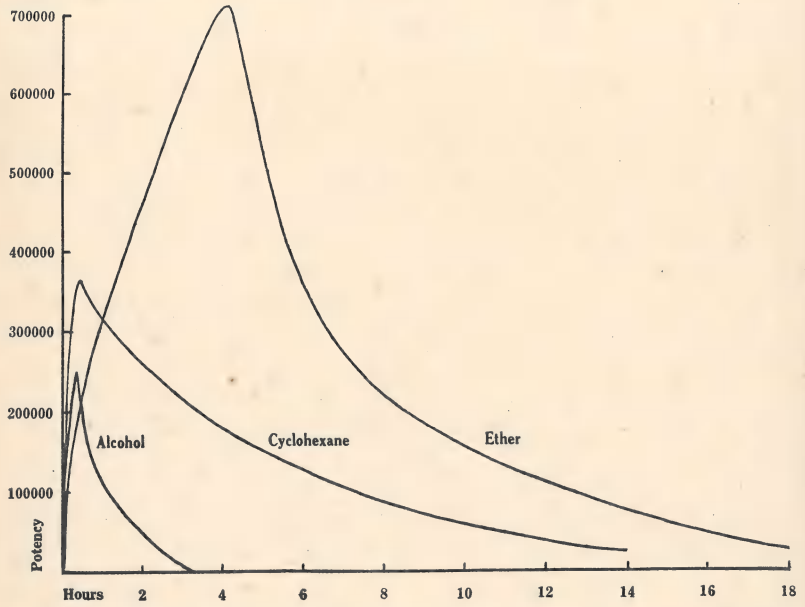


FIG. 32.—Effect of the solvent on the potency of irradiation of ergosterol. (From Bills.)

the same irradiated ergosterol, which they had already shown to be toxic when fed in large doses (0.1 per cent of the diet, or 10 mg. in 10 gm. of food), and irradiated it for twenty-four hours longer. This overirradiated ergosterol retained only one-thousandth of its former vitamin D content as was definitely proved by tests on rachitic rats, and was entirely harmless when fed again in the same large quantities.

It is likewise true that very large doses of cod liver oil, or of its concentrates, will produce some of the results obtained with irradiated ergosterol. For example, Hess reports that excessive amounts of the oil may lead to a loss of inorganic salts from the skeleton and also that the blood

calcium of young rats may be raised to abnormally high levels by 30 to 40 times the minimal protective dose. "The reason hypercalcemia (abnormally high blood calcium) rarely develops in infants as a result of cod liver oil medication" he writes, "is simply that one cannot give more than about from 6 to 8 teaspoonfuls daily."

It seems very probable, then, that it is the vitamin D itself which is responsible for the harmful effects of the irradiated ergosterol. Apparently, although small quantities of the vitamin are essential for normal calcification, large quantities will stimulate the process, in certain tissues



FIG. 33.—Effect on the white rat of excessive doses of irradiated ergosterol. (From J. A. Callazo, P. Rubino, and B. Varela, *Biochemische Zeitschrift*, CCIV [1929], 347.)

at least, to the point where it is fatal to the organism. Harris and Moore have suggested

that there are two threshold values for vitamin D, a minimum and a maximum. Below the minimum, there result deficiencies in blood-phosphorus, or -calcium (or both), and a consequent deficient calcification: the primary factor is a diminished retention of these two elements. Above the maximum threshold value on the other hand, there result excessively high blood-phosphorus or -calcium (or both) and a consequent excessive calcification. To some extent, as we have seen, the blood-calcium in hypervitaminosis is prevented from reaching too high a level by increased precipitation of calcium deposits and by excretion.

Possible harm to children from the use of irradiated ergosterol.—That possible harm might come to children receiving too large doses of vitamin D, either as irradiated ergosterol, irradiated foods, or ultraviolet light, or a combination of the three cannot be denied. But it also cannot be too strongly emphasized that all of the doses which have proved fatal to animals have been at least ten thousand times and often one hundred thou-

sand times as large as the amount required to prevent or to cure rickets. Equivalent toxic doses for children have been variously calculated as 0.1 gm. to 2 gm. of irradiated ergosterol.

Actual experience with children indicates that some of them may be more sensitive to irradiated ergosterol than others. Sobel and Claman report that they have in several instances treated *rachitic* children with as much as 12 mg. daily for twenty days without noting any ill effects. Hess,

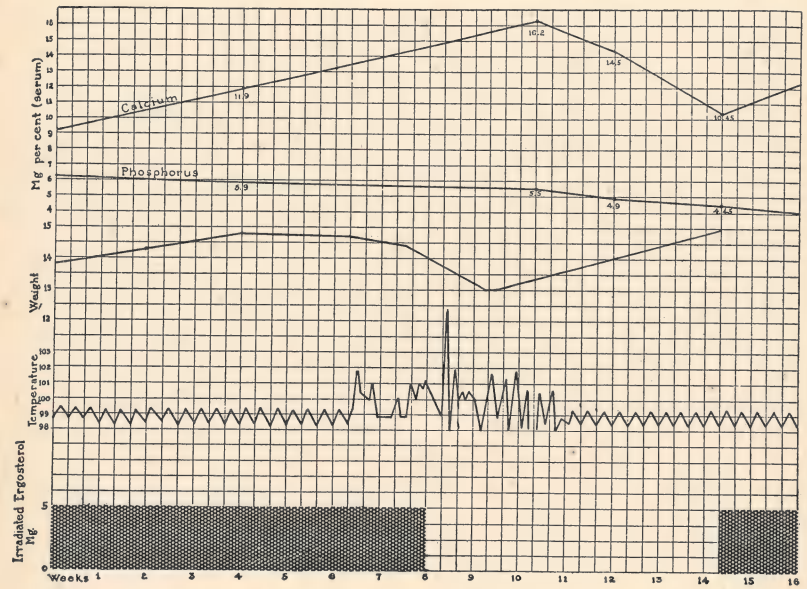


FIG. 34.—Hypercalcemia in normal infant. Note maintenance of high level of calcium for several weeks after irradiated ergosterol was discontinued. (From Hess and Lewis, *Journal of the American Medical Association*, XCI [1928], 787.)

on the other hand, observed abnormally high blood calcium levels in a number of *normal* infants and in two rachitic children on considerably smaller doses (2.5 to 5 mg.). Occasionally, also, excessive calcification of the bones was seen in the X-ray pictures, but in only two cases were there any other signs of an unsatisfactory state of health. These two children lost weight, developed a moderate degree of fever, a marked drowsiness, and a peculiar mental condition. The symptoms disappeared when the ergosterol was stopped but appeared again in one case when the ergosterol treatment was repeated a month later. In his latest report Hess states that a high blood calcium is the outstanding sign of the toxic reaction. In infants this is always accompanied and sometimes preceded by a decided failure of appetite, which furnishes the physician with an easily recognizable sign of over dosage. "Hypercalcemia," Hess writes, "may occur in infants when excessive amounts of irradiated ergosterol are given for prophylactic purposes, but rarely comes about in the course of curative treatment, in other words, simultaneously with active rickets or tetany."

The necessity for standardization.—The matter of satisfactory dosage for normal and rachitic children is one which still remains to be worked out by the medical practitioner in the clinic. But before he can solve this problem, it is imperative that he be supplied with a standardized product of uniform potency. Hess remarks in an article published in 1928.

> Although not yet available commercially, irradiated ergosterol, under various trade names, has been tested in many clinics both in this country and abroad. It is difficult to appraise the strength of the irradiated ergosterol in these preparations, owing to the fact that ergosterol itself is by no means a uniform product. This is evident from the gross appearance of the extracts; some are brownish and colloidal in nature, whereas others are white and crystalline.

According to a recent statement from Mead Johnson and Company, "the potencies of the five European preparations as determined in the Mead Johnson laboratory were 14, 40, 150, 800, and 2,500 respectively." Some of these purported to be solutions of pure "vitamin D" containing a definite number of milligrams per cubic centimeter, although of course pure vitamin D has never been isolated and the absolute amount present in any preparation must still be very uncertain.

In this connection, the Wisconsin Alumni Foundation, because of its control of the manufacture and sale of irradiated ergosterol as well as irradiated food in this country, will play an important rôle. According to Sobel and Claman,

> One leading pharmaceutical laboratory states that there will probably be four licenses (for the manufacture of irradiated ergosterol) under the Steenbock patent. The licensees have agreed to market a product of one and the same potency and to market it in containers of the same size. The standard potency will be controlled by Dr. Steenbock of the University of Wisconsin.

The standard which has just been adopted by the Wisconsin Alumni Foundation is a product one hundred times as potent as good cod liver oil. The Mead Johnson and Company preparation is made by dissolving the ergosterol before irradiation in peanut oil, in which it is only slightly

soluble, and causing the oily solution to flow in exceedingly thin layers into the field of light in the absence of air and ozone. The efficiency of activation is high but the solutions used are so dilute that the activated product requires only slight dilution to reach standard potency and the danger of putting too strong a solution on the market is slight. Two drops of the solution are equivalent in vitamin D potency to a teaspoonful of standard cod liver oil.

Preparations put out by the Abbott Laboratories and by Squibb & Sons are irradiated in ether solution, and that made by Parke, Davis & Company is irradiated in alcohol. All of these after irradiation are dissolved in maize oil and adjusted to proper potency.

Viosterol.—The Council on Pharmacy and Chemistry of the American Medical Association has just (August 31, 1929) accepted irradiated ergosterol under the term "viosterol." "Viosterol in oil" designates irradiated ergosterol dissolved in oil. The Council has also provisionally adopted the qualifying phases 100 D, 5 D, etc., to designate the vitamin D potency of the various preparations as multiples of the vitamin D potency of good cod liver oil, in accordance with the standard of the Wisconsin Alumni Research Foundation.

The daily prophylactic dose for the average infant and child of this viosterol in oil 100 D is given as 8 to 10 drops, and for the premature and rapidly growing infant, 15 drops; the daily curative dose is 15 to 20 drops, and in severe cases and for adults, doses in excess of 20 drops may be given.

Viosterol will therefore henceforth be the accepted name in this country for irradiated ergosterol.

The movement, then, is toward control and standardization rather than abandonment of a product of such very great and generally conceded therapeutic value. Every writer who has observed the toxic effects of large quantities of vitamin D takes pains to point out that he does not wish his work to be interpreted as in any way deprecating the use of irradiated ergosterol in the treatment and prevention of rickets and all would agree with Harris and Moore as they remark, "Toxic effects at such enormous doses should not in any way discourage the rational use of the properly standardized materials at the ascertainable correct physiological levels." It must, however, always be used under the direction of someone thoroughly aware of its potentialities for harm as well as good.

Further experience with viosterol has shown that amounts of vitamin D

larger than those originally recommended may be used with safety, and with much better results in the treatment of rickets. It has been thought best, however, to increase the potency of the product rather than the size of the dose. Accordingly the Wisconsin Alumni Research Foundation and its licensees have decided to manufacture preparations having 10 and 250 times the potency of a standard cod liver oil, instead of 5 and 100 times, as formerly. These new preparations have been accepted by the Council on Pharmacy and Chemistry, and they will be put on the market beginning with October 1, 1930. See the report of the Council on Pharmacy and Chemistry, "Increased Potency of Viosterol Preparations," *Journal of the American Medical Association,* XCV (October 4, 1930), 1021.

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CHAPTER X

THE QUANTITY AND PROPORTION OF CALCIUM AND PHOSPHORUS IN THE DIET

The study of vitamin D and ultraviolet irradiation has recently thrown such brilliant light on calcium and phosphorus metabolism that questions of the actual quantities of these elements in the diet have rather been cast into shadow. Numerous cases have already been discussed in this book in which babies or animals, given cod liver oil or irradiated food or ultraviolet light, have stored satisfactorily from a moderate intake of the minerals. Some workers go so far as to think that if enough vitamin D or light is present, the quantities of the elements in the diet may practically be ignored.

TWO POINTS OF VIEW

This extreme attitude may be illustrated by a quotation from Mrs. Mellanby:

> The use of the expression "optimum calcium and phosphorus content of a diet" is to be deprecated, for the necessary amounts of these substances, particularly calcium, depend so much on other factors. It may be predicted with some certainty that, if there is an abundance of vitamin D in the food, or if the animal is exposed over long enough periods of time to ultra-violet radiations, the calcium-phosphorus ratios are negligible from the point of view of the development of perfect teeth, and that even the absolute amounts of calcium and phosphorus in diets made up of ordinary foodstuffs are of but little significance.

The opposite point of view is expressed by Sherman's often-quoted statement that "both city and country dietaries in the United States are more often deficient in calcium than in any other chemical element so far investigated." He bases this conclusion upon study of more than two hundred dietaries representing ordinary food habits and comparison of them with the standards for adequate intake determined from balance experiments.

With the limited distribution of vitamin D and with the tendency of civilized man, especially in cities, to stay long hours indoors out of the sunshine, we seem hardly justified in ignoring the calcium and phosphorus of the diet. To quote Sherman again: "Confidence in the value of the

antirachitic vitamin must not lead to any lack of care in providing a liberal supply of calcium and phosphorus during growth."

EXPERIMENTS WITH VARYING CALCIUM AND PHOSPHORUS INTAKE

There is a fair amount of proof on human beings that increased intake means increased retention, though recent experiments on children are not numerous and comparison with earlier ones not very satisfactory because the effect of variations in sunlight and vitamin D was not understood. Two sets of experimental observations will be given first and then a brief survey of published balances on non-rachitic children of different ages.

Shohl's experiment.—One striking though short-time experiment has just been reported by Shohl and his co-workers at Yale. They worked with an eight-months-old baby boy who had recently recovered from bronchopneumonia and rickets and who had been given ultraviolet irradiation and cod liver oil, but before, not during, this experiment. His serum calcium and phosphorus had become normal after his illness, but he seems to have been still somewhat underweight. In the two balance periods observed, the child had a diet of a liter of skim milk with 10 per cent cane sugar, but during the first period the salt content was made twice as great as in the second by adding a salt mixture equal to the salts in the milk.

As a result of this addition, the calcium and phosphorus intake of the baby was very high, much higher than the other figures reported in the literature, and the retentions were also much higher than the others known. With the extra salts the child stored 0.87 gm. of calcium and 0.49 gm. of phosphorus daily, and without the salts 0.44 and 0.26 gm., respectively, a doubling of the quantities retained. The child gained weight rapidly in the period with the added salts and lost slightly without the salts. The authors' final statement is: "Too far-reaching deductions should not be drawn from a single metabolism experiment. The conclusion that seems warranted from this study is that a baby on a skimmed milk diet, after the salt constituents are doubled, retains salts in approximately the same proportion, but in twice the amount." A less cautious deduction might be that although the diet already contained calcium and phosphorus in generous amounts, doubling their quantity much increased their retention.

"Data such as those given are rare in the literature," Shohl also says, "and more studies are urgently needed."

