A British Medical Association Lecture

ON

DEFICIENCY DISEASES, WITH SPECIAL REFERENCE TO RICKETS.*

(With Special Plate.)

BY

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RECENT investigations on diet have profoundly modified our views on nutrition, so that emphasis on the importance of quality of foodstuffs, which developed as the result of the discovery of vitamins, has now in turn been supplemented by equal emphasis of the importance of balance and interaction of dietetic elements. With the advance of knowledge the question arises as to the adequacy of the term "deficiency diseases," about which it is suggested I should address you this evening. The phrase is obviously only adequate, at least as regards rickets, if it be remembered that "deficiency" is merely a relative term, and what may be an ample amount of a food factor allowing good health in one diet and under one set of conditions may be a real "deficiency" having dire results in other circumstances. At all points of the advance in knowledge of this new aspect of nutrition the pathological side of the subject has forced itself upon the notice of the investigator, and, speaking from both the laboratory and clinical point of view, I propose in this lecture to show how some widespread diseases are related to common dietetic faults.

As regards the two earliest known and best recognized of the deficiency diseases—scurvy and beri-beri—I do not propose to say much, because, neither from the academic nor the practical standpoint, has recently acquired knowledge of these diseases greatly modified or extended the earlier views. Although both diseases are comparatively rare as definite syndromes in this country, we still do not know to what extent they are responsible for milder conditions of ill health whose cause escapes detection. In the case of scurvy most recent work is concerned with the relative amount of antiscorbutic vitamin in different foodstuffs, and more especially in the different forms of milk, including dried milk, on the market. On the whole, as regards this latter point, the general opinion among workers is that milk dried by the roller process has a greater amount of antiscorbutic vitamin than spray-process milk. My own experience is in agreement with this view. Many practical points remain to be cleared up in connexion with scurvy, for we are still ignorant both as to the nature and mode of action of the antiscorbutic vitamin. There are, however, but few diseases which yield so readily to treatment as does scurvy to the addition to the diet of foods rich in antiscorbutic vitamin such as oranges and lemons.

The rapid disappearance of beri-beri which is reported from Japan and other parts of the world where the disease was very common, as the result of the application of facts concerning the relation of this disease to vitamin B, is a triumph of which the pioneer workers on this subject, including among others Eijkman, Grijns, Braddon, Fraser, and Stanton may well feel proud. There are still, however, some authorities who do not believe that the etiology of beri-beri is fully explained by the simple dietetic deficiency of vitamin B, and this view has recently been revived by McCarrison.[1] The subject merits further work.

Great attention has been given both by physiologists and those interested in experimental medicine to fat-soluble vitamin, or vitamins if they should ultimately prove more than one, during recent years. The reason for this interest is no doubt the feeling that deficiency of these particular substances in the diet of many people in this country is a reality, and is responsible for great defect both of bodily structure and of health. As I propose to spend most of the time this evening describing the defects for which these vitamins are responsible, as well as their mode of interaction with other dietetic substances and with the environment, it may be well to point out that intrinsically vitamin A is of no greater importance than any other element of the diet which is essential to life. Actually, however, it seems to be of greater importance to us as medical men, for a number of circumstances have assisted in bringing about a state of affairs so that a deficient intake of this vitamin has become of serious import in the national life. In the first place, the distribution of the vitamin is restricted to comparatively few foods—such as milk, eggs, green vegetables, etc.—and these are often dear or difficult to procure. Secondly, the element calcium, with which vitamin A works in conjunction, is also deficient in the average diet. Thirdly, cereals, which are cheap and therefore form a large part of the dietary, contain some substance or substances which actively antagonize the action of the fat-soluble vitamin in some important respects. Finally, the climate of this country, and especially the lack of sunshine, is such that we require relatively large quantities of the vitamin to bring about normal development and health.

I shall now describe to you the evidence—most of it obtained by experimental work on animals—which indicates that some of the physical defects commonly seen among the people in this country can be ascribed to simple dietetic errors, whose mode of action centres round fat-soluble vitamin. After dealing with the experimental side of the subject I shall briefly sketch attempts made to apply the facts to the treatment of various clinical conditions.

Fat-soluble Vitamin and the Bone Abnormalities of Rickets and Osteoporosis.

The most potent factor in the diet so far discovered which stimulates the formation of bone is vitamin A, or a substance having similar distribution and properties as vitamin A. Whether this calcifying substance, or the antirachitic vitamin as I have elsewhere called it, is identical with vitamin A—that is, the vitamin discovered by McCollum and Davis—and a substance necessary for growth of young rats and for the prevention of keratomalacia, is still uncertain. Some of the apparent differences between vitamin A and the antirachitic vitamin I have previously discussed, and other points of difference have been emphasized by McCollum and his co-workers, and also by Goldblatt and Zilva. The point will not be settled until the synthetic diets used in the growth experiments and in the rickets experiments on rats are identical. In the experiments on rickets carried out by these workers the diet used has been deficient not only in the antirachitic vitamin but also in phosphorus, whereas in the growth experiments only vitamin A has been deficient. Accurate comparison between the properties of growth formation and bone calcification is therefore impossible. A more complete consideration of this problem as to whether vitamin A is identical with antirachitic vitamin can be found in the recently published Report on the Present State of Knowledge of Accessory Food Factors (Vitamins) [Special Report Series, No. 38 (revised), Medical Research Council]. In this lecture I shall use the term "antirachitic vitamin" when referring to rickets and allied problems, but shall use the term "vitamin A" when referring to growth and keratomalacia.

The experimental work upon which is based the view that the antirachitic vitamin controls bone calcification was carried out on puppies, and was as follows. When puppies eat diets made up of food, such as separated milk 150 to 300 c.cm., lean meat, bread or other cereal, yeast, orange juice, and some vegetable fat such as olive oil—that is to say, diets which are physiologically perfect so far as is known, except for a deficiency of fat-soluble vitamin—the calcification of their bones is defective, and has the structure typical of rickets or of osteoporosis. A similar diet to which some foodstuff rich in fat-soluble A, such as cod-liver oil, egg yolk, whole milk, butter, or suet, is added, will bring about improved bone calcification to varying degrees, often resulting, in fact, in perfect bone calcification and a normal animal. It is possible in some cases to destroy the antirachitic vitamin by heat and oxidation, and then the food will no longer bring about improved calcification of

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bone. For instance, although the fat-soluble vitamin content of cod-liver oil is high, it can be destroyed by heating the oil to 120° C., and at the same time bubbling air through for about thirty-two hours. If this oil after heating be now added to the diet described above, the bone calcification remains defective. In the case of butter the vitamin content is more readily destroyed, and four hours of the same treatment will leave a substance with little or no power to stimulate bone formation.

