VITAMIN A DEFICIENCY IN CHILDREN

Part I—Present knowledge of the clinical effects of vitamin A deficiency, with special reference to children

BY

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An experimental investigation, undertaken by the author at the Queen's Hospital for Children in London (see Part II of this report), suggested that artificial feeding of a type frequently given to infants in this country may not provide sufficient vitamin A for their needs, and that the earliest symptoms of this deficiency in babies may be an increased susceptibility to minor infections of the skin. Up to the present time, vitamin A deficiency in the human subject appears to have been diagnosed with certainty only when eye symptoms (night blindness, xerophthalmia or keratomalacia) were present, and these are probably by no means the earliest effects of such a deficiency. The author can claim little first-hand knowledge of the effects of established vitamin A deficiency, but it should be useful to try and construct a clinical account of the disease in children by collating the records of different observers. Such an attempt, however, is complicated by the frequent co-existence of other diseases.

Severe grades of the disease are common at the present time in certain parts of the world, and the author's investigation on babies suggests that slight grades of vitamin A deficiency may be common in Great Britain. Moreover, G. A. Dawson¹⁸, medical officer of health for Darlington, found during a survey in 1928-29, that there were approximately 100 cases of night blindness and xerophthalmia attending nursery and elementary schools in his area. Is this disease equally common, but passing unrecognised, in other distressed areas of Great Britain and the western world?

Clinical studies concerned with vitamin A can be roughly divided into three groups: 1. Studies of cases of night blindness, xerophthalmia and keratomalacia and their response to treatment; 2. Studies of the effect of administering vitamin A to groups of individuals, either as a prophylactic measure or in the course of acute infections; and 3. Estimations of the amount of vitamin A found in human organs under different conditions.

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Part II entitled 'Vitamin A Requirements of Babies: Skin Lesions and Vitamin A Deficiency' will appear in the next issue.

The ophthalmic symptoms and signs of vitamin A deficiency have been frequently described, but in this paper attention will be concentrated on the less well-known changes observed in other parts of the body. No attempt will be made to summarize the mass of work carried out on animals on the subject of vitamin A deficiency.

For those who wish to pursue the matter further, a very useful paper by Eusterman and Wilbur²⁴ with a fairly extensive bibliography on vitamin A deficiency in man appeared in 1932, and Blegvad's paper⁵ in 1924 gave a large number of references to the literature of xerophthalmia and keratomalacia. Among older papers those of Stephenson^{94, 95}, published in 1898 and 1910, gave valuable bibliographies.

Effects of vitamin A deficiency in animals.—Before considering vitamin A deficiency in the human subject, the disease in the rat is worth recalling. This vitamin is stored by the rat mainly in the liver, and the rapidity of onset of symptoms on a vitamin A deficient diet varies with the amount of this store and the age of the rat. In young rats the diet of the mother may influence the amount stored in the young, and hence their resistance to a deficient diet⁶². Deficient growth, or arrested growth, followed by loss in weight, are perhaps the symptoms most often stressed in the literature. Eye changes are usually a marked feature. Their appearance often coincides with cessation of growth, but may occasionally precede it, or may not develop at all⁸⁹, hence the stage of the disease at which xerophthalmia develops is very variable. Its incidence in rats suffering from gross deficiency of vitamin A varies widely, say from 98 per cent. in Emmett's records²³ to 38 per cent. in Green and Mellanby's³³, presumably depending on the diet employed and the age of the rat⁸⁹. The eye symptoms are in part the direct result of deficiency, and in part due to superadded infection; the first symptom is often puffiness of the lids with conjunctivitis, followed later by purulent and haemorrhagic discharge⁸⁹, and opacity of the cornea³⁷. As regards the skin changes, there is striking evidence of 'cutaneous malnutrition,' which is said by Steenbock, Sell and Buell⁹³ to be more common in rats over 4 months old. This shows itself in scabbiness of the tail or ears, sores which heal with difficulty on the nose and feet, and thin and bushy hair. Gudjónsson³⁷ states that the earliest change in the rat is in its hairy coat, and that changes in the texture of the skin, loss of agility, and a hoarse voice all precede the eye changes. Tyson and Smith¹⁰² found that epithelial hyperplasia of the tongue was regularly present before xerophthalmia. Nasal discharge, sneezing and coughing often occur in the early stages of the disease⁹³, and diarrhoea is common⁸⁹. Priapism is said to be common in males³⁷, and inflamed glands and abscesses may appear in the neck. Rapid loss of weight, probably accelerated by infections, occurs terminally.