Sherman and Hawley's experiment on varying milk consumption.—Another much more extensive series of balance experiments on children with variation in the calcium and phosphorus intake is Sherman and Hawley's well-known work on milk. The investigators fed several normal

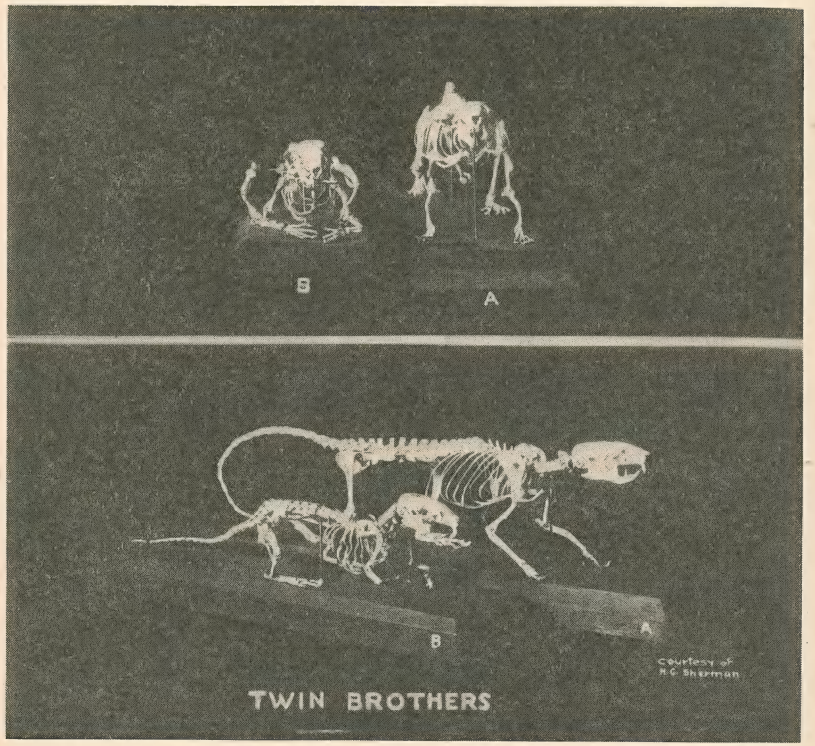


FIG. 35.—Front and side views of skeletons of twin brothers (albino rats), one of which had received a diet of normal calcium content (wheat, meat, and milk) while the other had received a low calcium diet (wheat and meat). (From Sherman and MacLeod, *Journal of Biological Chemistry*, LXIV [1925], 450.)

children of three, six, and twelve years a diet which contained in the different periods 250, 500, 750, 1,000, and 1,500 gm. of milk. The children's retention of calcium and phosphorus was lowest from the smallest milk-feeding, went up with each increase to 1,000 gm., and with 1,500 gm. was little or no greater than with 1,000 gm. That is, the increased intake increased the retention but only up to a certain amount.

Because of his observations on his two families of rats living on diets

with different quantities of milk (see chapter i), Sherman is led to believe that the advantage of the higher milk diet for the children is due chiefly to the increase in minerals, not, as might equally well be imagined, primarily to added vitamin. It will be remembered that both families of these rats were fed a diet—adequate for many generations—of whole dry milk and whole wheat, one group with one-third milk and two-thirds wheat and the other with one-sixth milk and five-sixths wheat.

The race of rats on the lower milk diet which had been eating not much more than half as much calcium and vitamin were found to have less calcium in their bodies than those of the stronger race on the better diet, not only a smaller total quantity but a smaller percentage of their less robust bodies. Sherman, experimenting to determine whether this inferiority of the poorer diet was due to comparative lack of vitamin or of calcium, found that adding cod liver oil did not increase the percentage of calcium in the animals' bodies but adding calcium lactate brought it up to the high level of the other group of rats. Thus a fair storage of calcium from a diet fair in calcium and vitamin D was changed to an optimal storage by the simple increase in the calcium of the food.

Sherman also shows, and refers to similar work of others before him, that animals on very low calcium have much smaller skeletons, much less calcium in their bodies, than those on normal calcium. Further, he finds that animals which have had a good or fair calcium intake and which as young adults are changed to a very low one, lose calcium from their bodies. That is, even the adult has daily need for calcium which must be met by the food if the skeleton is to be preserved normally.

All of these experiments show clearly that adequate calcium in the diet is necessary for optimal physiological behavior.

HOW MUCH CALCIUM AND PHOSPHORUS DOES OR SHOULD A CHILD STORE?

These experiments by Shohl and by Sherman naturally lead to the questions, How much calcium and phosphorus may a child be expected to store in his body every day, what are average storage figures, and what is the "optimum" for optimum growth?

Dr. Daniels' answer.—Unfortunately, only incomplete and tentative answers are available, especially as to the "optimum." The best seems to be Dr. Amy Daniels'. She bases her conclusions on her extensive series of balance experiments on children with and without antirachitic treatment, experiments which have already been discussed in chapter iv in connection with the influence of cod liver oil and irradiation. "For opti-

mum growth," she says, "infants between the ages of two and nine months should retain between 40 and 50 mg. of calcium and between 20 and 25 mg. of phosphorus per kilogram of body weight."

Answers from other experiments.—In order to obtain further light upon the questions, two tables (XVI and XVII) have been prepared bringing together the majority of recent calcium- and phosphorus-balance experiments on non-rachitic children. (Early work is summarized by Czerny and Keller.) In the first of the two tables are the figures on infants up to fourteen months, and in the second those on older children, ranging in age from three to thirteen years. The experiments on the infants are listed in order of their retention of calcium per kilogram of body weight; those on the older children are merely grouped according to the investigator. Many of the experiments included are discussed in detail elsewhere in this book, especially in chapters iv and xi, "The Calcium and Phosphorus of the Body" and "The Effect of Different Foods on Calcium and Phosphorus Metabolism."

Truly the variables in these lists of experiments are many and not always clear—the nutritive condition of the children, the presence or absence in the diet of eggs and much whole milk with their by no means negligible antirachitic effect, other variations in the diet, and probably by no means least the season of the year and the amount of sunshine to which the children were exposed. Yet certain points do stand out, especially for the babies.

The infants' retention.—The most striking point is that higher calcium retentions come with the higher intakes. With one exception, every infant or group of infants consuming more than 1 gram of calcium stored more than infants consuming less. The high amounts retained range from 0.07 to 0.14 gm. per kilogram—far above Daniels' estimate of what babies should retain. These high-retention babies, as it happened, were all taking large quantities of cow's milk and were not having cod liver oil. Are these cases of "supermineralization" on cow's milk, or is this large storage desirable?

Next in order come Wang's few infants on human milk, far ahead of their relative position in order of intake. Next is Daniels' larger group, uniform in age, and with closely similar intakes, which show the strong influence of antirachitic treatment. These babies retain the 0.050 to 0.040 gm. she considers satisfactory when the cod liver oil or irradiated food is present, and decidedly less without those agents.

High intake of calcium, breast-milk instead of cow's milk for the

TABLE XVI

CALCIUM AND PHOSPHORUS RETENTION IN NON-RACHITIC INFANTS
(IN GRAMS PER TWENTY-FOUR HOURS)

INVESTIGATOR	CHILDREN		CALCIUM			PHOSPHORUS			CA/P		REMARKS ON DIET
	Age in Mos.	Number	Intake	Retention		Intake	Retention		Intake	Retention	
				Total	Per Kg.		Total	Per Kg.			
Shohl *et al.* *	8	1	3.11	0.87	0.14	3.07	0.49	0.08	1:1	1.8:1	Milk+added salts; no cod liver oil
Flood†	11	1	1.57	1.24	0.13	.....	.....	.....	.....	.....	Cow's milk; no cod liver oil
Flood	10	1	1.29	0.94	0.12	.....	.....	.....	.....	.....	Cow's milk; no cod liver oil
Wang *et al.*‡	1–6	5	1.01	0.57	0.096	.....	.....	.....	.....	.....	Cow's milk; no cod liver oil
Shohl*	8	1	1.55	0.44	0.07	1.32	0.26	0.042	1.2:1	1.7:1	Cow's milk; no added salts; no cod liver oil
Wang‡	1–6	5	0.51	0.31	0.068	.....	.....	.....	.....	.....	Breast milk; no cod liver oil
Daniels *et al.*§	4	2	0.79	0.288	0.045	0.63	0.202	0.0315	1.3:1	1.4:1	Irradiated olive oil
Daniels	5	5	0.84	0.272	0.040 (0.020–0.055)	0.66	0.136	0.020 (0.012–0.027)	1.3:1	1.9:1	Irradiated milk+cod liver oil
Daniels	4	17	0.84	0.227	0.036 (0.021–0.066)	0.67	0.151	0.024 (0.007–0.044)	1.3:1	1.5:1	Boiled milk+cod liver oil
Daniels	4	6	0.78	0.186	0.031 (0.025–0.035)	0.64	0.180	0.030 (0.026–0.038)	1.2:1	1.0:1	Pasteurized milk+cod liver oil
Daniels	4	15	0.72	0.149	0.027 (0.011–0.051)	0.56	0.121	0.022 (0.004–0.041)	1.3:1	1.2:1	Boiled milk; cod liver oil before
Daniels	4	4	0.82	0.144	0.024 (0.0035–0.0388)	0.66	0.168	0.028	1.2:1	0.8:1	Pasteurized milk; cod liver oil before

TABLE XVI—*Continued*

Investigator	Children		Calcium			Phosphorus			Ca/P		Remarks on Diet
	Age in Mos.	Number	Intake	Retention		Intake	Retention		Intake	Retention	
				Total	Per Kg.		Total	Per Kg.			
Sato‖.....	14	1	1.48	0.174	0.022	.....	.....	.....	.....	.....	Cow's milk; no cod liver oil
Daniels.....	6	14	0.89 (0.61–1.05)	0.1005	0.015 (0.0023–0.0329)	0.71	0.080	0.012 (−0.0006–0.0247)	1.3:1	1.2:1	Boiled milk; no cod liver oil
Daniels.....	6	9	0.89	0.025	0.0042 (−0.0113–0.0223)	0.72	0.045	0.0075 (−0.0039–0.0125)	1.2:1	0.5:1	Pasteurized milk; no cod liver oil
Orr *et al.*¶..	14	1	1.00	0.26	.....	0.71	0.20	.....	1.4:1	1.3:1	Cow's milk; no cod liver oil

* A. T. Shohl, A. M. Wakeman, and E. Y. Shorr, "Mineral Metabolism on a High Mineral Diet," *American Journal of Diseases of Children*, XXXV (1928), 576.

† R. G. Flood, "Calcium Balance with Hydrochloric Acid Milk," *American Journal of Diseases of Children*, XXXII (1926), 550.

‡ Chi Che Wang; David B. Witt; and Augusta R. Felcher, "A Comparison of the Metabolism of Some Mineral Constituents of Cow's Milk and of Breast Milk in the Same Infant," *American Journal of Diseases of Children*, XXVII (1924), 352.

§ A. L. Daniels, G. Stearns, and M. K. Hutton, "Calcium and Phosphorus Metabolism in Artificially Fed Infants: I, Influence of Cod Liver Oil and Irradiated Milk," *American Journal of Diseases of Children*, XXXVII (February, 1929), 298.

‖ A. Sato, "The Effect of Alkali and Malt Preparations on the Retention of Calcium in Infancy," *American Journal of Diseases of Children*, XIV (1918), 293.

¶ W. J. Orr, L. E. Holt, Jr., L. Wilkins, and F. H. Boone, "The Relation of Calcium and Phosphorus in the Diet to the Absorption of These Elements from the Intestine," *American Journal of Diseases of Children*, XXVIII (1924), 574.

TABLE XVII

Calcium and Phosphorus Retention in Children from Three to Thirteen Years
(In Grams per Twenty-Four Hours)

Investigator	Children		Calcium			Phosphorus			Ca/P		Remarks
	Age in Years	Number	Intake	Retention		Intake	Retention		Intake	Retention	
				Total	Per Kg.		Total	Per Kg.			
Burton*.....	3–5	4	1.49	0.78	0.048	1.21	0.63	0.036	1:1	1.2:1	Cream of wheat, milk, etc.; some ultraviolet light
			1.36	0.69	0.037	1.70	0.65	0.038 (0.027–0.044)	0.8:1	1:1	Oatmeal, milk, etc.; some ultraviolet light
Burton.....	12,13	2	0.95	0.27	0.007	1.48	0.58	0.015	0.6:1	0.5:1	Cream of wheat, milk, etc.
			0.68	−0.04	−0.002	1.35	−0.13	−0.001	0.5:1	neg.	Oatmeal, milk, etc.
Chaney and Blunt†.....	10,11	2	0.39	0.10	.....	0.86	−0.03	.....	0.5:1	neg.	Mixed diet; no orange juice
			0.67	0.10	.....	1.05	0.04	.....	0.6:1	2.5:1	Mixed diet; no orange juice
			0.44	0.14	.....	0.97	0.18	.....	0.5:1	0.8:1	Mixed diet; orange juice
			0.75	0.20	.....	1.12	0.12	.....	0.7:1	1.7:1	Mixed diet; orange juice
Herbst‡.....	6–14	6	.....	0.21 to 0.39	0.010 to 0.016						
Kramer *et al*§.....	7–12	5	1.05	0.46	0.016 (0.010–0.025)	0.67	0.33	0.011 (0.009–0.014)	1.6:1	1.4:1	Fresh milk; mixed diet
			0.99	0.29	0.010 (0.007–0.015)	0.66	0.26	0.009 (0.005–0.011)	1.5:1	1.1:1	Dry milk; mixed diet
Sherman and Hawley‖...	3–6	4	0.89	0.19	0.010	1.10	0.14	0.008	0.8:1	1.3:1	750 gm. milk; mixed diet
Sherman and Hawley....	6–10	4	0.80	0.28	0.010	0.92	0.13	0.005	0.9:1	2.1:1	750 gm. milk; mixed diet
Sherman and Hawley....	10–13	4	0.99	0.41	0.011	1.36	0.37	0.010	0.7:1	1.1:1	750 gm. milk; mixed diet
Sherman and Hawley....	4,5	2	0.39	0.14	0.008	0.70	0.18	0.010	0.6:1	0.8:1	250 gm. milk
			0.68	0.20	0.011	0.91	0.22	0.012	0.7:1	0.9:1	500 gm. milk
			0.94	0.23	0.012	1.15	0.29	0.015	0.8:1	0.8:1	750 gm. milk
			1.197	0.28	0.014	1.01	0.26	0.015	1.1:1	1.1:1	1,000 gm. milk
			1.722	0.27	0.014	1.68	0.24	0.011	1.1:1	1.1:1	1,500 gm. milk

TABLE XVII—*Continued*

Investigator	Children		Calcium			Phosphorus			Ca/P		Remarks
	Age in Years	Number	Intake	Retention		Intake	Retention		Intake	Retention	
				Total	Per Kg.		Total	Per Kg.			
Sherman and Hawley	12	1	0.43	0.22	0.007	0.87	0.17	0.005	0.5:1	1.3:1	250 gm. milk
			0.75	0.43	0.012	1.17	0.40	0.012	0.6:1	1:1	500 gm. milk
			1.01	0.64	0.018	1.41	0.44	0.013	0.7:1	1.5:1	750 gm. milk
			1.27	0.71	0.020	1.59	0.47	0.014	0.8:1	1.5:1	1,000 gm. milk
			1.79	0.83	0.023	2.01	0.46	0.013	0.9:1	1.8:1	1,500 gm. milk
Sherman and Hawley	6	1	0.96	0.25	0.014	1.08	0.26	0.015	0.9:1	1:1	750 gm. milk
			0.89	0.11	0.006	0.83	0.03	0.002	1.1:1	3.7:1	375 gm. milk+vegetable
Sherman and Hawley	10, 13	2	1.03	0.35	0.008	1.29	0.16	0.004	0.8:1	2.2:1	750 gm. milk
			1.00	0.16	0.004	1.00	−0.03	−0.0005	1:1	neg.	375 gm. milk+vegetable
Wang *et al.*¶	5–12	10	1.44	0.23	0.009 (0.006–0.012)						Children normal
Wang	5–13	13	1.04	0.17	0.009 (0.002–0.020)						Normal in weight only
Wang	5–12	16	1.15	0.23	0.011 (0.006–0.016)						5–10 per cent underweight
Wang	4–13	16	1.14	0.25	0.013 (0.006–0.020)						10–15 per cent underweight
Wang	6–11	13	1.10	0.21	0.011 (0.003–0.016)						More than 15 per cent underweight
Willard and Blunt**	3,4	2	1.12	0.21	0.013	1.02	0.24	0.015	1:1	0.9:1	Evaporated milk, etc.
			1.04	0.14	0.009	0.96	0.13	0.008	1:1	1:1	Pasteurized milk, etc.
Willard and Blunt	8,12	2	1.31	0.55	0.022	1.22	0.28	0.012	1:1	2:1	Evaporated milk, etc.
			1.26	0.51	0.021 (0.013–0.028)	1.22	0.16	0.006	1:1	3.5:1	Pasteurized milk, etc.