Butter has presented the same difficulties as regards its fat-soluble vitamin content both in growth experiments in rats and in the problem of rickets in puppies, because its action is rather different from that of cod-liver oil. In the case of cod-liver oil, even when the calcium of the diet is low, the influence of the oil on bone calcification and growth is great. But the effect of butter on bone calcification and growth is small so long as the calcium of the diet is small in amount, but when extra calcium in a correct form is added to the diet the butter influence becomes correspondingly great. The practical importance of this observation is that the separation of butter from milk spoils both products from the point of view of antirachitic effect. To get the best antirachitic effect from butter extra calcium, preferably in the form of calcium carbonate, ought to be added to the diet.

The antirachitic action of whole milk has been found to vary greatly according to the diet of the cow and the degree of exposure to sunlight. These facts have been worked out recently by Luce,[2] who found that, when the cow was pasture-fed and exposed to sunlight, 2 c.cm. of its milk had approximately the same antirachitic action, when tested on rats, as 15 c.cm. of milk of the same cow when fed on a diet of white maize meal, gluten meal, oats and barley, and mangolds, and kept in a dark stall.

A closely related point of importance, made evident by animal experiment, is the necessity of including in the diet during pregnancy and lactation a good supply of foodstuffs containing fat-soluble vitamin as well as other vitamins and substances which cannot be synthesized by the animal body. Under these conditions the maternal organism must supply these substances to the developing foetus, and, if her own intake is reduced, the sacrifice of her own stores may be more than she can afford, thus bringing about ill health. No doubt both the maternal organism and the offspring frequently suffer from defective feeding, either because she sacrifices too much of her own essential stores or because the young are insufficiently supplied. Experimentally we find that, when bitches are poorly supplied with antirachitic vitamin in the diet during pregnancy and lactation, especially when associated with excess of cereal, the puppies develop rickets more easily than when the maternal diet during the same period includes a liberal supply of this vitamin, especially in the form of cod-liver oil.

The Interaction of Cereals and Antirachitic Vitamin.

The effect on bone formation of antirachitic vitamin would be a more simple problem from a practical standpoint were it not that other dietetic influences are at work modifying and interfering with its action. Generally speaking, the more food that is eaten by a growing animal, the more rapid is the growth. Consequently there is always the question of a race between growth of pre-bone tissue and its calcification to be considered. The greater the growth the more the need for those dietetic factors stimulating bone calcification. This is not the end of the matter, however, for certain foodstuffs actually prevent calcification independently of their effect on growth. Cereals appear to have this anticalcification effect to varying degrees. Of the cereals examined, oatmeal is the worst, while, other things being equal, white flour and rice are the best cereals from this point of view. A mixed diet deficient only in antirachitic vitamin and containing a lot of oatmeal cooked in the form of porridge produces bad rickets, the intensity of the rickets depending on the amount of oatmeal eaten. Thus, if a puppy eats 100 grams of oatmeal a day under these conditions it will develop much worse rickets than if it eats only 50 grams daily. Another cereal product which interferes with the action of the calcifying vitamin is the germ of wheat. It might be expected from this that wholemeal flour would give worse rickets than white flour. There is, however, such a comparatively small amount of germ in wholemeal bread that it can have but little influence. Thus the wheat kernel only contains 1.5 per cent. embryo, and this amount does not, according to my experiments, have a powerful influence. The presence of the rickets-producing substance in wheat germ does not, therefore, present a problem as regards ordinary human diet, but may be of great importance, as I have pointed out elsewhere,[3] in cases where animals are largely fed on cereal offal.

A point of interest about the cereal effect is that it is most potent in those foods having the largest calcium and phosphorus content. Oatmeal, for instance, which contains most calcium and phosphorus, opposes most strongly the retention of these elements in the body in the form of calcium phosphate in bone. I have discussed elsewhere the possible cause of the rickets-producing effect of cereals, and pointed out that it appears to be best explained by assuming that there is in cereals a substance or substances actively preventing bone calcification. This substance, whose composition and properties are unknown, appears to act in a diametrically opposite way to the antirachitic vitamin. The cereal effect can be completely antagonized by the antirachitic vitamin, especially by cod-liver oil. Milk and egg yolk and butter, if associated with calcium salts, are all capable of antagonizing completely the cereal effect. On the other hand, the more the cereal eaten and the more potent from the point of view of rickets the type of cereal in the diet, the greater must be the antirachitic influences necessary to produce normal development.

The Effect of Fat-soluble Vitamin and other Dietetic Factors on the Structure of Teeth.

It has been shown by M. Mellanby that the structure and arrangement in the jaws of teeth of animals depend largely on their nutrition during the period of development, so that it is now possible to produce almost any degree of imperfection of the teeth by arranging the diet of puppies. Here again a fat-soluble vitamin plays a powerful part, and those substances containing it, such as milk, egg yolk, cod-liver oil, suet, and green vegetables, all favour the production of perfect teeth, while cereals, and especially oatmeal, tend to the production of badly formed teeth. It seems reasonable to suppose that, if teeth are badly formed, they will be more susceptible to caries, but when this was suggested by M. Mellanby it was met by opposition. Dental authorities said there was no relation between dental structure and caries, because when the deciduous teeth of children are examined only 1 to 3 per cent. are badly formed, whereas 90 per cent. of children in this country develop carious teeth. It is true that, according to present standards, the temporary teeth of children on naked-eye examination seem well formed, but examined microscopically these teeth show quite a different picture. In fact, of 302 teeth examined microscopically by M. Mellanby after being ground down, as many as 85 per cent. were defectively formed, whereas the dentists supplying them reported that only 2 to 3 per cent. were hypoplastic. Of 226 temporary human molar teeth examined only one was perfectly formed and quite free from caries. It seems clear therefore that, generally speaking, more perfectly formed teeth are more free from caries. For exceptions to this rule the original papers ought to be consulted. If this be true the first method to be employed to reduce the scourge of tooth defect in this country is to improve the formation of children's teeth by better feeding of the mother during pregnancy and lactation and of the children so long as the teeth are being calcified—that is, for the first eighteen years. Better feeding means the greater consumption of such foodstuffs as promote good teeth formation and the diminished consumption of foodstuff antagonizing this development. These experimental results have completely changed the point of view as to the causation of dental defect, for previously all attention has been directed to the action of bacteria and their end-products externally on the teeth, and the toothbrush has been the great stand-by. It has proved but a bruised reed. It will be realized from this

brief account how very important, even considered from the point of view of teeth alone, are the calcifying vitamin and the substances with which it reacts.