The symptoms of vitamin A deficiency, however, vary in different species of animals. For example, xerophthalmia is apparently not a prominent symptom in monkeys or in guinea pigs. In monkeys it would seem that gastro-intestinal symptoms and loss of weight are the outstanding features^{100, 101}. Tilden and Miller¹⁰⁰ state that out of 11 monkeys dying as a result of vitamin A deficient diets, none had xerophthalmia, though post mortem 9 showed in other parts of the body the epithelial changes typical of vitamin A deficiency. These monkeys showed no special susceptibility to infections of the respiratory tract. In guinea pigs the chief signs of vitamin A deficiency during life are said by Wolbach and Howe¹⁰⁶ to be loss of weight, with desiccation and often necrosis of the margins of the pinnae of the ears, but without eye changes—although post mortem extensive epithelial changes are found in various parts of the body. Hence in different species of animals it seems that different groups of symptoms predominate, and for this reason alone it is not possible to determine from animal work what will be the exact clinical picture of vitamin A deficiency in man.

The post-mortem changes are, however, illuminating and similar changes are found both in man and in animals. The characteristic changes due to vitamin A deficiency are alterations in epithelial structures. This apparently holds true for all the different species investigated post mortem. S. Mori in 1922⁷⁵ first described these changes in the larynx, trachea and in ducts of various glands of the rat. Wolbach and Howe¹⁰⁶ showed similar changes in other parts of the body. The normal columnar or cuboidal epithelium is changed to epithelium of a stratified, keratinized type in many parts of the body, including eyes, air passages, alimentary tract, renal tract, and salivary and other glands. It seems that this alteration in and keratinization of epithelium precedes, and is the direct cause of, the many local infections found in rats dying of vitamin A deficiency (see Wolbach and Howe¹⁰⁷, Cramer¹⁵, Harris, Innes and Griffiths³⁸).

Thatcher and Sure⁹⁹, working with white rats on a diet deficient in vitamin A, found that there might be metaplastic changes in the posterior part of the tongue, in the salivary glands, in the respiratory and in the urinary tract, before there had been any external signs or symptoms.

Immunological reactions, it is held, have not indicated a reduction in general immunity (see Zilva¹¹⁴, Cramer and Kingsbury¹⁶, Harris, Innes and Griffiths³⁸), though on the other hand to what extent reduced resistance to infection is commonly reflected in the known immunological reactions seems a moot point.

The sequence of events in vitamin A deficiency appears to be that patches of keratinization of epithelium develop simultaneously in different parts of the body, and at various sites the altered epithelium allows organisms to gain entrance, and these set up localized abscesses and other inflammatory changes. The proportion of infections occurring at different sites seems to have varied in different laboratories, but Green and Mellanby's figures³³ seem fairly typical. Post-mortem examinations of 92 rats on vitamin A deficient diets revealed an abscess at the base of the tongue (probably originating in salivary glands) in 72 per cent.; middle ear abscess and septic nasal sinuses in 20 per cent.; genito-urinary infections or calculi in 44 per cent. and lung infections in 9 per cent.

Mellanby⁶⁷ has carried out on animals work demonstrating the experimental production and prevention of degeneration of the spinal cord; for instance dogs getting ergot in their diet which was deficient in vitamin A developed demyelination of the cord, whereas if the diet was not deficient in vitamin A these changes were prevented. It seems possible that vitamin A deficiency may play a part in the etiology of certain diseases of the central nervous system in man, but as the main purpose of this paper is to give an account of vitamin A deficiency alone, and the clinical implications of Mellanby's investigations are not yet clear, this important work is not further considered.

Studies of night blindness and keratomalacia in man.

Geographical distribution of vitamin A deficiency in man.—To ascertain the distribution of proved cases of vitamin A deficiency, we must examine the records of acquired night blindness, of xerophthalmia and of keratomalacia.