* H. Burton, unpublished paper.
† M. S. Chaney and K. Blunt, "The Effect of Orange Juice on the Calcium, Phosphorus, Magnesium, and Nitrogen Retention and Urinary Organic Acids of Growing Children," *Journal of Biological Chemistry*, LXVI (1925), 829.
‡ Herbst, quoted by Sherman, *Chemistry of Food and Nutrition*, p. 313.
§ M. M. Kramer, E. Latzke, and M. M. Shaw, "A Comparison of Raw, Pasteurized, Evaporated, and Dried Milk as Sources of Calcium and Phosphorus for the Human Subject," *Journal of Biological Chemistry*, LXXIX (1928), 283.
|| H. C. Sherman and E. Hawley, "Calcium and Phosphorus Metabolism in Childhood," *Journal of Biological Chemistry*, LIII (1922), 375.
¶ C. C. Wang, M. Kaucher, and M. Frank, "Metabolism of Undernourished Children: IV, Calcium Metabolism," *American Journal of Diseases of Children*, XXXV (1928), 856.
** A. C. Willard and K. Blunt, "A Comparison of Evaporated with Pasteurized Milk as a Source of Calcium, Phosphorus, and Nitrogen," *Journal of Biological Chemistry*, LXXV (1927), 251.

youngest, and antirachitic agents seem to be the three considerations for high calcium retention for the infants.

Storage by the older children.—For the older children (Table XVII) the observations are much less clear-cut. About the only statement that can be made is like that for the babies but slightly less definite: usually but not always the higher retentions per kilogram follow the higher intakes. This is particularly noticeable with Sherman and Hawley's group and also with several others. The age of the children seems to make no consistent difference. As a whole, the older children do tend to run lower per kilogram than the infants and no storages by the older ones are as high as those of several of the babies. Yet the storages of many of the older children are as high as those of many of the infants, and some of the highest figures for the older group belong to twelve-year-olds.

Conclusions as to the effect of cod liver oil on older children cannot be drawn, for so far as the authors are able to find, balances with cod liver oil have not been done on children past infancy. The one experiment with ultraviolet irradiation (Burton's four little boys) shows much the highest retention of the whole group, as high as Daniels' infants with cod liver oil. Of course this one experiment, which was designed to study storage with different cereals (see page 170) and therefore had no non-irradiation control on the same subjects, cannot be considered more than suggestive as to the effects of antirachitic treatment. It is clear that the point needs investigation.

Omitting these high figures of Burton's, it may be said that when the children's intake of calcium is approximately a gram or above with considerable milk, the retention of calcium ranges from about 0.01 to 0.02 gm. per kilogram. The phosphorus retention figures in the better cases run a little lower than the calcium.

THE CALCIUM-PHOSPHORUS RATIO

For children.—Another thing which stands out in the two tables is that the *ratio* between the calcium and the phosphorus retained shows very little variation; it is almost always between 2:1 and 1:1. The chief exceptions are cases illustrative of less satisfactory behavior—Burton's older children, Chaney and Blunt's on the poor diet, Daniels' infants on pasteurized milk without cod liver oil. To quote Daniels again: "Optimum development would seem to demand the retention of optimum amounts of calcium and phosphorus in the ratio of approximately two parts of calcium to one part of phosphorus." With this proportion nor-

mal bone development appears to take place. The *size* of the skeleton may depend upon the actual *quantities* retained.

The ratios in the diets, also, vary little. In the majority of cases the calcium-phosphorus ratio is between 1.5 and 0.9:1. In several (though not all) of the cases with the poor retention, however, the ratio is lower—0.5 or 0.7 of calcium to 1 of phosphorus. With much milk, breast-milk or cow's, the child's diet is fairly sure to have a ratio close to the favorable value.

The calcium-phosphorus ratio, therefore, cannot be a major consideration in children's rickets, though it is in that of animals. Infants do develop rickets on both cow's milk and less frequently on human milk with their apparently good ratios. Thus, while lack of vitamin D and radiant energy seems to be equally significant in human and animal rickets, a bad calcium-phosphorus ratio does not.

Yet the very few experiments which have been done on children with artificially arranged ratios in the diet have given markedly abnormal results like those on animals. On two children, one somewhat undernourished but otherwise apparently normal and the other rachitic, calcium and phosphorus balances and blood serum findings were obtained when the children were on milk alone, and on milk plus, first, calcium chloride and, second, sodium phosphate. With the high calcium the retention of calcium and the serum calcium were increased as might be expected, but the phosphorus figures were decidedly *decreased* to values abnormally low. With the high phosphorus, the opposite changes took place (Orr and others). These results lead to the conclusion that artificial additions of one of the elements alone, as is sometimes done with therapeutic intent, may be really harmful.

High calcium-low phosphorus for rats.—With rats, as has been frequently stated throughout this book, the question of the calcium-phosphorus ratio is vitally important. Rats, unlike children, develop rickets only when the ratio is abnormal and are cured when the element lacking is added. For example, the diet of rats on the common rachitogenic ratio of 4.1:1 (Steenbock's diet No. 2965) was altered by adding enough sodium acid phosphate to make the ratio 2:1. The rats on this diet no longer showed signs of rickets, their bones were normal histologically, the blood calcium and phosphorus were improved, they ate more food, retained more calcium and phosphorus in their bodies, and they grew faster. The addition of the phosphorus giving the better ratio much improved the animals.

However, though the rats had no rickets, they were by no means optimal animals. Interestingly enough, when they were given cod liver oil, marked betterment was brought about all along the line, and if some of the diet was irradiated, as well as cod liver oil given, the improvement was even greater. Rectifying the mineral ratio helped, but the two antirachitic agents helped still more. The weekly gain in weight was more than three times as great. Addition of butter, it should be remarked, instead of the cod liver oil did *not* help. This information is the result of recent clear-cut work of Shohl and his co-workers at Yale. A few of their especially striking figures are brought together in Table XVIII.

TABLE XVIII

RESULTS OF ADDING PHOSPHATE AND COD LIVER OIL TO A RACHITOGENIC DIET AND OF IRRADIATING THE DIET

(SELECTED FROM SHOHL, BENNETT, AND WEED)

DIET	CA/P OF DIET	BLOOD PHOSPHORUS, MG. PER CENT	FEMORA		AVERAGE WEEKLY GAIN IN WEIGHT, GM.
			Dry Weight, Gm.	Ash, Gm.	
Steenbock's 2965+10 per cent lard (A)	4.1:1	2.6	0.671	0.168	3.0
Diet A+NaH_2PO_4(B)	2.0:1	4.2	1.035	0.530	4.2
Diet B+4.0 per cent butter (C)	2.0:1	.....	0.876	0.358	4.1
Diet B+2.0 per cent cod liver oil (D)	2.0:1	8.0	1.321	0.725	8.9
Diet D with corn irradiated	2.0:1	6.9	1.463	0.766	14.3

The low calcium-high phosphorus diets.—The harm of the other abnormal ratio, low calcium and high phosphorus, has also been shown, chiefly on dogs. Mellanby, in England, has done most of his work with this kind of rickets-producing diet, and Shohl and Bennett in this country have also experimented on dogs. On the low calcium-high phosphorus diet (Ca/P=0.66) blood calcium goes down even to the extent of causing tetany, and blood phosphate stays normal or almost normal; but, rather surprisingly, while the retention of the calcium is low, the phosphorus retention is sometimes even lower. Two of Shohl and Bennett's dogs on Mellanby's low calcium diet actually retained a larger weight of calcium than of phosphorus, not only a larger percentage of the quantities fed. "Even on a diet high in phosphorus and low in calcium, the most marked deficiency lies in the phosphorus retention."

Thus, according to these observations on rats and dogs, a disproportion of calcium or phosphorus in either direction, without vitamin D, means that the phosphorus retention is lowered even more than the calcium and that therefore the ratio of the retentions of the two is high.

THE ACID-BASE BALANCE

Closely related to this question of the proportions of the calcium and phosphorus in the diet is the difficult and much confused question of its acidity or basicity. Adding calcium carbonate or calcium lactate not only raises the calcium and changes the Ca:P ratio, but increases the potential alkalinity. Adding calcium chloride, on the other hand, increases the potential acidity. The acid-base effect with phosphates will vary, depending upon whether the primary NaH_2PO_4, secondary Na_2HPO_4, or tertiary Na_3PO_4 is used.

Besides the inorganic salts, there is the potential acidity or alkalinity of the main constituents of the diet to be considered—whether when they burn in the body they leave an acid residue, as do meat and eggs and cereals, or a basic residue, as do fruits and vegetables.

Still a third point which seems highly important is where in the body the acidity or alkalinity is developed. Most of the inorganic salts mentioned have the same potential reaction, the same buffer value, while they are still in the intestinal tract as after they are absorbed into the blood. Many of the foods, the cereals, for example, are neutral before absorption and do not develop their acidity till they are burned and leave their residue in the blood stream. But some foods, especially some fruit juices, are acid in the intestine but alkaline after combusion. Orange juice, for example, is acid in the digestive tract and hence must help give the low pH which favors absorption of calcium and phosphorus. Yet it gives a basic residue on combustion. The improvement in calcium and especially phosphorus retention in children when orange juice was added to the largely cereal diet is probably to be explained by this double effect (Chaney and Blunt).

With all these possible variations it is not surprising that the work on the effect of changing the acid-base balance of the diet is full of contradictions. Only two sets of experiments will be given here, both done by Shohl and his co-workers at Yale, one on two children several years ago, and a recent one on rats.

The children, seven and nine months old, were fed first their usual diet of milk, and then to one 250 cc. of 0.1N hydrochloric acid was given

and to the other the equivalent of 473 cc. of 0.1 N sodium carbonate. (As both these chemicals are frequently added to babies' diets this procedure was not so heroic as it sounds.) Each addition diminished the children's retention of both calcium and phosphorus, the calcium especially being very much lowered with the alkali. That is, the non-combustible acid and alkali both lessened the retention from the neutral milk.

The later rat experiments by the same investigators are more elaborate. Groups of rats on the usual Steenbock high calcium-low phosphorus rachitogenic diet were given four different phosphate additions all containing sufficient phosphorus to bring the ratio to 0.95:1 but producing different acidities. The Steenbock diet is potentially alkaline, equivalent to 530 cc. 0.1N alkali. Different phosphates, Na_3PO_4, NaH_2PO_4, H_3PO_4, or H_3PO_4 and HCl, added to different portions gave a very alkaline, moderately alkaline, approximately neutral, and moderately acid diet (equivalent to 859, 311, 37 cc. of 0.1N alkali, and 313 cc. of 0.1N acid, respectively).

A surprising observation made early in the work was that a sudden change from the Steenbock alkaline diet to the neutral killed the rats immediately; all had convulsions and all died. When the change was made gradually, there were no fatalities, and the rats showed up best of all the groups. But Shohl warns that gradual change "should be important in establishing therapeutic procedures." The following statements and figures are those from the gradual change to neutrality.

As was to be expected, the rickets was cured in all cases in which the calcium-phosphorus ratio was 1:1, no matter in which form the phosphorus was added. But the retention of both elements was highest on the neutral diet and lowest on the acid; the deposition of ash in the bones was highest on the neutral, smaller with the alkaline, and least with the acid diets. The growth differences, naturally parallel with these others, were quite striking—most on the neutral averaging 16.0 gm., as against from 0.5 to 1.0 gm. on the other two. In the rachitic controls there was an average loss of weight of 5 gm.

Plainly, provided there is no sudden change, the neutral diet is much the best for these rats and presumably for normal children.

SUMMARY

Thus, increasing the quantity of the calcium and phosphorus in the diet has been shown to increase storage by both infants and older children. From a moderately high and constant intake, cod liver oil or ir-

radiated foods increase retention of the two elements by infants, but the influence of these substances on older children is not known. Irradiation with ultraviolet light, in the one experiment in which it was used on normal older children, was associated with high storage. The better storages reported for infants are higher than those for older children, Daniels' daily "optimum" for infants being from 40 to 50 mg. of calcium.

The ratio of calcium to phosphorus retained under good conditions ranges from 2:1 to 1:1, and the ratio in children's diets with much milk does not vary far from these same figures. Much lower ratios of intake, such as may occur in diets which are not impossibly poor with very high cereal or meat and little milk or fruit and vegetables, or such as have been developed by experimental additions of phosphorus salts, have been found to lead to lower retentions.

For animals the actual quantities of the elements in the ration are of importance and also the ratio, the latter being more significant for animals than for children, since most experimental work on rats or dogs described throughout this book has been done on abnormal ratios and the resulting rickets often cured merely by changing the ratio to approximately 1:1.

A diet not only with a good ratio of the two elements, but neutral, has been shown to give the best retention both by children and by rats.

Plenty of milk for high calcium and phosphorus in good proportion, a neutral residue maintained by plenty of fruits and possibly by vegetables with their basic residue to balance the acid residue from meats and cereals, and, for babies at least, antirachitic treatment—these seem to be the main requisites for satisfactory calcium and phosphorus storage.

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CHAPTER XI

THE EFFECT OF DIFFERENT FOODS ON CALCIUM AND PHOSPHORUS METABOLISM

All foods, or mixtures of foods, do not seem to give up their calcium and phosphorus to the body equally readily and completely. The presence of much lactose in the diet, for example, seems to increase the calcium retention, and much sucrose, or crude fiber or sometimes vegetables, to decrease it. The kind of milk makes a difference, quickly boiled and evaporated milk giving a child somewhat more of the calcium and phosphorus than pasteurized. Most startling and much discussed have been experiments showing actual "anticalcifying" properties in cereals.

These and other differences in foods are probably not as important as the vitamin D of the diet, or the adequate quantities or proportions of the two elements, but they are too important to be ignored.

CEREALS AS "ANTICALCIFYING SUBSTANCES"

Anticalcifying substances.—Following quickly on the heels of Dr. Mellanby's first announcement of the dietary cause of rickets came the second startling statement from his laboratory that cereals, especially oatmeal, not only do not contain vitamin D but do contain some definite anticalcifying substance. A long series of experiments, again on dogs, showed quite clearly that *on a diet which was deficient in vitamin D,* when other dietary and environmental factors remained the same, doubling the amount of cereal made the rickets distinctly worse. Moreover, the kind of cereal seemed to influence the results, oatmeal being the most harmful, while equal amounts of maize, barley, rice, and whole wheat flour were successively less so. Polished rice and white flour were the least harmful of all, but large quantities of wheat-germ substituted for the white flour produced a type of rickets almost as severe as the oatmeal cases.