Fat-soluble Vitamins and Muscle Structure and Function.

So far attention has been confined to the effect of the fat-soluble vitamin on processes of calcification. But in rickets other organs besides the bones are abnormal, and among these probably the most noticeable is the condition of the muscles, as evidenced by the flabbiness and lethargy of the average child suffering from this disease in an active form.

Recently a more detailed study has been made into the effect of diet on the muscles, and the preliminary results described to the Physiological Society (1923) by Clifford, Surie, and myself. Degenerative changes in muscles of animals suffering from scurvy have also been described (Hayem,[4] Aschoff and Koch,[5] Hart and Lessing[6]). Our results are, briefly, that those dietetic changes which are responsible for rachitic changes in bones are also, on the whole, responsible for certain defects in muscle. These defects, besides being evident from the weakness of the muscles, can also be determined and analysed by their microscopic structure and alteration of their chemical constituents. Fat-soluble vitamin, again, plays a dominant part in controlling the muscular structure and function, and is opposed in its work by the cereal portion of the diet, as described above in the case of bone structure. A diet deficient in fat-soluble vitamin and containing excess of cereal is capable of producing muscles which are extraordinarily defective in structure, and have the appearance of pseudo-hypertrophic muscular dystrophy. In the case of puppies it is possible, by slight alterations in feeding, to produce all degrees of muscle change, so that the animals may show the greatest activity or all grades of abnormality down to absolute paralysis. Results of this type demonstrate clearly the dominant position held by diet over muscular activity, and show that, given a normal young animal, its activity can be controlled by its diet rather than by the space allowed it in which to move about. It is interesting also to note that Nature has so arranged matters that a strong active muscle is developed along with a well calcified bone, and a weak muscle with a defectively calcified bone. Teleologically this arrangement would be expected.

I have described from an experimental point of view a number of tissues of the body whose structure and function are controlled by a few dietetic factors—factors which there is reason to believe bring about the same defects in corresponding human tissues in a widespread manner. Other physiological functions are undoubtedly interfered with by the same apparently small dietetic abnormalities, and these are gradually coming to light. On the other hand, it is equally certain that other dietetic elements not dealt with here are fundamentally responsible for many pathological conditions, and that these will also be unfolded gradually by investigation. Before attempting to show how the experimental results are being applied to clinical problems, I shall first discuss briefly the recent work on light treatment, and give the evidence which indicates that the influence of light, as regards some physiological processes at least, is closely bound up with the dietetic factors, the fat-soluble vitamins and cereals.

The Relation of Light Radiations to Deficiency Disease.

Although the therapeutic influence of light radiations has been long recognized, more particularly in respect to bone tuberculosis, it is only in the last two years that the subject has been put upon an experimental basis. The experimental work already done has led to the discovery of interesting facts, so that it can now be claimed that light therapy has been raised from a position of empiricism to one with some scientific foundation. It is true that the foundation is as yet fragile, but this drawback will undoubtedly rapidly disappear in view of the many investigations now being made on the subject. I do not propose to deal here with the great pioneer work carried out by various clinicians on this subject, but will simply mention the more recent results which are germane to the subject of deficiency diseases, and which have brought it under the scrutiny of the investigator both in the laboratory and the hospital. In 1919 Huldschinsky described the curative effect of exposures to the ultra-violet rays of a mercury-vapour lamp on rickets in children. These observations have been abundantly confirmed both as regards children (Chick, Dalyell, *et al.*) and in the case of experimental rickets in rats (Hess, Unger and Pappenheimer, Shipley, Park, Powers, *et al.*), and in puppies by myself. Before and throughout the period during which the effect of light on rickets was being investigated, the above described results dealing with the influence of antirachitic vitamin on bone calcification were also being widely discussed, and it soon happened that the two influences became associated in the minds of those investigating the diseases.

It was found that the effect of the ultra-violet rays striking the skin was a more general one than at first imagined. Huldschinsky, for instance, described cases of latent and actual tetany cured by exposure to these rays, whereas Powers, Park, Shipley, McCollum, and Simmonds found that sunlight brought about a greater consumption of food in rats, stimulated their activity, improved their appearance, and increased their reproductive capacity when fed on vitamin-deficient diets. In general, exposure of animals to ultra-violet rays acted in many respects like adding fat-soluble vitamin to their diet when devoid of or deficient in this substance. Of the two hypotheses, then, suggested as to the mode of action of the radiations—namely, (1) the possible synthesis of the vitamin, or (2) the activation of the fat-soluble vitamin already stored in the body, it is now known that the second is the true one. The establishment of this hypothesis rests largely upon the experiments published respectively and simultaneously by Hume (1922) and Goldblatt and Soames (1922). It will be remembered that both these investigations dealt with the effect of exposure to ultra-violet radiations on the growth of rats, and the results were in close agreement. When young rats were fed on a diet devoid of vitamin A, and exposed at the same time to the ultra-violet rays, they were stimulated to grow at the normal rate for a period if the rays were applied at an early stage of the diet. In course of time—that is, after about eight weeks—all growth ceased, presumably because the vitamin A supplies of the body were exhausted. This cessation of growth took place in spite of the continued application of the radiations. Other evidence pointing to this conclusion was that the longer the period on vitamin A-deficient diet before the rays were applied, the less was the effect on growth produced by the exposure, so that, after a period of eight weeks on the vitamin-deficient diet, the radiations lost all influence and the rats declined in weight and died.

Further suggestive evidence pointing to the interaction of exposure to light and the liberation and activation of fat-soluble vitamins has been referred to previously in connexion with the observations of Luce[2] on the influence of diet and light on the antirachitic effect of cow's milk. Miss Luce does not claim that her experiments have definitely proved that sunlight has a specific influence on the antirachitic vitamin content of milk, but it would appear probable that such is the case.