Nearly all observers agree that young children develop symptoms of vitamin A deficiency more readily and suffer more severely than older persons; though naturally night blindness (the earliest eye symptom) is unlikely to be detected in an infant or very young child. Hence wherever the disease is reported among adults, it is likely also to be present among children.

That it has been, and still is, common in certain parts of the world, is clearly shown by the widespread popular knowledge of the means of cure, such knowledge dating apparently from very ancient times. Liver therapy was advised for night

blindness, so Blegvad⁵ states, in a papyrus of about 1500 B.C., and also by Hippocrates in the fourth or fifth century B.C., and it is still employed by the people in Russia⁶⁶, in Labrador and Newfoundland¹, in India¹¹³, and in China³⁸, though in Tientsin it is said that the Chinese frequently treat the wrong eye diseases with liver: and liver may be mistakenly used in this disease as an external application to the eye instead of being taken internally, as was noted by de Gouvêa in Brazil in 1883¹⁹. In Japan the popular remedy since olden times has been, according to S. Mori⁷⁵ writing in 1904, a fish rich in fat, and fowls' livers are also used⁵.

During the nineteenth century it was probably a fairly common disease in many European countries as well as in America and in Asia. Stephenson⁹⁵ gives to Joseph Brown the credit for the first clear clinical description of keratomalacia which he described in the *Edinburgh Journal of Medical Science* of 1827, and also notes that thirteen years later, in 1840, William Mackenzie said he had repeatedly seen keratomalacia in this country in emaciated infants with diarrhoea. In 1876 in Sheffield, Snell⁹¹ was successfully treating with cod-liver oil and iron children who suffered from night blindness and Bitôt's spots. The disease was described by many German writers, and in Berlin in 1866 von Graefe said that he sometimes saw 3 to 4 cases of keratomalacia a month⁹⁵. It was also reported from France and Russia; for example Bitôt⁴, whose name has been attached since 1863 to a characteristic appearance in the eye, was a French physician in Bordeaux, and Blessig⁶, writing from Petrograd about the same time, remarked on its occurrence in Russia, especially during the Lenten fasts. Many outbreaks in prisons, workhouses, schools and asylums were reported in various countries, as Blegvad⁵ has noted. In this country Stephenson's figures⁹⁴ show that at the end of the last century xerophthalmia was present in nearly all the poor law and industrial schools and orphanages where he examined the children. Out of 6,209 school children examined by him, 116 or 1.87 per cent., were suffering from xerosis of the conjunctiva. The frequency of keratomalacia in some parts of India at the end of the last century is shown by the fact that Herbert³⁹ in Bombay was able to collect 100 cases in 4 months. Turning to America we are told that the disease was common 40 to 50 years ago among negro slave children in Brazil¹⁹ and in South Carolina⁵⁰.

It appears that in recent years xerophthalmia is still common in many countries. In China and Japan, Pillat^{78, 79} reports that the disease is widespread and common, and Lossouarn⁵⁸ says that at an eye clinic in Tientsin in 1929-30 one in every seventeen patients was suffering from xerosis of the conjunctiva. In India, Kirkpatrick⁴⁹ finds that the children's ward at the Madras Government Ophthalmic Hospital is rarely without a case of keratomalacia, though it is commonest in times of scarcity. Wright¹¹¹ states that it is the commonest cause of preventable blindness in India at the present time, a statement in which the professors of ophthalmology in Calcutta, Bombay and Lucknow apparently concur. In Yucatan in Central America Carillo¹² writes of xerophthalmia as a common deficiency disease in 1932, and Aykroyd¹ finds a large percentage of the population of Labrador suffering from night blindness. Severe outbreaks of the disease have been reported recently from prisons in Uganda⁷¹. During the time of privation following the Great War, and during the War, children with xerophthalmia and keratomalacia were seen in many clinics in Austria and in Germany; for example, Gralka³² says that at the Breslau Kinderklinik in 1922 he saw 30 cases of keratomalacia, whereas at the same clinic between 1912 and 1921 there were only 6 cases. Austrian physicians reported that during the War night blindness was common among prisoners of war in Russia, and occurred also among the peasants⁶⁶. Non-belligerent countries did not escape either,

and in Denmark, Blegvad, writing in 1924, had collected 582 cases occurring between 1909 and 1920, and it is said that vitamin A deficiency is now the commonest cause of blindness in that country.