It was a great surprise to find that the substances containing the most calcium and phosphorus (oatmeal and wheat-germ) were the most rickets-producing, while those that contained the least mineral (white flour and rice) were the least detrimental. The effects of the different cereals, therefore, could not be explained on the basis of their calcium and phosphorus content. Neither could they be explained on the basis of the ratio

of calcium to phosphorus in the different cereals, since the ratios in oatmeal and white flour are similar and comparatively low (1:5.7 and 1:4.6, respectively) while those of rice and wheat-germ are also fairly close and relatively high (1:10.7 and 1:14.8).

The introduction of the larger amounts of cereal would certainly increase the potential acidity of the diet, but again there is not enough difference in the acidity of the ash of different cereals to explain the results. According to Sherman's figures, for example, the excess of acid over base in a 100 calorie portion of oatmeal amounts to 3.0 cc. of normal acid while in rice it is 2.7 cc.

All the evidence, then, seems to point to the presence in the cereal of a substance actually antagonistic to the deposition of calcium in the bone. This substance Dr. Mellanby now calls a "toxamin." Both he and a second investigator, Dr. P. H. Holst, of the University of Oslo, have been able to obtain some positive proof of its existence.

Dr. Mellanby first of all found that if the oatmeal were saponified by boiling with alkali, acidified, and the saponifiable portion extracted with petroleum ether, this ether extract when added to a diet which would otherwise produce slight rickets intensified the symptoms considerably. According to Holst, the rickets-producing substance can also be extracted by dialyzing through parchment paper or by boiling the oatmeal with 0.5 per cent hydrochloric acid (time unstated). On the other hand, Dr. Mellanby states that if the oatmeal is boiled with a 1 per cent solution of hydrochloric acid, the neutralized product is found to have lost its power of interfering with the calcification of the bones.

The presence of the anticalcifying substance can be demonstrated only when the diet is deficient in vitamin D. Mellanby himself soon proved that feeding a source of vitamin D, such as cod liver oil or egg yolk or irradiated fats, or irradiating the animal or even the cereal itself, entirely nullified its antagonistic qualities. The addition of calcium salts, even in the absence of vitamin D, improves the situation somewhat, but is not so effective as the vitamin.

Practical significance.—What then is the practical value of this discovery? Cereals are a cheap source of calories and to a certain extent of proteins, which may be used to advantage as a supplement to the more expensive proteins of milk, eggs, and meat. They contain valuable minerals, particularly phosphorus and iron, and it has been our habit for years past to urge their use, especially in children's diets. Can we overdo

the matter? Is there any danger in advocating the generous use of oatmeal, for example, as a breakfast cereal and otherwise?

In answer to such questions one immediately calls to mind the fact that whole races of people, notably the Highland Scotch and many peoples of the Orient, have lived for generations on diets consisting largely of cereals. The Highland Scotch particularly have been a sturdy race, noted for their fine physical development. Their diet has, however, been well calculated to overcome the deficiencies of the cereal, since it has contained an abundance of milk and fish. In tropical countries the sunlight undoubtedly performs the same function.

The problem, then, especially in the northern countries where the supply of sunlight is limited, is to find a satisfactory supplement to the cereal diet. If this be found, according to recent experimental evidence collected by Dr. G. R. Cowgill and his assistants, almost unlimited amounts of cereal may be used as the foundation of the diet, at least for rats and very probably for human beings as well.

Successful supplements to cereal diets: rat-feeding experiments.—In his first group of experiments Dr. Cowgill fed young white rats on rations in which various cereals furnished from 62 to 93 per cent of the total calories, amounts far in excess of the average consumption of cereal in the United States, or even in China where cereal furnishes from 66 to 72 per cent of the energy of the diet. The supplemental food for these animals consisted of a mixture of meat residue, an adequate salt mixture, cod liver oil, liver, and 15 gm. of fresh lettuce daily. The liver and lettuce were used because Osborne and Mendel had recently shown that these two foods afforded unusually rapid growth in rats on so-called "complete" experimental diets. In all groups save one, extraordinarily rapid growth was attained, much in advance of the "normal" rate for the rat. The one exception was the group receiving 93 per cent of cereal, but even in this group the growth could still be called normal. None of the rats presented any signs of nutritional disorder or of vitamin deficiency, and in all cases in which the animals were bred reproduction was highly successful.

That milk furnishes the most satisfactory supplement for cereals in human food has been a very common assumption in this country. But in China, where cereal forms so large a portion of the diet, milk is used in very small quantities if at all, and the foregoing experimental diets contained no milk whatever. To discover whether other simple foods which ordinarily enter into the human dietary may be used to supplement the cereal, Dr. Cowgill organized a second group of experiments in which he

fed the rats the same amount of cereal, combined this time with relatively small amounts of egg, molasses, and lettuce. In explaining his choice of supplements, Dr. Cowgill says, "Egg was selected because of its content of good protein, calcium, phosphorus, and iron, and vitamins A, B, and D. . . . . Cane molasses was chosen because of its high content of ash," and "fresh lettuce was selected to represent the uncooked vegetable portion of the ration." Results in this set of experiments were good, although not quite so good as in the previous ones. In no case were there any signs



FIG. 36.—The little boys who served as subjects in Burton's experiment

of rickets or of other vitamin deficiency disease, nor was there any evidence of anemia. Satisfactory growth, reproduction, and lactation occurred with diets containing 65 per cent of cereals. With the cereal at 80 per cent, growth was "good to excellent," the animals were fertile but lactation was not always successful. When the cereal was increased to 93 per cent, growth was not so rapid, in some cases reaching normal levels and in some cases not. Since rickets did not appear, nor any other sign of vitamin deficiency, it is probable that the failure in growth was due to an inadequate amount of protein.

Growth of children on high cereal diets.—That a diet fairly high in cereal, either oatmeal or refined wheat, is by no means incompatible with

excellent calcium and phosphorus retention, has been clearly shown by balance experiments on children recently carried out in the authors' laboratory. Four little boys, from three to five years of age, were fed a pint and a half of milk daily, a liberal quantity of vegetables and fruit, a little meat, and at each of the three meals cereal in some form—breakfast food, bread or wafers, and cookies. The figures for the retention of the two elements are included in Table XVII in the preceding chapter (page 157), and, it should be noted, are the very highest of all those listed, the values with the refined wheat products being even above those with the oats. The high balances may be in part due to the fact that the children were receiving ultraviolet irradiation at their nursery school during the experiment. Whatever added explanation there may have been, the high intake of cereal and the high retention went together. Much less satisfactory results were obtained on two older girls who were not irradiated (Burton).

Oriental diets containing much cereal are usually not well supplemented with foods high in vitamin D, but the long hours of sunshine rich in ultraviolet rays prevent the appearance of rickets in the children. Very recently Appleton has made an extensive statistical study of the growth of Japanese and Filipino children in Hawaii, 1,200 Japanese and 861 Filipinos being included. The diets of both of these peoples consist largely of cereal, with little or no milk. The Japanese diet contains generous amounts of vegetables, especially green vegetables, and small quantities of meat, fish, and eggs, and is somewhat better than the Filipino diet, which includes little or none of these supplementary foods. The women of both races suckle their young for long periods. Infant mortality is low for the Japanese and higher for the Filipinos—a fact which Appleton believes is due chiefly to these differences in the maternal diet.

There thus seems to be no good reason for doubting that cereal, if wisely used, may be given an even larger place in the human dietary than it has today. In those parts of the world and at those times of the year when the supply of ultraviolet light is limited, we must exercise particular care to see that a diet containing very large amounts of cereal contains also a generous quantity of vitamin D and other vitamins and minerals. *Provided such precautions are observed,* there is every reason to believe that the relatively inexpensive cereal may be used in almost any quantities that are practical or desired.

LACTOSE, SUCROSE, AND OTHER CARBOHYDRATES

Different carbohydrates—sucrose, glucose, starch, dextrin, lactose—added to the diet in large quantity have decidedly different effects on the

absorption of calcium and phosphorus. Recent observations on rats have been reported by Bergeim, of the University of Illinois College of Medicine. With from 25 to 50 per cent of sucrose or glucose and even maltose and starch, absorption of the minerals was lowered, sometimes decidedly lowered. It looks as if here is an argument against too much candy.

Bergeim is not sure of the reason for the depressing action. He writes,

> It is known, however, that strong sugar solutions depress gastric secretion of hydrochloric acid which might assist in calcium solution. There exists an impression that high carbohydrates are unfavorable to calcium assimilation in some other way. There is, of course, on high carbohydrate diets a danger of inorganic and vitamin deficiency and sugars have a depressing effect on hunger and appetite.

Lactose behaved quite differently, actually increasing the absorption, and dextrin increased it to smaller extent. As Bergeim suggests, these differences are well worth considering in making up infants' milk mixtures. The lactose probably helps the absorption, according to Bergeim, because of its fermentation to lactic acid in the intestinal tract and the resulting increase in solubility of the calcium phosphates in the acid medium. It itself is much less soluble than the sucrose and so would not depress gastric secretion as do strong sucrose solutions, and the latter, in turn, do not so readily undergo acid fermentation. It is logical enough, therefore, to find that they behave differently.

VEGETABLES AND CRUDE FIBER

As to the availability of the minerals in vegetables, results are somewhat contradictory—a rather unfortunate condition, since vegetables are an important source of calcium in the diet of persons not using milk and cheese.

Children.—The only quantitative experiment on children is that done by Sherman and Hawley in connection with their work to determine the best amount of milk for maximum calcium retention (see page 152). Having found that good retention was to be expected from 750 gm. of milk, they cut the milk down by half and added vegetables to give the same amount of calcium as the milk removed. If the calcium of the vegetables had been as satisfactory as that in the milk, the calcium retention would have been about the same in the two periods, but instead it went down in the vegetable period. In another experiment they compared the children's retention on 500 gm. of milk and on 500 gm. of milk plus vegetables containing calcium equivalent to another 500 gm., but without getting the increased calcium retention which they might have expected. The only

conclusion which they could draw was that for their children the calcium of vegetables is not as readily available as from milk.

They are careful to prevent the use of these experiments as argument against vegetables for children. "The writers entertain no doubt as to the desirability of a liberal use of vegetables in the feeding of children," they say, "but the vegetables should be used in addition to a liberal allowance of milk and should not be allowed to reduce the amount of milk consumed."

Experiments on dogs.—Considerably earlier than this work of Sherman and Hawley's were observations in Mendel's laboratory at Yale that two grown dogs could use little or almost none of the calcium from spinach or carrots, raw or cooked. On the diets given, the dogs were always in negative calcium balance, but the losses were not nearly so great when the calcium came from milk or from calcium carbonate as they were when it came from the two vegetables. In the most extreme case, the carrot experiment on one dog, the loss was 96 per cent of the intake; or to say the same thing in another way, only 4 per cent of the carrot calcium could be used to prevent the negative balance. The output was almost twice the intake. On the other dog the losses were not quite so great though still rather startlingly high—67 per cent of the intake for the carrot diet and 72 per cent for the spinach. It looks as if one might draw either of two conclusions from this work—that the calcium of these two vegetables is of low value, or that the dogs' digestive tract is not adapted to the vegetables which they do not ordinarily eat. Herbivorous animals, however, cows and goats, do have improved calcium balances when fresh, green plants like fresh, green alfalfa and oats are added to their diet (Hart, Steenbock, *et al.*).

Value of spinach for rats.—Some recent English work by Boas shows beautifully the value of spinach and its limitations, at least for rats and probably by inference for many other species. Three groups of rats were given a basal diet with a fair quantity and good proportion of calcium and phosphorus but not fat-soluble vitamins. One group had in addition cod liver oil and the other fresh winter spinach (previously proved to lack D). The basal group grew fairly well and retained a fair amount of the minerals, but the other two grew decidedly better. On the spinach, in spite of the lack of D the rats gained in weight and in general well-being, but their skeletons grew poorly, the bones being a relatively small proportion of the body weight. The spinach was highly valuable probably for the minerals it added, and vitamins other than D, but it did not accomplish everything.

That the lack of D, however, is not the whole of the story has recently been shown in rat balance experiments by Margaret A. Bloom in the authors' laboratory (Table XIX). Four groups of rats were fed a good basal diet containing plenty of vitamin D (dried whole milk, flour, yeast, butterfat, and cod liver oil) plus for each group either (1) dried spinach raw or (2) cooked or (3) the ash from the same amount of spinach or (4) the ash and finely divided filter paper. Thus the mineral content was identical in all four rations, and the cellulose supposedly the same for three.

Retention of the calcium from the diet with the spinach ash alone, without the cellulose, was remarkably high—very much higher than in Boas' experiment—93 per cent of the intake for the younger set of rats

TABLE XIX

CALCIUM METABOLISM OF RATS*

(GRAMS FOR THREE RATS FOR SEVEN DAYS)

	Low Crude Fiber	Raw Spinach	Cooked Spinach	Filter Paper
Weight of three rats	171	147	141	189
Calcium intake	0.58	0.48	0.50	0.53
Weight of feces	5.0	7.9	8.5	19.3
Calcium excretion				
Urine	0.02	0.01	0.01	0.02
Feces	0.02	0.27	0.25	0.05
Total	0.04	0.28	0.26	0.07
Calcium retention	0.54	0.20	0.24	0.46
Per cent calcium intake retained	93	42	48	87

* Unpublished data by Margaret A. Bloom.

and 58 per cent from a slightly older group, showing that the spinach ash was excellent. When the spinach itself was included, the retentions while still fair were much lower, ranging around 45 per cent for the younger and 30 per cent for the older, but rather surprisingly the rats eating the filter paper and spinach ash kept much more calcium than on the spinach, almost as much as on the ash alone. In order to confirm this lack of influence of the cellulose, the experiment was repeated, using filter paper equivalent to several fold the crude fiber in the spinach, but without significant change in the results. Some characteristic of the spinach other than its actual content of pure cellulose and its lack of vitamin D does lower the availability of its calcium for growing rats.

Apparently only one experiment has been published on crude fiber as such. Sjollema, in 1923, added roughage (oat straw, or oat straw and sawdust) to the diet of one adult rabbit and found the calcium retention

decidedly diminished. The air-dried feces weighed approximately twice as much in the high roughage period as in the first low.

Women.—For adult human beings vegetable calcium and phosphorus seem to be valuable. Three independent sets of experiments have been performed: by Rose at Columbia, on two women and repeated on two others to strengthen her conclusions which were so different from the Yale ones on dogs then just published; by Blatherwick and Long at Santa Barbara, on two women; and by McLaughlin at the Bureau of Home Economics, on seven women. All workers performed balance experiments, including a large amount of some one or more vegetables in the diet—carrots (Rose), cabbage, celery, squash, spinach, lettuce, and asparagus (Blatherwick and Long), and spinach (McLaughlin). Usually the subjects were on a low calcium intake, the diet being so chosen as to give not much more than the minimum on which equilibrium could be maintained. Thus if the calcium of the vegetables was not available, decided negative balances would be expected to appear. Blatherwick's work was planned to study phosphorus particularly, the calcium intakes being high, and higher on the vegetable period than on the milk.