Thus the experimental work on vitamins and the light influence is not only bringing together into close accordance clinical and laboratory observations as to the influence of diet and environment respectively on the development and cure of rickets—observations which at first sight appear to have no point in common with one another—but is also providing a working hypothesis as to the mode of action of the ultra-violet radiations which reopens the question of light therapy. It is no doubt true that light striking the skin acts in other ways besides mobilizing the fat-soluble vitamin supplies of the body, but what these other ways are we have no knowledge as yet. In the meantime we realize some of the important actions of these vitamins in the body, and on this basis alone it seems possible to understand, partially at least, some of the physiological and therapeutical effects of the ultra-violet rays. But this interaction of fat-soluble vitamin and light is not the whole of

our present knowledge, for just as vitamin A and cereals are opposed in their actions on bone and muscle, so also is the light effect antagonized by cereals. When the antirachitic vitamin in the diet is greatly reduced the influence of ultra-violet radiations depends on the amount and type of cereal in the diet. If it is small in amount light has a good stimulant effect on calcification and other physiological processes, but as the cereal increases the light influence becomes more and more negligible. There are undoubtedly other dietetic factors involved in the action of light, but even now it is clear that there is a constant battle going on in relation to calcium and phosphorus metabolism, for, on the one hand, the light influence is constantly stimulating and making more prominent the antirachitic vitamin supplies of the body, and, on the other hand, there is the antagonistic influence of other food constituents, especially the cereals, which are tending to deprive this vitamin of all influence. The practical outcome of the battle, at least so far as animal experiments indicate, is almost as might be expected. When the diets are only moderately defective from the point of view under discussion, the influence of the light radiations is potent and the bone formation and general condition of the animal is much improved. When the diet is very defective in make-up, containing much cereal and little or no fat-soluble vitamin, the influence of light is negligible, so that, for instance, intense rickets may be produced in spite of exposure to the rays. Even so far as diets of moderate defect are concerned, however, when calcification is used as evidence of intensity of action, the addition of vitamin A in large quantities, as by adding cod-liver oil to the diet, is much more effective than exposing the animal to ultra-violet radiations. If the influence of light on calcification be interpreted in terms of antirachitic vitamin, it means that the addition of a large supply of this substance to the diet is more potent than the stimulation to activity of supplies already in the body. The same facts apply to the calcification of the teeth (M. Mellanby[7]). Further evidence of the relative potency of diet and light can be seen in the fact that a good diet rich in antirachitic vitamin will prevent the development of rickets even when the animal is brought up in the dark.

It may be asked, What is the effect of combining a good diet of strong calcifying influence with exposure to ultra-violet radiations? It might be thought that the effect of the combined action would be very intense and that such a procedure would have great therapeutic possibilities. It is this combination that we are endeavouring to develop at Sheffield, both by animal experiments and clinically. Reference will be made later to this type of therapy.

To summarize: sunlight and ultra-violet radiations of a mercury-vapour lamp increase the effectiveness of fat-soluble vitamin in the body, and thereby greatly improve the nutritional value of moderately defective diets of the type mentioned. Absence of sunlight aids in the development of such a deficiency disease as rickets for the same reason. A good diet can more than counterbalance darkness or absence of ultra-violet influence, but sunlight and other radiations cannot make up for a really defective diet.

Clinical Application of the Foregoing Facts.

Many of the above described results are known to apply also to man. The effect of antirachitic vitamin in stimulating bone calcification in children is definite, while, as to the action of light, the fact was originally observed by Huldschinsky in the case of rachitic children and only later was the subject studied on animals. Until all the points have been tested on human beings it is impossible to dogmatize on the subject, but it is probably permissible to assume, in view of the direct and indirect evidence, that most of the facts I have described can be extended to man.

If, then, diets are to be made up for the preventive and curative treatment of particular clinical conditions, more especially those affecting bones, they ought to be so constituted as to contain an abundance of fat-soluble vitamins and calcium without excess of cereals, and especially of oatmeal, as well as having the other qualities of what is usually regarded as a good diet.

Some specimen diets that I have used are as follows:

Child 3 Months Old.
Milk 2 oz.
Water 1 oz.
Egg ½.
Cod-liver oil ½ drachm *bis in die.*
Orange juice ½ drachm *bis in die.*
Milk 16 oz. in 24 hours—3-hourly feeds.

Child 5 Months Old.
Milk 5 oz.
Egg 1.
Marmite 1 drachm.
Cod-liver oil 1 drachm *bis in die.*
Orange juice 1 drachm *bis in die.*
Milk 25 oz. in 24 hours—4 feeds during day; 1 feed early morning.

Child 9 Months Old.
Breakfast:
Milk 7 oz.
Lunch:
Milk 7 oz.
Bread ½ oz.
Cod-liver oil 1 drachm.
Orange juice 1 drachm.
Dinner:
Scraped raw meat ½ oz.
Potatoes ½ oz.
Rice pudding.
Marmite 1 drachm.
Cod-liver oil 1 drachm.
Orange juice 1 drachm.
Tea:
Milk 7 oz.
Egg 1.
Supper:
Milk 7 oz.
Cod-liver oil 1 drachm.
Orange juice 1 drachm.
Milk 36 oz. in 24 hours; water *ad lib.*

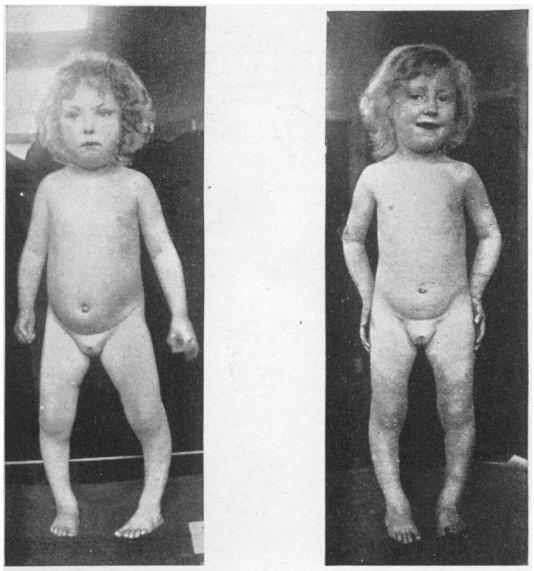
Diet for Adults.
Breakfast:
Milk ½ pint.
Bread 3 oz.
Egg 1.
Butter ½ oz.
Cod-liver oil 1-3 drachms.
Dinner:
Meat or fish 3 oz.
Potatoes 4 oz.
Green vegetables 4 oz.
Milk pudding.
Half an orange.
Cod-liver oil 1-3 drachms.
Tea:
Milk ½ pint.
Bread 3 oz.
Egg 1.
Butter ½ oz.
Jam.
Cod-liver oil 1-3 drachms.
Supper:
Milk ½ pint.
Bread 2 oz.
Add: Calcium carbonate 10 grains thrice daily.

The above diets only represent general types given to hospital patients at the different ages. It may be necessary to make other modifications, such as increasing, decreasing, or diluting the milk or adding extra carbohydrate, especially in the case of the younger children, either in the form of cereals, malt, or cane sugar. I avoid the numerous empirical manipulations of the diet, especially the milk portion, which have become so popular, including such procedures as adding barley water and lime water, adding cream and sugar to diluted milk, and making protein milk. Care must be taken in giving cod-liver oil, as both children and adults can be easily upset when the doses are too large. I seldom give more than two drachms thrice daily to any patient. Larger doses may be well taken by some adults, but even so they will sometimes develop tachycardia and cardiac discomfort. Until the child is a year old the egg is uncooked and mixed up with the milk. Moderate amounts of extra cereal or carbohydrate can be given to young children with impunity, so far as rickets is concerned, if the diet is constituted as described.