Lastly, let us consider some records from our own country during the present century. In 1910 Stephenson⁹⁵ described 31 cases of keratomalacia in infants, most of which he had seen in the space of a few years at the Queen's Hospital for Children and at the Evelina Hospital, both in London. In contrast to this, during the last 12 years, the author, also working at the Queen's Hospital in what is still a very poor district, has seen no keratomalacia and only one case of xerosis of the conjunctiva. Hence in spite of the poverty prevalent nowadays, both the standard of living and the care of infants has improved sufficiently in the last quarter century to make gross A deficiency as evidenced by keratomalacia a rare condition in London. The provision of a milk grant for young children of impoverished families probably plays a very important part in this improvement. It has, however, been suggested that certain outbreaks of eye symptoms and 'distorted pneumonia' in industrial schools during the present century have resulted from vitamin A deficiency⁶³. In this country, it seems probable to the author that owing to the medical care bestowed on infants, eye symptoms, should they occur, are more likely to be found in older children as xerosis of the conjunctiva. This seems to be borne out by the following records:—

In 1921 Dr. Tyrrell, one of the Assistant School Medical Officers for the West Riding of Yorkshire, in his Annual Report, cited 19 cases of night blindness and dryness of the conjunctiva discovered in the Doncaster area after the coal strike of 1921. Under treatment with a diet containing milk, eggs, butter, green vegetables and fruit, the night blindness was cured in four to six weeks, and the dryness of the conjunctiva in two to three months (personal communication from Dame Janet Campbell, Ministry of Health). In 1928-29 G. A. Dawson¹⁸, medical officer of health for Darlington, after seeing cases of xerosis of the conjunctiva in children admitted to the local fever hospital, carried out an investigation and found approximately 100 cases among children then attending nursery and elementary schools in his area. The diagnosis was confirmed by A. T. Paterson. Spence⁹², in Newcastle-on-Tyne, has been able to collect 17 cases of xerophthalmia and night blindness in one year, 11 of these being children under 15 years old; but he saw no babies suffering from the disease.

If individual investigators are able to find as many cases as this in one district, or attending one hospital, it seems probable that considerable numbers exist in other distressed areas of the country at the present time, and one wonders whether in this country, as a whole, eye changes due to vitamin A deficiency are not more common than the paucity of records would lead one to suppose. The author's work at the Queen's Hospital for Children strongly suggests that slight vitamin A deficiency, insufficient in grade to produce eye changes, is common among infants, but these cases are in no way comparable to the cases of keratomalacia and xerophthalmia which have been under consideration.

Seasonal incidence of xerophthalmia and keratomalacia.—A seasonal incidence has been noted in many parts of the world. M. Mori⁷⁴ found the disease developing in Japan in the 'diarrhoea months,' i.e., July to September, the slighter cases undergoing spontaneous cure in late autumn

and winter, and perhaps relapsing again next year. Stephenson⁹⁵, in this country, also found that keratomalacia was a disease of the diarrhoea season (summer), and that xerosis in school children developed during the spring and summer. He considered the increased exposure to light in the summer an important aetiological factor⁹⁴. On the other hand, the Danish cases developed chiefly between December and May, with a peak at the end of winter about March or April; the fall in incidence corresponding closely with the date when stall-fed cows were driven out to grass⁵. Gralka³², in Germany, found a similar seasonal distribution. Small epidemics among Japanese workmen in Manchuria were at their height in February and March, and this was attributed to the scarcity and high price of fish in these months (Mori quoted by Medical Research Council⁶⁶). It seems, therefore, that the seasonal incidence varies with local conditions; any local condition tending to a decrease in the vitamin A content of the diet at a given season no doubt affecting the incidence.

Age incidence of xerophthalmia and keratomalacia.—Eye changes due to vitamin A deficiency may occur at all ages, and keratomalacia has even been recorded in an infant at birth⁶⁴. Other factors being equal, young and rapidly growing children are the most likely to show signs of the deficiency, and Blegvad⁵ brings out clearly the greater rapidity of the illness in young infants than in older ones. In descriptions of outbreaks of keratomalacia (that is the advanced stage of the eye changes) the majority of the children attacked have usually been under 1 year, whereas in descriptions of xerosis of the conjunctiva (which is a relatively slight change) we usually find the greatest incidence in older children.