All three sets of experiments show the same thing—the vegetable minerals were satisfactory for the adult subjects, the calcium from Rose's and McLaughlin's work, the phosphorus from Blatherwick's.

McLaughlin's article is the most recent of these and has some points of particular interest. She gave her subjects 0.5 gm. of calcium daily, about three-quarters of it being from milk in the milk period and from the spinach in the vegetable periods. This meant an average of 280 gm. (more than half a pound) of cooked spinach daily—a goodly amount as anyone who has eaten it for six days can testify. (The average serving of cooked spinach is not far from 100 gm.) The rest of the diet consisted of apple, bread, butter, cream, meat, and potato. The milk given the first period was replaced by spinach and cream the second period. The average percentage of calcium in the milk and in the cooked spinach was almost the same—0.1338 and 0.1322.

All seven of her women on *both* the diets stored a little calcium, the daily retention averaging higher on the milk (0.097 gm.) than on the spinach (0.042 gm.). The difference is too small to justify a quantitative comparison of the two foods, but that there should be storage at all on the spinach can be assumed to demonstrate good utilization of its calcium.

Somewhat surprisingly, the feces were excreted at the same speed, as shown by the appearance of the colored marker, on the two diets, and had

about the same percentage of moisture. On neither diet was there a tendency toward diarrhea or constipation. The much talked-of effect of the high residue diets was thus not apparent in the consistency of the stools.

The oxalic acid of spinach is something of a puzzle. This cooked spinach contained on the average 0.712 per cent of it, so that the subjects ate about 2 gm. daily. Yet no digestive disturbances were noticeable, and in spite of the extremely slight solubility of calcium oxalate, the retention of calcium was not interfered with.

From this not large group of experiments, then, it looks as if the calcium and phosphorus of vegetables are satisfactorily absorbed by adult human beings, but not dogs, only fairly well by growing rats, and, especially important, not very satisfactorily by children. We are therefore right, apparently, in including the calcium from vegetables in calculations of diets for adults, but not strictly for children.

ORANGE JUICE

How about the effect of fruit juices? They have no crude fiber and they have a basic residue, which, like the basic residue of the vegetables, may change the high acid-residue of a cereal-meat diet to a nearly neutral one. Also through their own initial acidity they may possibly help keep an acid condition in the upper intestine.

To get an answer to the question, two little girls, ten and eleven years old, served as subjects in balance experiments carried out in the authors' laboratory. They were first given for six to eight days a not very inspiring diet of white bread, oatmeal, rice, Irish potatoes, sugar, oleomargarine, lean beef, and whole milk powder. This menu, which unfortunately was not markedly unlike that of the orphanage from which the children came, had an acid residue and was low in vitamins. On it for this experiment the girls stored a moderate amount of calcium, and half the time a small amount of phosphorus. Then from 600 to 700 cc. of unstrained orange juice was added. The children improved in spirits, lost the distaste they were beginning to show for the first diet, and, as shown by the analyses, stored decidedly more calcium and more than three times as much phosphorus.

The acidity of the urine decreased from a pH of 5.6 or 5.9 to 6.45. The children also stored more nitrogen and gained in weight more when the oranges were included, but these effects may have been due merely to the added calories of the fruit rather than to the other factors which probably explain the favorable mineral changes.

It is of interest that the children could burn almost all of the large amount (about 21 gm.) of citric acid which they consumed daily in the orange juice. They excreted only 6 or 7 per cent of it in the urine, thus confirming the results of other workers for adults who drank orange juice or ate other fruits.

DIFFERENT KINDS OF MILK

Pasteurized versus boiled.—The perennial question as to whether babies deprived of breast milk do better on raw or boiled or pasteurized milk or evaporated, condensed, or dried is of course only in part answered by studies of calcium and phosphorus retention, important as these may be. The answer from such studies, however, seems rather definite. Pasteurization of milk, with the resulting cutting down of infectious diseases, is generally recognized as one of the greatest life savers of recent years, but the process does diminish the availability of the calcium and phosphorus.

Dr. Amy Daniels, of Iowa City, has been one of the workers to emphasize this weak point in pasteurized milk. Some years ago she pointed out that babies and laboratory animals thrive less well on the slowly and long heated pasteurized product than on the quickly boiled. She reports still more results of the same kind in the recent important article that has been often quoted in this book. Her many babies retained three times as much calcium per kilogram from the boiled feedings as from the pasteurized and also considerably more phosphorus. When she added cod liver oil to the two kinds of feeding, the mineral retention went up for both, but on the quickly boiled it was still a little better. Dr. Daniels even thinks it probable that a baby fed pasteurized milk for a long time without cod liver oil or light treatment may actually be getting too little calcium for growth needs. Other workers do not go so far as this, but agree on her main point.

This difference shown with babies is also supported by similar observations on young pigs. For these the pasteurized was less good for retention of calcium and phosphorus than was raw fresh milk or raw sour, and fresh milk and boiled milk were about alike.

Variation in fresh milk.—That fresh milk is by no means invariable in composition and nutritive value has been shown frequently in this book. It varies both in its proximate composition and in its content of vitamins with the food and general management of the cow. Therefore the retention of its calcium and phosphorus might be expected to vary, a fact that has already been shown in discussing the vitamin D of milk from cows given sunshine and a good diet.

Evaporated milk.—Present-day evaporated milk seems to show up well for babies. This product, made by the evaporation in a partial vacuum of approximately 60 per cent of the water of the milk, homogenization, and sterilization in the can, should not be confused with the older sweetened condensed milk. It may owe the successes which are being reported for it to its uniformity of composition, its fine curd, finer than that from raw or pasteurized or even boiled milk, its homogenized fat or the condition of its salts, possibly kept better in suspension in the more viscous, homogeneous liquid. The latter point particularly needs further investigation from a chemical viewpoint.

One recent clinical report will be mentioned since it gives indirect evidence, through the good growth of the babies, in regard to the calcium and phosphorus retention. Doctors Marriott and Schoenthal, in St. Louis, used evaporated milk as the basis of the feeding formula for 752 young infants and compared them with a control series of 670 infants breast-fed or fed on other forms of milk modification. The evaporated milk group was mostly made up of normal newly born infants in the St. Louis Maternity Hospital who for some reason, such as inadequacy of the mother's milk supply, could not be nursed. In addition it contained babies in the dispensary and in private practice and some sick infants in a hospital. All were given cod liver oil and orange or tomato juice in addition to the milk. Eleven of the infants were premature. The evaporated milk babies did at least as well as the others and in some respects better. A larger percentage of the newly born infants on evaporated milk regained the birth weight at the end of fourteen days than did those on the other feedings. The average daily gain in weight of well babies on the evaporated milk was exactly equal to that of babies fed exclusively on breast milk or on formulas prepared from bottled pasteurized milk; the average gain of the sick infants was somewhat better on the evaporated, and the gain of the premature was especially good.

The pediatricians' conclusion, therefore, is that the "evaporated milk is, from the nutritional standpoint, the full equivalent of pasteurized or boiled whole cow's milk" and has "distinct advantages which recommend it for general use as milk for infants."

Laboratory experiments give similar results. Two little boys and two girls of eight and twelve years served as subjects for balance experiments in the authors' laboratory. They all had a satisfactory diet containing al-

most a quart of milk daily—evaporated in one period and pasteurized in the other. All of the children ingested generous quantities of calcium and phosphorus and all showed high retentions on both kinds of milk. But the phosphorus retention was higher on the evaporated for all cases and the calcium and nitrogen higher for three of the four. The evaporated milk, therefore, was a thoroughly satisfactory source of calcium, phosphorus, and nitrogen, slightly superior to the pasteurized (Willard and Blunt).

Much to the point is the fact that the bones of young pigs may vary in strength with the kind of milk fed. On raw milk, according to Washburn and Jones in Vermont, the breaking strength of the pig's femur was 297 pounds, as opposed to 263 on the evaporated and 200 on the sweetened condensed.

Dried milk.—Four children who served as subjects in experiments at Kansas State Agricultural College retained less calcium and phosphorus from "a standard brand of dried milk made by the spray process" than from fresh milk. A number of adults also showed less favorable balances on the dried than on fresh milk (Kramer and others).

From all this evidence the conclusion seems to be that fresh and evaporated milk and quickly boiled are superior to pasteurized or dried milk, as sources of calcium and phosphorus. Work on babies in hospital or clinic, on children in the laboratory, and on various young animals seems to point in the same direction. It should be repeated, however, that pasteurization of milk is one of the most important of public health measures. But if pasteurized milk is used, antirachitic treatment to insure good bone development seems to be especially advisable.

SUMMARY

The kind of food which makes up the diet does thus have considerable influence upon the calcium and phosphorus metabolism. Cereals seem to have a real anticalcifying effect, the whole cereal more than the refined, but that this effect may be completely overcome by adequate supplements, even when the diet contains a large proportion of the cereal, has been shown by both animal and human observations.

Sucrose depresses and lactose elevates calcium retention when taken in large quantity. Manipulations of milk may change it as a source of the two elements, they being more readily stored from raw or quickly boiled or evaporated than from pasteurized or dried.

From vegetables the calcium and phosphorus seem to be entirely satisfactory for adult human beings but less satisfactory for children, less than the calcium and phosphorus in milk. Orange juice, on the other hand, increases a child's storage of calcium and phosphorus by an amount greater than that added in the fruit.

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CHAPTER XII

PREGNANCY AND LACTATION

The three periods in life when calcium and phosphorus are especially needed are the growth period, when the material is being stored in the individual's own body; pregnancy, with the demand for the developing fetus; and lactation, with the requirement for the large amounts secreted in the milk. The two latter periods are discussed in this chapter.

During pregnancy, the important questions are: How much of the elements does the fetus require? Can the whole of this quantity be obtained from the food or must the mother's own reserves in bones and teeth be drawn upon? During lactation, there are similar questions: first, Is the milk always adequate for the child's needs or does its composition as well as its quantity vary with the treatment of the mother? And, second, Is the mother's own body necessarily sacrificed to the milk?

Of the very incomplete answers available to these questions those on human beings will be given first.

THE CALCIUM AND PHOSPHORUS OF THE HUMAN FETUS

Studies on the composition of the human fetus date well back into the last century. In 1877, the German chemist, Fehling, determined the ash content of eleven fetuses of different stages of development, and since then something like sixty-six analyses for calcium and fewer for phosphorus have been reported in Germany, France, and America.

It is hardly surprising that the different results are not very consistent one with another. It is difficult to measure the age of the fetus, and especially it is difficult to be sure that the fetus is normal in composition in view of its very availability for analysis. The weight of the fetus at six months, for example, according to the different authors, varies from 362 to 1,165 gm., and figures for the total ash and for the calcium and phosphorus vary more than for the whole weight.

Even at term there is considerable variation in composition; the calcium of the newborn babe is as much as 33 gm. in some cases and less than half of this in others. Plainly, infants may come into the world with quite different amounts of minerals in their bodies. Unfortunately, we cannot tell whether the babies with high minerals, if they had lived, would have

been much better off and less subject to rickets than those with low minerals, but animal experiments do give evidence of the superiority of the higher ash content. Particularly interesting, also, is the fact that the lowest figures from any investigation for a given fetal age appeared in the post-war period in Germany when rickets and osteomalacia were prevalent.

This amount of 33 gm. of calcium which may be deposited in the fetus during the whole period is by no means an inconsiderable quantity for the woman to save out of her daily diet, often, apparently, too large a quantity. This is shown by the very slight positive balances in some of the pregnant women in the Chicago study discussed here. Most of this calcium is laid down in the latter months of pregnancy. Measurable daily calcium deposition begins the fourth or fifth month, and then increases slowly and fairly steadily, but it is during the last two months that almost two-thirds of the total calcium deposition takes place. In Figure 37, page 185, are given the average daily fetal demands for calcium as determined by the analyses of two investigators—0.34 gm. a day at the end, according to one set, and 0.28 gm., according to the other.

The phosphorus storage, being in fetal muscle as well as bone, begins in considerable quantity a little earlier than does the calcium, but for it also two-thirds of the total is deposited in the last two months. The final quantity reported is lower for the phosphorus—around 17 gm. at term, according to one set of analyses.

So much for the probable calcium and phosphorus of the fetus. How about the retention of the minerals by the woman? Does she retain enough from her food or must her body meet this fetal demand? The best way to answer the question is a balance experiment.

BALANCE EXPERIMENTS ON PREGNANT WOMEN

Until recently there have been just two reports of mineral balances on pregnant women. Both of these include phosphorus but only one calcium.[1]

Hoffström's study.—In 1905, Hoffström, at the University of Helsingfors, determined the retention by one woman of calcium, phosphorus, nitrogen, magnesium, sodium, potassium, sulphur, and chlorine weekly for the last twenty-three weeks of gestation—a large and important investigation. The different weeks show much fluctuation, some with actual negative and some with high positive balances, the variation probably being in part at least due to delayed excretion of the feces which he did not separate by markers. In reporting his results, however, he calculated the total amounts stored at the end of certain fairly widely spaced periods of the pregnancy, so that the irregularities are smoothed out and definite trends shown.

[1] The survey of the literature concerning balance experiments on pregnant women is quoted from the doctoral dissertation of Mrs. Callie M. Coons, University of Chicago, 1929. (See reference list at the end of this chapter.)

He found that at the fortieth week the woman had stored a total of 34.3 gm. of calcium—more, that is, than the probable amount in the fetus—and was storing for the last ten weeks at the high average rate of 0.32 gm. daily. For phosphorus the total retention was a surprisingly large amount (56.0 gm.), though the final storage rate was about the same as for calcium. He concludes, therefore, from comparison of his retention results and average figures for fetal composition that the mother had saved a little calcium for herself during the entire pregnancy and considerable phosphorus and nitrogen (the figures being 4, 38, and 209 gm., respectively). These extra materials were presumably used in part for the growth of the placenta, the woman's own muscles, mammary glands, etc., but beside this, according to Hoffström's interpretation, there was much "rest material" retained in the woman's body, pregnancy thus being a period of actual material gain for the mother. Certainly she did not seem to give her own reserve to the child she was carrying. It is noteworthy that the mineral intake of this woman was high, including on the average 1.7 gm. of calcium and 2.0 gm. of phosphorus.

Landsberg's study.—The other retention study was a German one, reported by Landsberg in 1912. He observed the balance of phosphorus, sulphur, and nitrogen (not the calcium) for six different women for four- or five-day periods scattered over the latter half of pregnancy. The data therefore show the rate of retention at different times rather than the total retention throughout pregnancy as did Hoffström's.

His women, like Hoffström's, were all retaining phosphorus in excess of the supposed needs of the fetus. The range of storage was from 0.19 gm. in the eighteenth week to 0.36 gm. in the thirty-seventh. The phosphorus intakes were also high, about 1.8 gm. a day.

THE UNIVERSITY OF CHICAGO STUDIES

These two early foreign investigations, important and valuable though they are, seemed inadequate to show how the elements are being stored during the pregnancy of American women today. Mrs. Callie M. Coons,

at the University of Chicago, therefore undertook to secure further data. She has determined the calcium, phosphorus, magnesium, and nitrogen balances of nine women during one or more periods from the eleventh to the thirty-ninth week of pregnancy. She went to the homes of her women to weigh the food and take samples for the analyses and to secure their constant co-operation in collection of excreta. The women meantime lived their usual lives, with their usual household tasks, family duties, rest, and recreation, and ate as their own habit and inclination dictated or their physicians ordered. Some of the subjects were members of the University community and others were attending the clinics of the Infant Welfare Society of Chicago. All were themselves eager to find out what was happening in their own bodies and were willing to forego meals out and submit cheerfully to the régime of the investigator's thrice daily visits during the five-day periods. Two women served as subjects during five periods, three during three, and the other four for one period only.