The Treatment of Rickets.

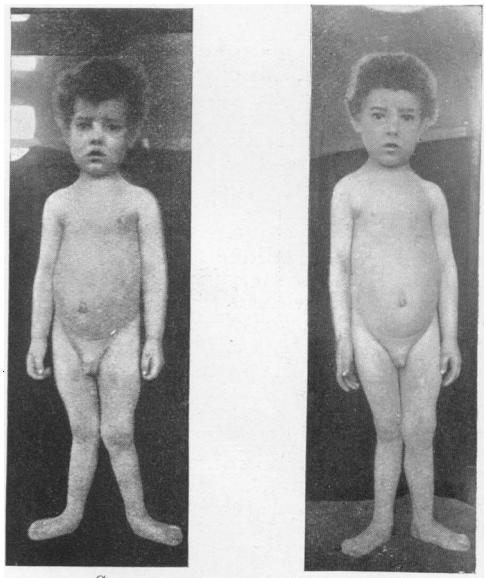
Rachitic changes improve rapidly on the above diets. Bone calcification and growth are resumed, and can be readily observed by radiographic examination (see Fig. 5). Concurrently with the bone change the clinical condition is transformed: lethargy is replaced by activity, even when the infant is confined to a cot, the flabbiness of the muscles disappears, and with this the protuberant abdomen becomes less prominent. When great bone deformity has been produced by rickety changes the restoration to healthy growth will ultimately bring about striking reduction in this deformity, but the process is slow. Figs. 1 (A and B), 2 (C and D) illustrate the reduction in deformity of the legs in cases of genu varum and valgum respectively after the children had been eating the above diets for about six months. No doubt the legs would still further improve and become practically normal if the feeding of the children continued along these lines for a longer period. Fig. 3 demonstrates the reduction in size of the abdomen resulting from improved muscular tone following good feeding over the same period.

In the case of adult rickets—a disease rarer than it was a few years ago—treatment is not so satisfactory as in the case of children. The bones begin to calcify on giving the



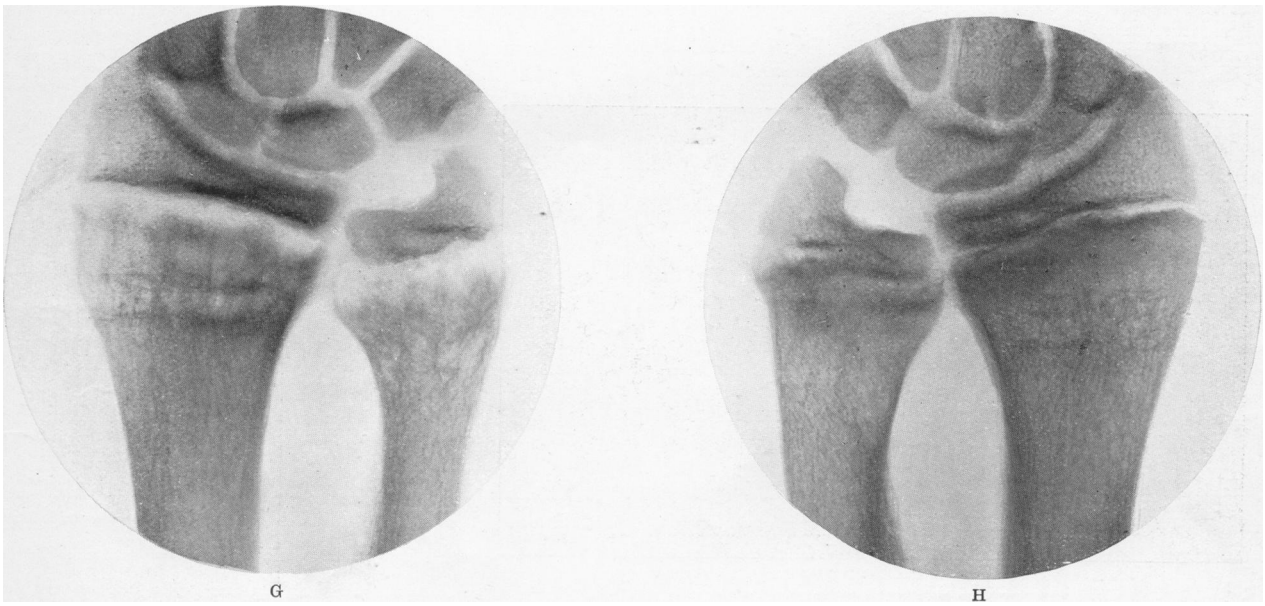
A B

FIG. 1.—A, child, aged 3 years, with leg deformity (genu varum) owing to rickets. B, shows improvement after six months on diet described in text. No splinting or other treatment.



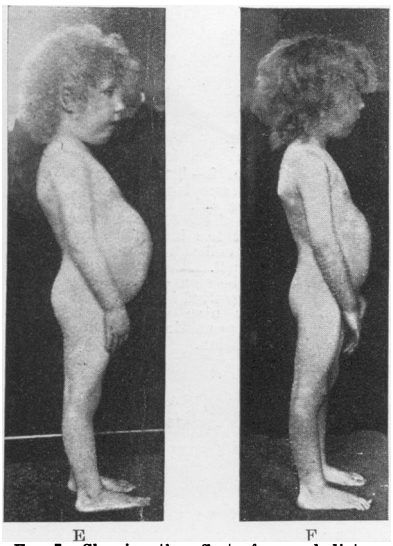
C D

FIG. 2.—C, child, aged 5 years, with leg deformity (genu valgum) owing to rickets. D, shows great improvement after six months of calcifying diet described in text. No other treatment.



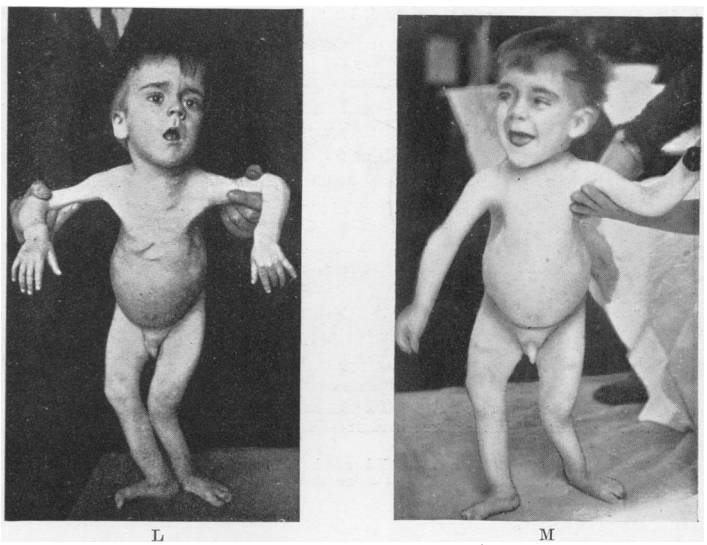
G H

FIG. 4.—Radiographs of wrist of youth, aged 17 years, with late rickets and osteoporosis. G, as on admission; H, after three months of diet described in text. Note the curative changes both as regards rickets and osteoporosis.