The age incidence of eye symptoms in any particular area is likely to depend to a great extent on local factors. Thus in Denmark the disease was largely one of bottle-fed babies given skimmed milk⁵; whereas in Japan, where breast feeding was presumably the rule and no cow's milk was available, the disease occurred chiefly after weaning, in children of 2 to 5 years old⁷⁴. Spence's cases⁹² in Newcastle varied from 2 to 54 years old; though the majority were children, there were no infants among them, and this may well be accounted for by the milk grant available for infants of the poorest families in this country.

Diets which have caused xerophthalmia and kerotomalacia.—It has long been recognized that xerophthalmia and keratomalacia are diseases of defective nutrition, and likely to occur on diets deficient in animal food (de Gouvêa¹⁹). Mori⁷⁴, about 30 years ago, attributed it to deficient fat. In spite of the widespread and ancient use of liver as a therapeutic agent, however, it is only since animal experiments established the existence of vitamin A that it has been possible to determine the specific cause of this disease.

Xerophthamia and keratomalacia appear only to have been recorded in children living on extremely ill-balanced diets, or in breast-fed babies whose mothers were on such diets. So that in human beings a diet sufficiently lacking in vitamin A to cause xerophthalmia or keratomalacia is usually very

deficient in other respects also, and it must be very rare to find a human diet deficient only in vitamin A. Vitamin A is present in full cream milk and milk products, eggs, fat fish and meat fat, green vegetables, carrots, tomatoes and other fruits and vegetables containing carotene. All these foodstuffs usually appear to have been either absent or deficient in the diets of xerophthalmia patients, hence it is not surprising that other deficiency diseases are often reported in association with this condition. The following are some examples of 'xerophthalmia diets':—

Mori's Japanese cases⁷⁴ usually lived on rice, barley and other cereal food, beans and vegetables; Frazier and Hu²⁸, in China, describe a diet consisting chiefly of rice, maize, millet and occasionally wheat flour with white cabbage and salted vegetables; the diet of Spence's cases⁹² in Newcastle consisted chiefly of wheat flour bread (often in very large amounts), margarine, jam, vegetables and tea, with no milk except in tea, and a few ounces of meat in the week; Dawson's cases¹⁸ were living mainly on white bread, margarine and tea; many of Bloch's Danish cases⁷ (for the most part children under 12 months old) had been fed on skimmed milk (pasteurized and reheated), oatmeal gruel and 'barley soup.' Commenting on the dietary of Bloch's cases, McCollum and Simmonds^{5,9} state that when the cereal consumption was large the children would have suffered from a deficiency of inorganic elements, and that the diet was probably on the borderline for rickets, scurvy and beri beri. Bloch's own findings⁸ support this statement. He found pronounced evidence of rickets in nearly one third of his cases, scurvy in at least one, and a number with a condition described as 'carbohydrate dystrophy' with oedema (a condition also noted by Mori in some of his cases and probably the same as the so-called 'war oedema' or 'hunger oedema' which may be a protein deficiency). Some of Bloch's cases, like a few others recorded in the literature, suffered from muscular hypertonicity which may have been due to another dietetic deficiency; or possibly Mellanby's work⁶⁷ on degeneration of the cord in dogs may throw further light on such cases. Forest and Wolff²⁶, in Strasburg, observed the development of xerophthalmia in babies fed from an early age as follows: dried skimmed milk 10 per cent.; sugar 5 per cent.; and a preparation of rice 5 per cent.; the calorie allowance was about 120 calories per kilogramme body weight daily. The ration provided about 15.3 centigrammes of fat daily.

Sometimes it is the mother's diet which is grossly ill balanced. Thus Thalberg⁹⁸, in 1883, reported a number of cases of keratomalacia in breast-fed babies in Russia, the babies were for the most part very wasted and the majority were children of ill-nourished women who had undergone a religious fast. In the post-war years breast-fed babies with xerophthalmia were reported from Germany by Gralka³², and Thatcher and Sure⁹⁹ have recently reported such cases from America.