The calcium balances.—The chart of the calcium balances is reproduced on page 185. It gives the daily retentions of all the subjects at the various periods and also, for comparison, the daily increment to the fetus during each week as calculated from the published figures of fetal composition by two investigators.

The two most interesting women as seen by the chart, are Subjects A and B. Both of these, in their five observation periods, show fairly smooth curves of increasing calcium retention as the pregnancy progresses, and they both give calcium retention figures not far distant from the expected fetal demand. A, however, at the first observation was decidedly in negative balance and at the next was storing much more than the expected amount, an entirely logical situation since she was just recovering from a prolonged period of nausea and still eating very moderately when the experiment started, and by the second period was consuming the most calcium of any of her observations and apparently making up in storage for lost time. Subject A took cod liver oil from the twenty-fifth to the thirty-fourth week and then spent an hour or two sitting in the sunshine till the baby was born on June 8. Subject B did not take cod liver oil or sun baths and her baby was born in April.

These two women seem, therefore, to have stored about as much as probably went into their babies' bodies. So, too, did Subject I, who showed the highest retention of all during the one very late period which was obtained from her. Possibly a slight mineral reserve for lactation was being built up by these women.

The curve which may be taken as a tentative standard for calcium retention, based on the eleven observations of these three subjects, begins to rise about the fourth month, continues gradually to about 0.20 gm. a day by the ninth month, and then somewhat more steeply to a point

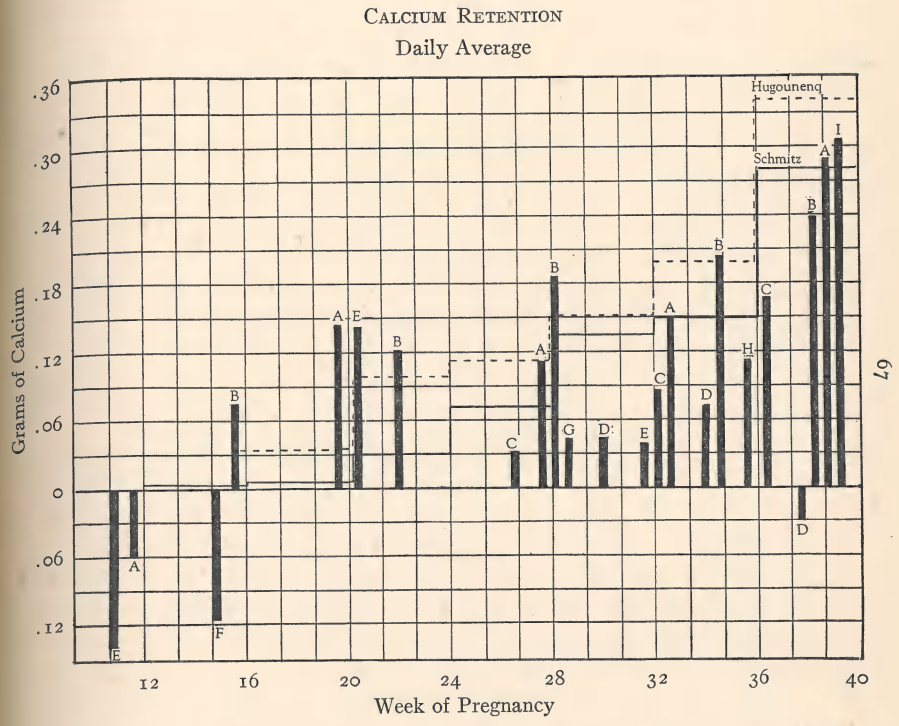


Fig. 37.—Daily calcium retention of nine pregnant women at different weeks of pregnancy. The horizontal lines represent the average daily calcium increments to the fetus computed from analyses by Schmitz and by Hugounenq. (From Coons and Blunt, *Journal of Biological Chemistry*, LXXXVI [1930], 1.)

around 0.30 gm. a day the last week before delivery. These figures are decidedly lower than those for Hoffström's woman who actually averaged a retention of 0.32 gm. for the entire ten-week period, whereas no woman in this study reached this figure even by the end of the pregnancy.

The behavior of the other six women tells a very different story. Their retention was always low, very low in some cases, and in three periods there was no storage but actual losses. Presumably they were

constantly withdrawing calcium from their own bones and teeth for depositing in the fetus, or possibly at the same time the fetus was receiving an inadequate supply.

The explanation of these low retentions in contrast to the other three fairly high subjects is by no means clear from the material available. The quantity of calcium ingested is undoubtedly part of the difference, but not consistently so. All cases of intake less than one gram, except two of B's periods, resulted in low or negative balances, but high intake was not always accompanied by high storage. Little or no vitamin D in the diet and the passage of the latter months of pregnancy in mid-winter may have had something to do with the unsatisfactory behavior of Case D. This woman, whose low storage forms the worst picture of any subject for all elements studied, presented special problems of her own. In her final period she had intestinal disturbances with the passage of two or three stools daily, and as she had already been storing with little margin it did not require much change for her slight positive balance to swing to a negative one. Also her diet all along included much raw vegetable so that the too high fiber may have meant a lower really available calcium intake than shown by the food analysis.

The general conclusions to be drawn are not too encouraging. Here were six out of nine American women storing much less calcium than they probably were giving to the fetus. The cause of their inadequate performance is not clear—possibly low calcium intake, or low vitamin D and light, possibly in one case at least too high fiber and a resulting mild diarrhea.

The phosphorus balances.—The phosphorus balances are less clear-cut. For subjects A, B, and I they were high as was calcium. D was twice negative. The other subjects show better phosphorus retention than calcium. The general trend is a phosphorus retention considerably higher than the supposed fetal demand, and beginning with high figures much earlier in the pregnancy than for calcium. It looks as if the women were storing the phosphorus for the growth of their own muscles as well as for the child, and for Hoffström's "rest material."

X-rays of the babies.—As this study was concerned with pregnancy only and the babies after birth varied as to breast- or bottle-feeding, sunshine, cod liver oil, etc., the only X-rays that could have much significance were those taken early. Roentgenograms were, therefore, secured of the tibia and fibula and of the ulna and radius of all the babies, except Baby I, at eight days old—too young to show sharp signs of rickets.

The plates did, however, show some real differences. Mrs. Coons writes,

Examinations of them, in conference with Dr. Compere of the Billings Hospital of the University of Chicago indicate three possible groupings of the plates. The cases of poorest bone formation presented prerachitic evidences, such as definite cupping at the distal end of the ulna, or tendency to flattening and fringing at the ends of the other long bones. The epiphyseal ends of the diaphyses appeared to be lacking in density or were poorly outlined by calcification. Babies D and H showed these characteristics most markedly.



FIG. 38—X-ray of Baby H (Coons)

In the group showing the best bone formation, the ends of the long bones were normally rounded or pointed, well defined, and the most highly calcified portion, particularly of the ulna and tibia, was the growing end of the shaft. Baby C was the best example of this group. Babies A, B, and G comprise a third or intermediate group ranging between the extremes of the first two groups. In these cases there was no cupping at the distal end of the ulna, but occasionally there were irregularities in the smoothness of the ends of some bones, or absence of the dense margins of growth such as Baby C showed.

That Baby C should be the best supplies the surprising point in this statement because of the low calcium retention by the mother during the

first two periods observed (the twenty-seventh and thirty-third weeks) and the only fairly high retention during the third observation in the thirty-seventh week. Her phosphorus storage, however, was decidedly high. It is disappointing that one more balance two or three weeks later just before delivery could not have been secured, for one is inclined to think that then calcium retention must have been well up.



FIG. 39.—X-ray of Baby C (Coons)

THE MERRILL-PALMER STUDIES

A remarkably interesting series of observations has been made by Macy, Hunscher, and others at the Merrill-Palmer School, Detroit, on two wet nurses connected with the Children's Hospital. These nurses are becoming famous subjects of scientific research because of their serving as subjects in these experiments and because they are rather remarkable milk-givers.

So far only a preliminary report by Hunscher has been published and a somewhat fuller statement given at the Biochemical Society meeting in 1928, of the calcium and phosphorus balances of these two women at cessation of lactation, when milk production had been going on for eleven

and fourteen months. They had been producing large quantities, one woman from 40 to 113 ounces, and the other from 23 to 88 ounces, and eating meanwhile diets high in fuel value and also high in calcium and phosphorus—about 3 to 4 gm. of each daily.

The ten-day balance experiments which were conducted in the homes of the women at the time they chose to cease lactating showed each one actually storing a considerable quantity of calcium and phosphorus—about 0.6 and 0.2 gm. of calcium daily and 0.9 and 0.2 gm. of phosphorus. This storage might be interpreted in either of two ways—it seems to the authors of this book—either as an indication that lactation strain had not been causing loss, or, more probably, that the losses which may have occurred when milk production was at its height and when no balances were observed, were being made good by retention at the time lactation had much diminished. Other experiments soon to be published show that the latter of these two interpretations is the true one. Two other balances were secured by Hunscher on the same wet nurses during a second lactation after an intervening pregnancy, and two balances on a third woman—six balances in all at about the seventh and the twenty-seventh weeks of lactation. The women were living under the same régime as before, ingesting large quantities of calcium and giving large volumes of milk. All three at each observation were in *negative* calcium balance; they were taking calcium from their own reserves for the milk, in spite of the very high intake.

Very striking was the change when the women took cod liver oil for some weeks and then repeated the metabolism experiments.[2] Positive calcium balances were then observed. The vitamin D had apparently permitted the assimilation of enough food calcium to prevent loss from the women's bodies, and this in spite of continued high milk production—a remarkable demonstration of the prevention of strain of lactation. The details of this work and of other related investigations are eagerly awaited.

ANIMAL EXPERIMENTS

There is much in animal experimentation that may probably be transferred directly to the human mother and child. First, the question of the drain of reproduction on the mother's body.

The calcium content of female rats.—From Sherman's laboratory at Columbia has come an elaborate and most interesting series of calcium

[2] Macy, Hunscher, and others kindly permit the authors to report this work, which is soon to be published in the Journal of Biological Chemistry.

analyses of the bodies of the rats raised for generation after generation on his milk and whole wheat diet (chapters i and x). Most of the figures are for animals on the better of his two rations—that with one-third dry milk and two-thirds whole wheat—that is, on animals superior to the usual breed. The point of special interest here is that the females which had reared young had in their bodies consistently less calcium than females of the same age which had not reared young. The difference amounted to as much as 10 per cent. The losses were greater when the analyses of the mother-rat's body were made immediately after weaning the young and less when some weeks had passed. The loss due to the pregnancy and lactation was thus in part made up after lactation but the recovery was never complete; these rats never had quite the same amount of calcium as their sisters who had not contributed to the propagation of the race.

It is of interest, too, that females who had *not* borne young had a somewhat higher percentage of calcium than males, and that the loss due to rearing young brought the figures for the females down to just about the same as the males. It looks as if the female rat body on the superior diet contained extra calcium ready to hand over to its young.

BALANCE EXPERIMENTS ON PREGNANT AND LACTATING ANIMALS

A milking cow may secrete from a quarter to a half as much calcium and phosphorus in the milk as it excretes in urine and feces. It is not surprising, therefore, that negative calcium balances have been found for lactating cows on experimental diets and probably occur rather frequently on ordinary rations. Forbes, who has devoted much work to the study of mineral balances of cows, speaks of a cycle of calcium and phosphorus retention similar to that just found in part by Hunscher and Macy on their women—a loss during periods of high milking followed by a restorage during the period when the cow is dry. The loss of calcium may be lessened or prevented in some cases at least by increasing the calcium of the diet as by the addition of marl, but not, rather surprisingly, by ultraviolet light. In an early experiment, the Wisconsin investigators presented figures which they interpreted as meaning that a negative calcium balance was lessened (not checked) by outdoor sunlight but, after their work with artificial ultraviolet, they remark that the slight improvement "must be explained on a basis other than that of a direct irradiation effect." The light does improve the general condition of the cow but does not seem to lessen the mineral loss. Forbes writes that vitamin D and sunshine are

both "influential in the control of the metabolism of calcium and phosphorus."

Milking goats are more easily affected than are cows. Their negative calcium balance is changed to a positive by irradiation with a mercury quartz lamp, and also by giving cod liver oil or the unsaponifiable portion of cod liver oil dissolved in corn oil. Why the cows and goats should react differently to light is not clear—possibly differences in the secretory function of their skins or in the relative amounts of body surface in proportion to the metabolizing parts of their body and the volume of milk produced. Women apparently react more like the goats than like the cows.

THE EFFECT OF MATERNAL DIET ON THE COMPOSITION OF THE MILK

That vitamin D in cows' milk can be slightly but not markedly increased by improving the cow's rations has already been discussed in chapter viii. So, too, has the uncertainty about its increase by irradiating the cow, and the clear-cut proof of its doubling in the milk of a goat when the goat is irradiated. Irradiating the human mother puts vitamin D into the milk to at least a slight extent. Hess and his co-workers have shown this for human mothers, and so also has Gerstenberger. The effect of cod liver oil on women's milk is less sure, Hess reporting failure to find any increased antirachitic potency when the mother took the oil and Weech demonstrating slight improvement.

For the best controlled experiments on the effect on the milk of the various antirachitic treatments of the mother, experiments much easier to carry out than on human mothers or large animals, the investigator has as usual turned to the rat. The experimental method, however, has to be changed somewhat. The human milk and the cow's and goat's are fed in the usual way to rats on a rachitic diet, but the rat's milk cannot be obtained in quantity for any such procedure. Instead, the young from a female on diets rich or poor in vitamin D are given on weaning a rachitic diet. Observations are made on the time they take to develop rickets and on its severity. If the young are protected against the development of rickets, the conclusion is drawn that they had a store of vitamin D in their bodies when they were weaned, and that therefore vitamin D had passed into the milk of the mother from the diet. Precautions have to be taken that the young rats do not secure vitamin D directly from the mother's diet, so feeding the mother the vitamin D rich diet (cod liver oil) is discontinued usually after the first two weeks of lactation when the

young rats begin to move more about the cage and supplement their nursing.

Hess and Weinstock, using approximately this method in 1924, concluded that feeding cod liver oil to the mother rat did not protect the young against rickets and that therefore vitamin D does not pass into the milk. McCollum *et al.* (1927), however, criticize Hess and Weinstock's work on the ground that the rachitogenic diet which the young rats were fed was so severe that a slight protective action would not be noticeable. McCollum himself found that young from mothers fed cod liver oil gave a much better line test, and so showed that vitamin D had undoubtedly passed into the mother's milk from the diet.

The weight of evidence from a variety of animals and from women, therefore, seems to be on the side of urging the lactating woman to take cod liver oil or to be much in the sunshine, both for her own sake and her baby's.

Even the mineral content of a woman's milk may be low in extreme cases. Several years ago this was shown by Brown, Courtney, and coworkers in a critical study of two cases of rickets in breast-fed infants; for the milk of both mothers was much lower in calcium than normal breast milk. Neither woman drank milk; both ate very little vegetable and no butter at all, and one had no eggs. The calcium must have been very low in both diets and the vitamin D very low in at least one.