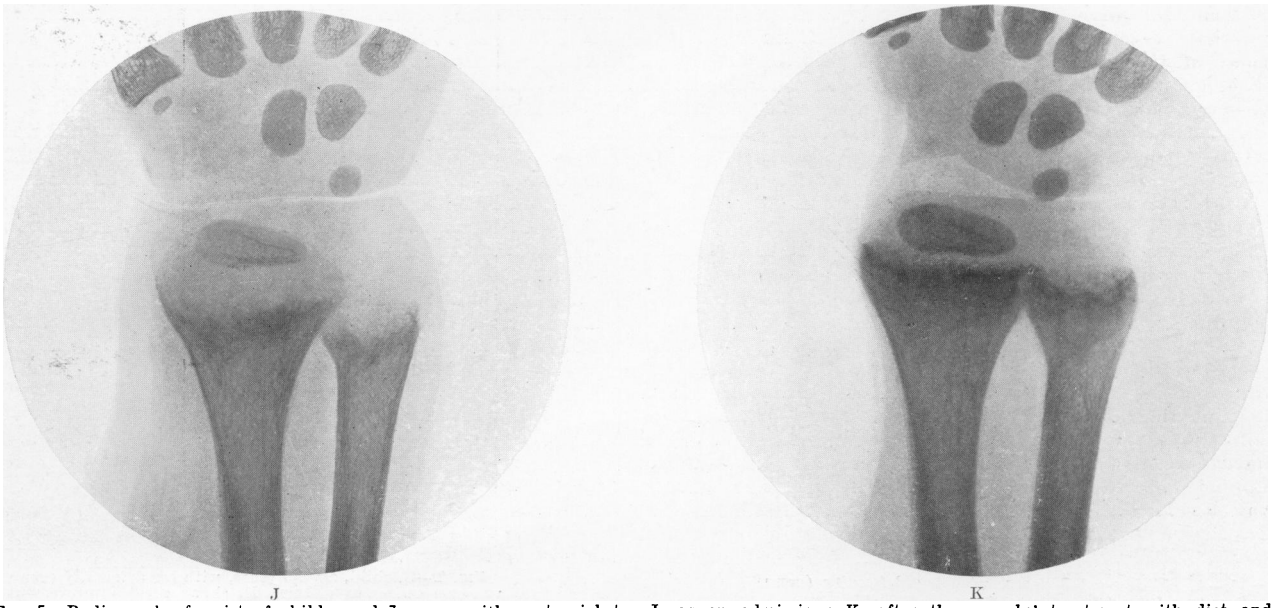
E F

FIG. 3.—Showing the effect of a good diet over a period of six months on the abdominal musculature in a case of rickets. E, as on admission; F after six months of diet. No other treatment.



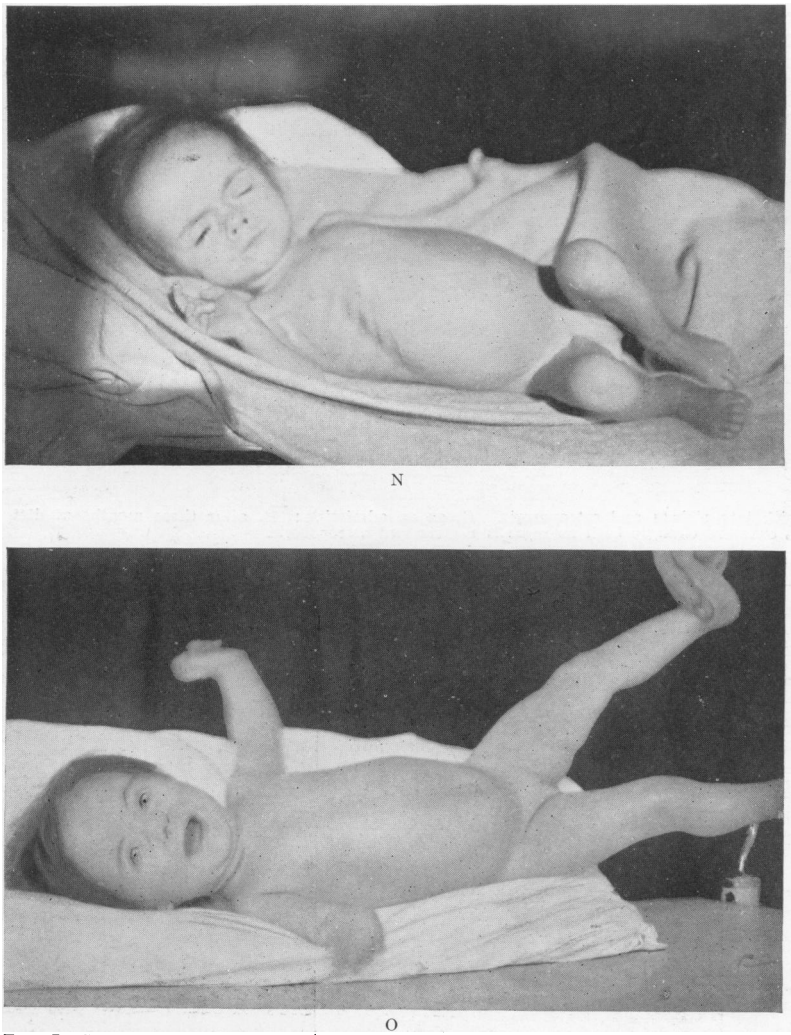
L M

FIG. 6.—Severe malnutrition and rickets of child aged 3. L, photograph taken a week after admission; M, photograph after one month of diet as in text.



J K

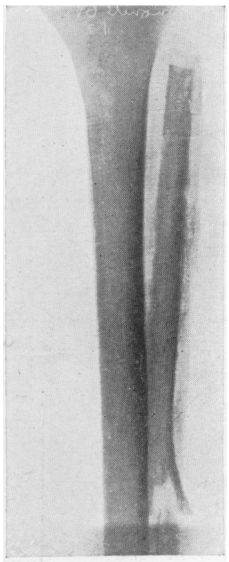
FIG. 5.—Radiograph of wrist of child, aged 3 years, with acute rickets. J, as on admission; K, after three weeks' treatment with diet and ultra-violet light. Note the great improvement in calcification.