Mori⁷⁴, in Japan, examined the milk of two mothers whose infants had xerophthalmia and found a fat percentage of 0.14 or less. Thus it is evident that the vitamin A value of human milk may be so low, that, though the child's diet consists wholly of milk, he is not protected from severe deficiency. This variability in the vitamin A value of a given foodstuff must be borne in mind, and such differences may account for some unexpected records. For example eggs are usually rich in this vitamin, and Lossouarn⁵⁸, in China, finds eggs a valuable therapeutic agent in this disease, but Spence⁹² reports that, according to the histories obtained, two of his patients had had one egg daily for at least four weeks without preventing the onset of eye symptoms. Again the vitamin A value of cow's milk may be largely destroyed by the treatment to which it is subjected: hydrogen peroxide, which has been used as a preservative in some countries, would presumably have this effect. Marshall Findlay, quoted by Cramer¹⁴, believed that he was able to correlate the

development of a chronic eye disease and 'distorted pneumonia' in an industrial school in this country in 1919, with destruction of vitamin A by a system of cooking under pressure which reproduced the conditions of an autoclave.

When the dietetic deficiencies are multiple the clinical picture will naturally be mixed, and sometimes one deficiency and sometimes another, may overshadow the rest. Moreover, the symptoms in the mother may be those of a different deficiency to that noted in her infant. Maxwell⁶⁴ reports an interesting case from China of a baby born with keratomalacia: the mother's symptoms, however, were not those of vitamin A deficiency but of vitamin D deficiency: she was suffering from osteomalacia. Again, Thalberg⁹⁸ found xerophthalmia in the breast-fed infant of a beggar woman with apparently hunger oedema. On the other hand, as would be expected, the babies of women suffering from xerophthalmia may show symptoms of the same disease³⁹.

It would therefore seem that xerophthalmia and keratomalacia have usually developed on high carbohydrate diets containing little animal fat or green vegetables, and such diets have usually been deficient in other substances besides vitamin A. Nevertheless, it should also be remembered that skimmed-milk feeding has sometimes been the cause of this trouble, and that even breast milk may be sufficiently deficient in vitamin A to cause keratomalacia if the mother has suffered great privation.

Duration of a deficient diet.—The time necessary for the development of xerophthalmia in a child on a deficient diet presumably varies as it does in young rats, and depends on such factors as the store present in the body at the outset, the degree of deficiency in the diet, the age of the child and the rate of growth. According to the observations of Forest and Wolff²⁸, babies fed from the age of $2\frac{1}{2}$ months or less on a skimmed milk and carbohydrate diet developed xerosis of the conjunctiva 3 to 4 months after starting the diet. Blegvad⁵ found that the disease may develop in under 2 months if the baby starts a deficient diet during the first quarter year of life, but that when the child was over 12 months of age the average duration of the deficient diet before the onset of symptoms was $8\frac{1}{2}$ months. His cases were all young children or infants. Herbert³⁹ says that patients may continue for many years, with intervals, to suffer from xerosis.

Symptoms of vitamin A deficiency in children.—Pillat⁷⁹, who has had the opportunity of studying many cases of xerophthalmia, summarizes the effect of vitamin A deficiency as: 'a system disease of the epithelial . . . apparatus of the body,' and states that 'keratomalacia is merely one symptom . . . of a general disease; for the skin, the hair, the nails and the various glands of the body, and the mucous membranes of the respiratory, digestive and urino-genital tracts are all concerned.'

GROWTH, NUTRITION AND GENERAL CONDITION.—Wasting is a prominent feature in most clinical descriptions of children suffering from keratomalacia, but in the majority it is quite impossible to say how far this is attributable to vitamin A deficiency, in view of the miserable diets and coincident illnesses reported. Rapid wasting is apparently more common, as one might expect,