It is undoubtedly true that good diet and antirachitic treatment given to the mother do more for the mother than indirectly for the baby, and that for the baby's protection its own direct treatment with light or cod liver oil is the greatest safeguard. Nevertheless some improvement of the milk to the baby's decided gain is possible and within the mother's control. To quote McCollum, "It is clear . . . . that the diet of the pregnant and nursing mother is of paramount importance in determining the quality of the milk she will produce."

SUMMARY

In summary of the incomplete knowledge of calcium and phosphorus metabolism during pregnancy and lactation, we may well emphasize the following points:

The elements are deposited in the human fetus from about the fourth month on, very slowly at first, then much more rapidly, about two-thirds of the total 25–35 gm. of calcium being laid down in the last two months. Pregnant women have been found to store quite different amounts of the two elements during gestation, in some cases well over the supposed fetal demand, in others decidedly under this amount, especially for calcium, as if the calcium for the child were being taken from the mother's body or possibly stored too scantily in the child itself.

Two vigorous lactating women, toward the end of a long period of high milk-giving, have been found to be actually storing calcium and phosphorus, but other observations made earlier during a second lactation showed them to be losing the elements; that is, when the milk production was at its height, their bodies could not assimilate enough even from a very high intake, but when milk production was low restorage began to take place. The loss was not observed, however, when cod liver oil was given—a most important observation.

Animal experiments have much to contribute to this subject. Lactating cows, like the women, usually show a cycle in their metabolism of the elements—a loss during periods of copious milking, followed by a storage when milking stops, provided the diet is adequate. Losses during lactation can be lessened for cows and goats and rats by making sure that the diet contains adequate amounts of the minerals and of vitamin D, and that the animals have plenty of sunshine or artificial ultraviolet. Bearing and rearing young does mean a drain on the calcium of the mother's body as is well shown by the fact that female rats which have raised young have less calcium than those on the same excellent diet which have not borne young. On a poorer diet the loss of the rat's calcium is much greater and is even extended to a low calcium in the young. The composition of the milk seems to vary somewhat but not greatly with variation in the treatment of the mother and results are not the same for all species. Irradiating a woman does more for her milk than does taking cod liver oil. The baby, however, gains more by direct irradiation or by having cod liver oil itself than by indirect treatment through the mother.

There thus seems to be little doubt that for women as well as for animals during pregnancy and lactation, care of the diet, including cod liver oil, and exposure to sunshine are vitally important for safeguarding the maternal organism and are also of significance to the offspring.

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CHAPTER XIII

DO ADULTS NEED VITAMIN D?

The answer to the question as to the adult's need for vitamin D clearly is, "Yes, but not so much as the growing organism." Short laboratory experiments on normal men and women have not as yet shown any effect from adding or withdrawing vitamin D, but in certain abnormal conditions its influence has been demonstrated, especially in a serious disease of the bones, osteomalacia. The latter disturbance, in one of its manifestations at least, appears to be a deficiency disease traceable to lack of vitamin D or light.

EXPERIMENTS ON NORMAL MEN AND WOMEN

The three following experiments, performed on normal men and women, were planned so that an influence from giving vitamin D might have been expected, but all of them showed only negative results.

Blood phosphorus.—Some healthy young men in England were found to show a certain amount of seasonal variation in the inorganic phosphorus of the blood, similar to that found in children not receiving antirachitic treatment. The value was low in winter (about 2.9 mg.) in contrast to high in summer (about 4.0 mg.). Yet unlike the effect with children the winter low figures were unchanged when the men were given irradiated ergosterol for twenty-one days or when their bodies were irradiated directly with a carbon arc lamp for sixteen days. Whether the elevation in summer is due to the increase in sunlight, as one tends to suppose, is made somewhat doubtful from the experiments.

Balance experiments.—It is not illogical to think, from analogy with children's balance experiments, that adults brought into slight negative calcium and phosphorus balance by a diet low in the elements would have this negative balance changed to positive by antirachitic treatment. Such, however, has not been found to be true, at least during the few days or weeks of the laboratory observations.

In the authors' laboratory, two groups of women, seven in all, served as subjects for calcium and phosphorus balance experiments including in one period a fairly large quantity of ordinary rolled oats and in the other the same amount of irradiated rolled oats, supplied by the courtesy of the

Quaker Oats Company and already proved by rat experiments to have decided antirachitic potency. All the subjects curtailed their calcium intake to from 0.23 to 0.275 gm. a day, so as to get themselves into slight negative balance in the hope that the vitamin D of the irradiated cereal would check the loss. For every woman, however, the negative balances were almost exactly the same on the two diets, the average losses of calcium being −0.10 gm. and −0.14 gm. a day for the first group and −0.11 gm. and −0.12 gm. for the second group (see Table XX). The phosphorus

TABLE XX

CALCIUM AND PHOSPHORUS BALANCE WITH PLAIN AND IRRADIATED ROLLED OATS* (GRAMS PER DAY)

SUBJECT	CALCIUM				PHOSPHORUS			
	Ordinary Rolled Oats		Irradiated Rolled Oats		Ordinary Rolled Oats		Irradiated Rolled Oats	
	Intake	Balance	Intake	Balance	Intake	Balance	Intake	Balance
I	0.275	−0.10	0.26	−0.19	1.21	+0.12	1.26	+0.04
II	0.275	−0.12	0.26	−0.13	1.21	+0.02	1.26	+0.04
III	0.275	−0.07	0.26	−0.09	1.21	+0.08	1.26	−0.10
Average	0.275	−0.10	0.26	−0.14	1.21	+0.07	1.26	−0.01
IV	0.23	−0.05	0.24	−0.04	1.00	+0.10	0.91	+0.01
V	0.23	−0.07	0.24	−0.09	0.94	−0.19	0.95	−0.08
VI	0.23	−0.18	0.23	−0.20	0.94	−0.23	0.97	−0.10
VII	0.23	−0.14	0.25	−0.15	0.92	+0.06	0.95	−0.01
Average	0.23	−0.11	0.24	−0.12	0.95	−0.07	0.95	−0.05

* Unpublished data from the Master's thesis of Anna Jaros, and from work by Misses Gillum, Lattin, Pittman, and Wing, and Mrs. Elder, Department of Home Economics, University of Chicago.

balances, on a higher phosphorus intake, showed a little more fluctuation but still no consistent differences on the two kinds of cereal.

The first group ate considerable potato with the result that the diet had a somewhat basic residue equivalent to about 6.5 cc. of excess normal alkali a day; the second group substituted bread for the potato, giving an acid residue equal to about 5.2 cc. of normal acid, but this change made no difference in the results.

In another somewhat similar experiment elsewhere, a young man was put on an acidotic diet low in calcium and phosphorus, and as a result he was losing minerals from his body; yet giving him cod liver oil and irradiating his body were without effect in lessening his almost constant negative balances (Hart *et al.*).

These few short-time experiments with negative results are not completely convincing in regard to possible advantage from cod liver oil dosage. Neither are the few animal observations listed later. The experience of some nutrition-workers, notably Dr. McCollum and Dr. Daniels, leads them to advise regular consumption of cod liver oil by adults during the winter months with the hope of maintaining vigor and lessening susceptibility to colds. It may be that the advantage noted comes from the vitamin A of the oil more than from the D. Very interesting would be a prolonged series of balance experiments on adults taking cod liver oil for several months, but the difficulty in such a series would be to keep conditions constant throughout.

Pregnancy and lactation.—That vitamin D has decided influence in pregnancy and lactation, both for the mother and the offspring, human or animal, has already been shown in the preceding chapter. It is in such conditions when there is the special biological demand for the calcium and phosphorus that the vitamin is most effective.

EXPERIMENTS ON ADULT ANIMALS

On adult animals there are a few experiments which seem to show a favorable effect on calcium and phosphorus metabolism from giving vitamin D, but there is also some evidence that much vitamin D may bring about *increased* excretion of calcium in adults. Greenwald and Gross, at the Roosevelt Hospital, New York, have recently reported feeding one normal dog a calcium-low diet for several weeks and then changing the 35 cc. of maize oil in the diet for the same quantity of cod liver oil. The calcium in the feces for the following twelve days gradually increased till it was much higher than the average on the maize oil—as much as 37 per cent higher, according to one method of computation. The nitrogen output diminished slightly and the phosphorus remained almost unchanged. If, however, allowance is made for the amount of phosphorus which might be expected to be retained in protein with the nitrogen retained, it is seen that the calcium excretion really was accompanied by phosphorus excretion, approximately in the proportion of 2 to 1. This ratio is that in bone and also in the increased excretion brought about by the administration of parathyroid extract. The probable relation between the parathyroid and vitamin D is discussed later.

Two earlier experiments not in accord with these results are adversely criticized by Greenwald and Gross—Sjollema's, which showed a favorable influence of cod liver oil on the calcium retention of a mature rabbit,

and Yoder's, with increased calcium and phosphorus retention by adult rats on a rickets-producing diet when cod liver oil was added or the animal irradiated.

It thus looks as if short time withdrawal of vitamin D or its addition in moderate amount has no measurable effect on the calcium and phosphorus metabolism of the adult but that addition of large amounts of it may possibly do harm.

ABNORMAL CONDITIONS

The negative results on adults, it should be repeated, have been obtained on normal, healthy individuals. In more or less abnormal or unusual conditions, when the body has special need for calcium, the reports are different. The healing of fractures, for example, has been hastened by taking cod liver oil or by irradiation. Carious teeth in an adult have been found to be decidedly improved by giving irradiated ergosterol. Mrs. Mellanby reports one such case, that of a young woman about eighteen or twenty years old whose wisdom teeth were decaying rapidly but whose other teeth were good. Treatment with radiostol appeared to stop the decay of the wisdom teeth. Other adult cases are under investigation.

OSTEOMALACIA

Osteomalacia, a serious but comparatively rare disease of adults in the same category as rickets in children, involves generalized softening of the bones. It is found chiefly in pregnant and lactating women and in old people, especially in famine districts or where peculiar religious or social prohibitions keep women indoors away from light.

An appalling account[1] of it in India is given in Kathleen O. Vaughan's recently published *Purdah System and Its Effects on Motherhood.* In Kashmir, according to this author, and particularly in Srinagar, which lies in a deep valley in the mountains, the Purdah system affects the better class of young girls from the age of eight or ten years until after marriage and the birth of one or two children. Because of religious and social taboos the girls are more or less confined to the house so as to be secluded from all men except their brothers or husband, and are closely veiled when they do go out. At childbirth the women are kept in dark, unventilated rooms, often for as long as forty days. The valley is shaded from the sun even in summer and especially during the long, cold winters. Osteo-

[1] Quoted in part from a review of the book in the *British Journal of Actinotherapy,* III (1928), 97.

malacia is common among these women, usually beginning with the first pregnancy, and is worse in winter and early spring. Women of the lower class who are out all day in the open air are of fine physique and entirely free from the disease. It is unknown, too, among the men and boys. That absence of light is a chief cause of the osteomalacia finds confirmation from other parts of India. In Bombay, for example, women of the weaver class who live in back rooms on the ground floor of eight- or ten-story buildings suffer badly from the disease, while it is uncommon among the Parsee girls and women who go out freely from childhood.

In China, too, especially in the northern and western portions, the disease is common in women of child-bearing age. Physicians are attacking it as a dietary deficiency disease due in part to recurring famine and unwise diet, which consists largely of cereals (millet) and a limited amount of vegetables, without milk, meat, or eggs. It may be cured or prevented by improving the food and giving cod liver oil. At Peking Union Medical College several calcium and phosphorus balances have been observed on four patients before and after receiving treatment. Three showed negative calcium balances at the beginning, and one, who had had a little previous treatment, a slight positive balance. Cod liver oil alone improved the balance, cod liver oil and a calcium salt much improved it, and olive oil and a calcium salt did not help. The blood calcium and phosphorus, low at first, were also raised, and the clinical gain was great—all good evidence that in China the disease seems to be especially of dietary origin owing to low intake of calcium and vitamin D. Limited exposure to light also seems to be contributory, since the women who work in the fields are much less apt to have osteomalacia than the middle class women who stay indoors.

The serious famine conditions in Vienna after the war brought many cases known as "hunger osteomalacia." The first were reported in the late autumn of 1918 and others through 1920, with increase in the winter and diminution in the summer. The years 1918 to 1920 were a period of great food deprivation in Vienna. The disease, as might be expected, occurred chiefly among the poorest inhabitants and especially the middle aged and old people of both sexes. The symptoms were pain in the sacral region and in the ribs on compression, a waddling gait, difficulty in mounting stairs, occasional tetany, and in a few cases spontaneous bone fractures. X-ray showed osteoporosis. The successful treatment consisted in improving the diet and giving cod liver oil.

A recent account of two cases of senile osteomalacia reports distinct

improvement, with increase of the serum calcium following treatment with irradiated ergosterol.

Osteomalacia, it may therefore be concluded, is a deficiency disease, due largely to a faulty diet and especially to lack of vitamin D and light. It is also occasionally found under less abnormal conditions of living and then, according to medical reports, seems to be associated with tumor or other abnormality of the parathyroids.

THE PARATHYROIDS AND VITAMIN D

The parathyroids have for some time been known to affect calcium metabolism and so, as shown throughout this book, has vitamin D. Only rather recently have efforts been made, with partial success, to show the relation between the two influences and to reconcile some of the numerous apparent contradictions. The article by Greenwald and Gross, just quoted (p. 198), helps greatly.

These authors and others before them set forth the view that the parathyroid hormone controls the internal calcium equilibrium. Removal of the parathyroids lowers the serum calcium and the calcium excretion; that is, the calcium is not mobilized from the bones or elsewhere. Administering parathyroid extract to animals or human beings increases serum calcium, mobilizes more calcium, which is held in the blood because of its increased calcium dissolving power. If the administration of parathyroid is prolonged, the calcium excretion is increased, so much being excreted that it must be drawn from the bones—enough so that the microscopic appearance of the bone trabeculae is decidedly changed.

Abnormalities of the parathyroid, such as parathyroid tumor, have been shown to bring about high blood calcium and high excretion of calcium, leading to continued negative calcium balance. Some cases of osteomalacia in this country in patients whose diet and light exposure seem to be normal have been traced to such a tumor, and have been cured by its operative removal.

Cod liver oil probably exerts its effect on calcium metabolism by stimulating the parathyroid tissue to increased activity, more parathyroid hormone being produced. Partial proof of this relation is found in Greenwald and Gross's experiment on the adult dog just described. The cod liver oil had just the effect of increasing calcium excretion that parathyroid extract would have had. Further proof is supplied by Hess, who quotes the following experiment. A monkey having a low blood calcium as the result of several months on a calcium deficient diet was fed large

quantities of irradiated ergosterol, which promptly raised the calcium of the blood to normal. After the parathyroid glands had been removed, however, the blood calcium fell once more and could not be raised by any amount of irradiated ergosterol.