N

O

FIG. 7.—Severe malnutrition of child aged 10 months. N, photograph before the treatment; O, photograph after two months of diet as in text.



P

FIG. 8.—Radiograph of lower leg of boy 16 years old. In the position of the fibula a bone graft has been fixed by my colleague Professor Connell. Much new bone can be seen surrounding the grafted bone. Taken after nine weeks of a diet promoting bone calcification.

diet (Fig. 4), but the limited powers of growth that remain do not afford the same chance of recovering from the bone deformity. In these cases, therefore, the assistance of the surgeon to correct deformity may be more necessary. Another cause of relative failure in the satisfactory treatment of late rickets is the difficulty of overcoming the tendency to infantilism and delayed general development so often met with in these cases. No doubt in infantile rickets there is the same cessation of all mental and physical development as in the adolescent, but in the former case curative treatment has a longer time and better chance of bringing the patient up to the normal standard than in the case of adolescent rickets.

After osteotomy for rachitic deformity it is essential that a diet with strong calcifying influence should be given, otherwise the deformity may be actually increased by the operation.

In cases of very bad deformity of the legs in young children it is possible, although I do not advocate the practice, to give a rickets-producing diet, and, while keeping the bones soft, straighten them by wrenching and splinting. Having improved the alignment the bone-hardening diet may then be started. In one case Professor Connell and I treated bad deformity of the lower limbs in this way and obtained a satisfactory result.

Malnutrition and Wasting of Infants.

Apart from the treatment of rickets, diets made up along the lines indicated will often be found to bring about great improvement in other conditions of malnutrition and wasting in infants. I do not put forward these diets as a panacea, more especially in the case of the marasmic child under 3 months of age, but the form of treatment has at least a rational and an experimental basis, and ought therefore to be tried, and, if possible, developed. The solution to the problem of the marasmic infant under 5 or 6 months seems to me to lie with the proper feeding of the mother during pregnancy. Experimentally it is easy, by feeding pregnant bitches on diets defective in the directions already discussed in this lecture, to produce litters of puppies which die off one by one in the first few weeks of life, and it is probable that the production of true marasmus in children has often a similar cause.

The older methods of feeding children suffering from malnutrition, still widely practised and even recommended by those who do not appreciate modern work on diet, are usually based on the teachings of either Czerny or Finkelstein. Since these methods were advocated before the development of recent views on dietetics, it is perhaps not surprising that sharp conflict exists between the old and the new views. The basis of this conflict has not, however, been previously formulated.

Any method of feeding sick children which begins by reducing or completely removing fat-soluble vitamins from the diet must, in my opinion, be wrong. While fat dyspepsia in infants is undoubtedly a reality, although probably greatly exaggerated, it is, after all, only symptomatic of a more general disturbance, and ill health cannot be permanently improved by cutting out of the diet what is definitely known to be an essential constituent. Reduction in the fat *qua* fat is probably of but little importance in the nutrition of children so long as they get sufficient food to eat, but if its vitamin content goes with it, then ultimately further ill health will ensue. Thus if fat is reduced in or removed from the diet it is essential that the concomitant reduction in fat-soluble vitamin should at least be restored by adding small quantities of cod-liver oil or egg yolk.

A specific instance of the detrimental results of the older views on infant feeding has been definitely proved by Hess, who found that *Eiweiss-milch* actually produced acute rickets in children. This fact is not unexpected in view of the results of my animal experiments. It can hardly be hoped that a concoction which produces rickets will prove an ideal diet, even over short periods, for other conditions of malnutrition in children.

The conflict between the old and the new views is not confined to the feeding of children, but embraces all dietetic treatment of disease. The following instance, recently brought to my notice by Professor Hall, illustrates this. The patient, a girl of 19, of well-to-do parents, had been first treated for dyspepsia at the age of 9 by having the fats removed from her diet. As her indigestion continued vegetables were then excluded, and ultimately she lived on little but bread and other cereals. The development of very bad scurvy associated with late rickets is not surprising in the light of our present knowledge, nor her rapid improvement when her diet was made complete. This is only a gross example of what is probably in a less degree a common result of dietetic treatment, but serves to emphasize that, although our knowledge of dietetics is still limited, we must feed wasting infants and other conditions of malnutrition by giving diets which experimental evidence has shown to be complete in quality and balanced in quantity. Only diets of this character are compatible with the proper development and functioning of each organ, including the alimentary canal. The results of treating two cases of severe malnutrition by the diets described can be seen in Figs. 6 and 7.

Combined Dietetic and Light Treatment.

Experimental evidence having shown that one method by which exposure to light works is by stimulating to activity the fat-soluble vitamin supplies of the body, and since the only means of access of this substance is via the food, it would seem desirable, when making use of light therapy in the treatment of disease, that the diet should be controlled at the same time. This is also borne out by the fact already described that, at least as regards bone calcification, the influence of light can be completely antagonized by a defective diet. Whether exposure to ultra-violet rays enhances the calcifying influence of a very good diet still remains to be proved. I have treated rickets and many other pathological conditions by the combined therapy, but in no case has it been possible as yet to control the results by treating precisely similar cases only by diet or only by exposure to light. Cases of rickets respond well to the combined diet and light therapy, as can be seen in Fig. 5, where intense stimulation to bone calcification is obvious after three weeks' treatment, but correct feeding alone also brings about rapid cure of this disease.

The diets given are those already described, and the mercury-vapour quartz lamp is used as the source of the ultra-violet radiations. Patients are exposed for intervals gradually increasing from five to thirty minutes back and front daily at a distance of about 5 to 6 feet from the lamp. Care is taken that only a mild degree of skin irritation is ever produced, and, of course, the eyes are protected during exposure either by dark spectacles or by bandaging in the case of infants.

For the past three years many of the cases of fracture of bones under the care of my colleague Professor Connell at the Royal Infirmary, Sheffield, have been placed on special diets with the object of hastening the calcification processes of repair. An instance of this is seen in Fig. 8, where there is a rapid laying down of new bone round a bone graft in the position of the fibula shaft in the case of a patient on a diet which strongly stimulates bone calcification.