It is not surprising, in view of this relationship, that growing animals and adults should react differently because of the great differences in the calcium equilibriums in their bodies. The young, with their constant need of calcium for bone growth, can dispose of the element almost as fast as they get it, so that stimulating the parathyroid and so increasing the calcium of the blood means *increased* retention. Adults, on the other hand, have only a smaller, steadier need for the mineral, so a temporary increase in the blood means *decreased* retention and actual loss. To quote Greenwald and Gross:

> If we assume that the parathyroid hormone, directly or indirectly, increases the calcium-dissolving power of the plasma and that cod liver oil stimulates the parathyroids, it may readily be seen that the addition of cod liver oil to a diet rich in calcium that is being fed to young animals, in which calcium deposition is rapid, or to lactating animals in which also large amounts of calcium are removed from the blood, might lead to an increased absorption of calcium; whereas the same addition, particularly when combined with a calcium-deficient diet, in the case of adult and non-lactating animals, in which there is no biologically imperative demand for calcium, would lead to an increased excretion of calcium.

Thyroid extract and hyperthyroidism also markedly increase the excretion of calcium and phosphorus, probably due to a direct stimulation of the anabolism of the bones; but, so far as the authors are aware, any relation between the thyroid gland and vitamin D has not been investigated.

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CHAPTER XIV

SOME RICKETS SURVEYS AND DEMONSTRATIONS

In earlier chapters have been discussed various instances of the occurrence and methods of cure of rickets among children. We have seen that it is a disease, the ill effects of which in its severe form can hardly be overemphasized. Not only are the bony deformities, which when well advanced can never be removed, a serious disfiguration which the child must carry throughout his life, but the curved spine and narrow chest predispose to diseases of the respiratory system and the deformed pelvis greatly increases the danger and difficulty of childbirth for women. It is said by one writer on the subject that "among women, the commonest cause of difficult labor or operative procedures in childbirth is the deformity of the pelvis following rickets in childhood." Fortunately, as we have seen, methods of prevention and control while not yet fully standardized are relatively simple to apply, though it yet remains to be decided which method will be the best and most practicable in the long run.

THE PREVALENCE OF RICKETS

Happily it may be said that *severe* rickets, resulting in marked deformities, is now in most communities comparatively rare. Popular public health campaigns broadcasting scientific advances as to the importance of sunlight and cod liver oil have been very effective. But even now a large part of the infant population is at least mildly rachitic. The dark-skinned races, especially the negroes but even the Italians, are particularly subject to the disease. Where the food supply is restricted, as in Berlin and Vienna during and after the war, severe rickets is very prevalent. With the use of X-ray pictures the disease may be detected in its earliest stages, and the figures given for recent surveys in the United States are based usually on roentgenological evidence as well as on the appearance of the various clinical signs.

In this chapter, even at the cost of some repetition, will be brought together several surveys or reports, mostly fairly recent, on rickets in children.

The New Haven demonstration.—Probably the most careful and extensive community study of rickets ever undertaken, at least in this country, is that carried out in New Haven by the Children's Bureau and the

Pediatric Department of Yale University. Analysis of the material is not yet finished and only a preliminary report has been published. Dr. Martha M. Eliot, director of the Child Hygiene Division of the Children's Bureau, who was in charge of the study, has kindly given the authors the following statement as to the procedure.

The U.S. Children's Bureau in cooperation with the Pediatric Department of the Yale School of Medicine carried on a three year study (1923–26) of the community control of rickets in New Haven, Connecticut. All babies born within a selected district of the city were examined at approximately 3 to 5 weeks of age and their mothers given instructions about the use of sunbaths and cod liver oil. These babies were followed over periods of time varying from six months to three years, averaging about eighteen months. Four hundred eighty records were suitable for analysis. Approximately one-fourth of the babies followed were of the negro race; those of the white race were a mixture of various nationalities, many being of Italian, Irish, Polish, or American born parentage. The socio-economic status of the families was also varied, ranging from the extremely poor to those of moderate means.

By means of roentgenograms made at frequent intervals (not oftener than once a month) through the first year and at less frequent intervals during the second and third years, objective permanent records were kept of the condition of the bones of the forearm. Repeated clinical examinations were made at the same time as the roentgenographic. Records were kept of all physical signs usually considered to be contributory to a clinical diagnosis of rickets and of certain physical measurements from which an estimate of rate of growth might be made. Data were also kept regarding tanning, sunlight, cod liver oil, diet, and various other factors having a bearing on the problem.

Examinations were made also of another group of children who did not come under the direct influence of the study, and serve as a basis for estimate of the amount and degree of rickets occurring in children who were actually living in the selected district at the time the study was started, or who were born during the period of the study but were living outside the district. From this group 1,186 records were found to be suitable for analysis.

For purposes of comparison of roentgenograms a short study of 584 babies was made in Porto Rico, a typical tropical community, in January, February, and March, 1927.

At the time of writing this summary the statistical analysis of the data is not complete and results can not be given. Analysis will include study of the influence of age, sex, race, growth, sunlight, cod liver oil, and diet on the incidence of rickets as shown by both roentgenographic and clinical examination. Studies are also being made of smaller groups of cases with regard to age of onset and duration of slight rickets and of single cases which show characteristic or particularly interesting data.

Dr. Eliot published her preliminary report of the demonstration in the *Journal of the American Medical Association* in 1925. At that time, thanks to the careful teaching of the mothers at the Children's Bureau office in New Haven, more than half of the infants studied had had regular treatment for an average of twelve months, each with an average total intake of 43.2 ounces of cod liver oil and most with "good" or "fair" sun exposure. Direct sun baths were given even during the winter, either outdoors or in a warm room through an open, sunny window. Irradiation from a mercury quartz lamp was also used for cases in which the disease was advancing.

In spite of this treatment only 4 per cent of the infants showed no signs of rickets at any time by roentgen ray. The clinical signs looked for were enlarged costochondral junctions, enlarged epiphyses at the wrist, enlarged cranial bosses, craniotabes, or Harrison's groove, and in all treated children they were merely slight. The X-ray manifestations always appeared earlier in the child's life than the clinical. Large, rapidly growing breast-fed infants and very fat infants uniformly showed definite evidences. "The well-known seasonal variation in rickets depends on the season of examination and not the season of birth. Slight rickets is found in young infants at all seasons of the year, moderate or marked rickets in the winter months."

That 96 per cent of treated children should give at least slight manifestation of rickets makes Dr. Eliot suggest that the slight degree may possibly be normal in our climate and our state of society, may merely mean that the impetus of growth is greater than power to calcify. Observations in the tropics would be necessary before such a theory could be accepted, and also earlier and especially prenatal treatment.

The extraordinarily encouraging thing about this New Haven demonstration is that this slight, possibly physiological rickets was not allowed to develop into pathological rickets. The infants of co-operative mothers showed very little "moderate" and no "marked" rickets—in great contrast to non-treated groups. The full report of the study is eagerly awaited.

New York City.—Hess's early demonstration that the almost universal rickets among negro babies could be successfully controlled by giving cod liver oil was the forerunner of several other New York studies. The Association for Improving the Condition of the Poor attacked the problem in 1923 in an Italian district. "The frightful incidence of rickets among the babies of this district" at that time was considered the chief

cause of the serious orthopedic defects found in fully 25 per cent of the children of preschool age, was responsible for a great deal of the malnutrition in this age group, and also, because of the deformed chests and low muscle tone which follow severe rickets, was in part accountable for the high children's death-rate from pneumonia and other respiratory diseases. By co-operation between the Association for Improving the Condition of the Poor, Dr. Josephine Baker of the Department of Health, and other leading pediatricians and nutrition experts, 150 infants were enrolled in a special campaign and given careful follow-up. At the end of three months 71 per cent of the babies who had been taking cod liver oil regularly showed no rickets by X-ray examination, in contrast to only 30 per cent of those taking no oil—a clear demonstration of the possibilities of gain through intensive control by persistent education of the mothers.

Boston Children's Hospital.—Not a survey nor a study of prevention but a demonstration of highly successful treatment of eighty-six cases of acute rickets by the mercury quartz lamp was given by Drs. Wyman and Weymuller in the out-patient department of the Boston Children's Hospital. The improvement was so marked that the mothers were willing to be persistent in taking the children for the thrice weekly treatments. There was steady gain in

> general condition, muscular tone and color, and disappearance of craniotabes, fretfulness, languor, and restlessness. One child of 2 years, who had not walked, was walking within a month. Many babies who were listless and fretful rapidly became more active and happy. They gained weight without change in the food. . . . . The roentgenograms showed increased calcium deposits at the end of two weeks.

The low serum phosphorus went up to normal or above and the low serum calcium of patients with tetany as well as rickets also increased. The general conclusion is that while ultraviolet irradiation can cure or prevent rickets the healing is hastened by also giving cod liver oil.

These same physicians also report that almost all Boston babies, especially winter-born babies, without antirachitic treatment show more or less severe signs of rickets. For instance, of four hundred babies between the ages of three and eight months who came to the out-patient department of the Children's Hospital and who had not had cod liver oil, 95 per cent showed either active or healed rickets.

In most encouraging contrast to the high incidence of rickets reported in this 1924 article is a three-years-later article by the same physicians.

The total number of babies treated at the clinic by this later date was steadily increasing, but the cases of rickets were steadily decreasing.

During the past winter we have had considerable difficulty in finding a sufficient number of babies with severe rickets in the Out-Patient Department for our studies in the hospital ward, whereas five years ago we had no difficulty whatever in finding plenty of babies with severe rickets. This striking decrease in the morbidity of rickets can be due only to widespread adoption of antirachitic measures which has resulted from public health propaganda and the recognition on the part of the general practitioner of the specificity of cod liver oil and sunshine.

There was also a marked falling off in admissions to the orthopedic ward for postrachitic deformities and in operations for correction of such deformities. The education of physicians and mothers had shown results.

Cincinnati.—That ultraviolet irradiation is a practical method of prevention on the large scale has recently been shown in one of the Cincinnati infant welfare stations (Selkirk, Greenebaum, and Mitchell). The mercury vapor quartz lamp was placed so that from one to three babies could be treated at a time, held by their mothers. The first treatment consisted of irradiation for one minute anteriorly and one minute posteriorly, succeeding treatments being lengthened by one minute on each side, till a total of ten minutes was employed. The babies coming regularly were treated twice a week. Some of the 237 babies whose records were analyzed had only one 2-minute treatment, and one child went up to 594 minutes in the eight months. Some babies also received cod liver oil ordered at other clinics to which their mothers took them, so that the subjects could be divided into four groups—with irradiation alone, cod liver oil alone, both, and neither. The encouraging results are given in Table XXI, but the facts are even better than these figures show, for no baby receiving more than 65 minutes total treatment up to eight months of age developed rickets, and most of the small number who showed rickets in spite of the light had gone for intervals of two or more months without treatment.

Ultraviolet irradiation at an infant welfare station therefore seems to be a thoroughly possible public health measure.

Rickets in older children.—Infantile rickets in the active stage is supposed to have disappeared by the time the child is two years old, but there are exceptions. A Montreal physician, Dr. M. W. Bloomberg, has recently reported on eight children over two in his practice with definite signs of severe, active rickets. Their diet had been chiefly cow's milk and bread, with breast-feeding at most for two months, and they had all had much

confinement indoors. Beside enlargement of costochondral junctions and epiphyses, they showed bad bowing of the legs (a late sign) and badly enlarged abdomens. The inorganic phosphorus of the blood serum in some cases tested was only 2.5 mg. and the calcium 6.2 or 8.5 mg. Large doses of cod liver oil (7.5 cc. three times daily) and sunlight cured them all in from six to thirteen months, but the deformities were not affected.

Greenland and Labrador.—Dr. W. A. Thomas, who has recently had opportunity for detailed observations, reports that there is no rickets among the Eskimos in Greenland. The children are nursed for four to six years, until their teeth are strong enough to eat meat. The Eskimos are

TABLE XXI

INCIDENCE OF RICKETS IN THE FOUR GROUPS STUDIED

(FROM SELKIRK, GREENEBAUM, AND MITCHELL)

TREATMENT	COLOR	NUMBER OF CASES	CASES OF RICKETS		
			Number	Per Cent	
Irradiation alone	Negro	78	15	19.2	17.4
	White	8	0	0.0	
Irradiation and cod liver oil	Negro	43	9	20.9	15.0
	White	17	0	0.0	
Cod liver oil alone	Negro	45	20	44.4	38.6
	White	12	2	16.7	
No irradiation; no cod liver oil	Negro	22	17	77.3	55.9
	White	12	2	16.7	

a carnivorous race, subsisting on whale, walrus, seal, sea birds, and fish, and eating the flesh and liver or the whole animal. It looks as if the mother's milk must acquire from this diet an antirachitic potency usually lacking in the temperate zone.

In Labrador, on the other hand, Dr. Thomas found that rickets and scurvy and a combination of the two are universal. The natives live largely on stock bought from the Moravian Missions and the Hudson Bay Company—dried potatoes, flour, canned goods, cereals, and cereal products.

Post-war Vienna.—Even in this cursory summary of rickets demonstrations, the remarkable post-war study in Vienna by English physicians must not be passed over without mention. It was made in 1919–22, including a period of the greatest food deprivation when rickets, in the light of our present knowledge, might well have been expected to be especially

severe and widespread. In response to rumors of the serious conditions, Dr. H. Chick and several other investigators were sent from England by the Accessory Food Factors Committee appointed jointly by the Medical Research Council and the Lister Institute.

They worked chiefly with the babies in the Kinderklinik of the University of Vienna, where the conditions for research were ideal, with strict control for long periods over the diet and external conditions of a large number of children. They were highly successful in showing the power of cod liver oil or direct sunlight or a mercury vapor quartz lamp to prevent or cure rickets—almost the first large scale, clear-cut demonstation of these facts. They also showed strikingly the seasonal nature of rickets, that it is a disease of winter, diminishing with the summer sun.

Professor Pirquet, in whose clinic the work was done, writes very appreciatively in the preface to the report:

> The crucial experiment was thus successfully made. The British workers succeeded with the accuracy of a laboratory experiment, in a city where rickets is extremely prevalent, in maintaining a large number of artificially fed babies free from the disease, and further, in the same wards, were invariably successful in healing children admitted with rickets already developed.

This and Huldschinsky's almost contemporaneous work in Berlin, referred to in chapter ii, are of great historical interest.

Summary of other work.—These illustrations may serve as a few of those on the large scale showing the prophylactic and therapeutic use of cod liver oil and ultraviolet light for infants. Throughout the book numerous others have been given of successful treatment not only by these two agents but by irradiated milk and other irradiated foods and by irradiated sterols.

The outlook seems very encouarging. While the problem of the slight rickets emphasized by Dr. Eliot in her New Haven demonstration is not solved, and many questions of etiology and bodily processes are still to be studied, yet moderate and severe rickets can be cured or prevented in most cases. Vigorous education—of parents and future parents—by doctors, nutrition teachers, public health workers can do much to eradicate active rickets. City smoke prevention and outdoor recreations can contribute an important share.

Two sentences from the chairman's address at the 1927 meeting of the Section of Diseases of Children of the American Medical Association are given to end this chapter:

> Cod liver oil, it seems to me, is our civilization's excellent, economical, and practical substitute—at least during the colder and darker half of the year—for exposure to sunlight. . . . . In order to prevent rickets, the administration of cod liver oil or the exposure of the child to the actinic rays should begin early—in our opinion not later than the beginning of the second week of life.

And from Gamble's chapter, "No Child Need Have Rickets," in *Chemistry and Medicine:*

> Already the incidence of the disease has been extensively reduced. Faith in the applicability of methods of chemistry to the discovery of the factors of disease has thus conquered a serious scourge with which man has for thousands of years unconsciously afflicted his offspring.

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