Cases of bone fracture and other bone conditions, including chronic osteomyelitis, chronic mastoid infections, as well as tuberculosis of bone, are now being treated by combined dietetic and light therapy. Under this treatment the general condition of the patients has improved, often very greatly, and some of the results have been sufficiently good to merit a further and closer study of the best means of using these therapeutic methods in combination. There are obviously at least two problems to be solved—one the effect of the treatment on a normal physiological process such as calcification, and the second concerned with the bactericidal and resisting powers of the body to infection. The successful treatment of bone and gland tuberculosis by light therapy seems to involve both of these actions, but of lupus only the second. The problems may or may not be closely related. The knowledge necessary for the best therapeutic results can only come through further accurate testing.

I have endeavoured in this lecture to show how recent experimental work has provided information as to the potent controlling influence of some dietetic factors over the

development and function of certain organs, and more particularly of the bones, teeth, and muscles. On the clinical side it would appear that most of these facts as regards nutrition are of immediate application, and the work has indicated the diets which are capable of bringing about the cure of rickets and also great improvement in the general health of many suffering from other diseases. It has also provided a scientific basis for light therapy which will stimulate interest and promote further investigation into this interesting method of treatment.

It must also be pointed out that the diets which bring about these curative changes will also prevent the development of the diseases treated. The application of the facts ought, therefore, to ensure not only the complete eradication of rickets from the country, but also the formation of teeth and jaws of a type which are far too rare at the present time. Thus, from the standpoint of preventive medicine also these facts about diet seem of great importance.

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For most of the references in this lecture and further discussion on some of the points see Report on the Present State of Knowledge of Accessory Food Factors (Vitamins), Special Report Series, No. 38 (revised), Medical Research Council.

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The Milroy Lectures, 1924,

ON

THE PLAGUE.*

BY

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I.—THE HISTORY OF PLAGUE.

THE study of plague presents a favourable opportunity to comply with the wish of Dr. Milroy, the founder of these lectures, that from time to time "spreading epizoötics should be weighed and sifted by medical men who have paid special attention to the study of the course of epidemics among the human race, in order to determine whether the natural laws which regulate or effect the development and progress of the two classes of morbid phenomena are analogous, or otherwise." "Such a comparative scrutiny," says Dr. Milroy, "could scarcely fail to advance the cause of general scientific truth, and would serve also to the elucidation of sound principles for the guidance of safe prophylactic and preventive legislation."

There are few diseases which can be followed into remote antiquity with greater certainty than plague. One of the earliest references to the disease is contained in the first book of Samuel, in the fifth and sixth chapters. The date when this book was written is not definitely known; it was probably compiled over a series of years extending from 900 B.C. The narrative tells us how the Philistines defeated the Israelites at the battle of Ebenezer, and captured the Ark of the Covenant. They carried it into their own country, depositing it in the temple of Dagon in the city of Ashdod. Shortly after the arrival of the Ark a grievous disease broke out among the people of Ashdod, so that many died. "And he smote the men of the city, both small and great, and they had emerods in their secret parts." After seven months of the pestilence the Philistines consulted their diviners and priests, who advised them to send the Ark back to Canaan, enjoining them to take care that it did not go back empty. They were instructed to prepare golden images of their emerods and the mice that marred the land. They were to place five of each of these images in the Ark, one for each of the lords of the Philistines, before they sent it back into Canaan.

The story of the plague in the land of the Philistines has been cited, not only because it is perhaps the earliest and clearest reference in history to an epidemic of bubonic plague, but also because the now well recognized association of rodents with the disease is referred to in the narrative. It is noteworthy that this feature of an epidemic of bubonic plague is seldom mentioned by the chroniclers of European epidemics, an anomaly for which an explanation will be advanced later.

Certain early epidemics of disease called plague (λοίμος) were probably not true plague epidemics, but epidemics caused by other diseases often confused with plague—for example, typhus, relapsing fever, or even influenza. Discarding these, let me instance certain epidemiological features of the well recognized epidemic of plague known to historians as the plague of Justinian. These have been recorded by chroniclers of the sixth century. A very complete list of these authorities has been compiled by Dr. Raymond Crawford in his book entitled *Plague and Pestilence*. The earliest is Evagrius, who lived at Antioch and was himself attacked by the plague (A.D. 540). He considered the disease to be contagious and to be acquired in various ways, such as by sharing beds, by actual contact, by visiting infected houses, or even by casual meeting in the market-place. He observed that some escaped in spite of running every risk of infection.

Procopius describes the plague as progressing by definite stages, expending its virulence in one country before passing to another, as though intent on overlooking nothing. Indeed, if at first it touched a place lightly it always returned to it subsequently, till the full measure of punishment was exacted. He observed that the disease almost always began at the sea coast, and that from there it spread into the interior, suggesting that infection was often sea-borne. This is an observation which has been made over and over again in the history of plague, and is therefore one which demands special attention. Procopius also observed that physicians, nurses, and those who buried the dead were not specially affected in spite of their constant contact with the sick; while many contracted the disease without any contact at all. This also is an observation which has been confirmed in many subsequent epidemics of plague.

Agathias continued the history of plague at Byzantium (Constantinople), and describes a sharp recrudescence of the disease in 558 A.D. He states that it never quite disappeared after the outbreak described by Procopius in 542. A like experience has been a feature of other epidemics of plague. Gregory of Tours testifies to the widespread diffusion of the disease in France. In 567 it caused a great mortality in Lyons, Chalons, and Dijon. It broke out at Marseilles in 587, brought there by a merchant ship from Spain. Rome was attacked in 590. The epidemic was preceded by a great flood. The Tiber overflowed, destroying on its banks many buildings which contained grain. We can imagine that on this occasion infection was imported into the city with grain brought thither to replace that which was destroyed. In recent times infection has frequently been carried in this way from one country to another.

Hirsch states that it is impossible to decide whether the outbreak of plague in the second half of the sixth century was the first general diffusion of the disease on European soil, or whether it had been epidemic there before, and, if so, to what extent. It is certain, however, that this outbreak gave it a firm hold in Europe, and that it kept its grip there for more than a thousand years.

Nevertheless, after an epidemic in Rome in the end of the seventh century (680 A.D.) which subsequently extended over the greater part of Italy, there seems to have been a lull of more than a century in the prevalence of the disease in Southern Europe. The disease, however, still lingered in Constantinople, and epidemics are again recorded in Southern and Western Europe at the end of the eleventh century. Here it will suffice to note that extended periods of quiescence in the epidemicity of the disease have been recorded in Europe.

Chroniclers of the Middle Ages frequently refer to pestilences, and from references to epidemics associated with buboes and high mortality there can be little doubt that plague figured prominently among these pestilences. It is equally certain that other diseases, such as typhus and relapsing fever and influenza, were confused with plague, and were probably epidemic at the same time.

* This course of Lectures has been slightly abbreviated for publication.