in the infant with keratomalacia than in the older child with only xerosis of the conjunctiva. There is some evidence to suggest that loss of weight is a much less dramatic feature of the disease in the relatively slow growing human child than it is in the rapidly growing young rat. For example, Spence⁹² states of his 11 cases in children that all but one 'had the appearance of well-nourished active-looking people.' Moreover, the administration of vitamin A and cure of the eye condition did not necessarily result in a coincident rise in weight or height. Stephenson⁹⁴ says of his children with xerosis of the conjunctiva that they were usually well nourished, though his standard would appear to have been rather low. Thalberg⁹⁸ and others have recorded xerophthalmia in individual instances in children who have looked in good general condition. Aykroyd¹ (probably referring to adults) states that night blindness may occur in persons otherwise apparently in good health. Forest and Wolff²⁶ in Strasburg, who observed the development of xerophthalmia in babies on a diet of skimmed dried milk and carbohydrate, state that the weight increase on this diet was regular though slow; in the period preceding the development of eye symptoms the average increase was 10 to 15 grammes daily, say $2\frac{1}{3}$ to $3\frac{1}{2}$ ounces weekly, as compared with the normal average of about 6 ounces weekly. As these babies probably also suffered from a deficiency of vitamin D, and possibly also of vitamin C, it is not possible to assess the influence of different factors on their rate of growth. Apparently with the development of eye symptoms the weight became stationary. There is no doubt that ultimately a deficiency of vitamin A, if sufficiently severe and prolonged, must cause wasting and death in children just as in experimental animals, but it is evidently possible for xerophthalmia (like scurvy and rickets) to be present in a child of approximately normal weight and height.

If the child survives the illness, Bloch⁸ states that his ultimate growth is not retarded: of 64 blinded children who were examined by him at 12 years old and upwards, few were under standard weight. Possibly if the children had been older when they suffered from vitamin A deficiency and the disease had been of longer standing and more chronic, a different result might have been obtained. The present author's impression is that a child under one year old with active rickets which is diagnosed and adequately treated, will usually show good growth, whereas it is well known that the child stunted with rickets at, say, 3 years old, will probably be well under standard height at 12 years old. Similar findings may well apply to vitamin A deficiency.

Some writers, among them de Gouvêa¹⁹ in 1883, have laid special stress on the apathy, mental dulness, and complete loss of energy and initiative of persons suffering from keratomalacia.

CHANGES IN THE EYES.—To assess the frequency of eye symptoms in persons suffering from vitamin A deficiency is impossible in the present state of our knowledge, since the diagnosis of vitamin A deficiency is usually only established because eye symptoms are present. Night blindness appears invariably to precede any objective eye changes, but in children under 2 years

old it is unlikely to be recognized. This no doubt partly accounts for the more advanced stage of the eye disease in most young children when treatment is first sought, but it is also clear that the disease is a more rapid one in young children than in older persons, and hence the stage of night blindness without xerosis is probably considerably shorter. Exposure to strong light may precipitate the development of night blindness, a point stressed by Stephenson⁹⁴ in 1898 and, even as long ago as 1883 by de Gouvêa, and recently emphasized by Aykroyd¹ in his description of the condition in Labrador. De Gouvêa notes that at dawn the vision is better than in the dusk of evening after exposure to sunshine during the day. Deficiency of vitamin A apparently leads to subnormal formation of visual purple in the retina, and so to night blindness.

The first characteristic objective eye change noticed is usually slight irregular dryness and the appearance of Bitôt's spots, with perhaps shrinking or wrinkling and loss of lustre of the scleral conjunctiva. Bitôt's spots are very characteristic: they are whitish or yellowish foamlike spots on the bulbar conjunctiva, looking as though they would easily brush off with a movement of the lids, but actually remaining unchanged when the lid is gently rubbed over them. In the babies observed by Forest and Wolff²⁶, Bitôt's spots appeared 10 to 15 days after the first signs of dryness of the conjunctiva. Later corneal changes make their appearance: the cornea loses its lustre and becomes hazy, dull and dry and loses its normal sensitivity, and may show whitish plaques. If the condition continues to progress, the cornea becomes greyish and then necroses. Not infrequently there is superadded infection even before the characteristic changes appear, and an early conjunctivitis may develop together with photophobia. The lids may be swollen in the early stages and blepharitis and stytes are common⁷⁸. In the later stages of keratomalacia a hypopyon may develop or the iris prolapse, and finally the whole globe is disorganized, perhaps with panophthalmitis. In the presence of infection the characteristic appearance of the eye may be masked (see Herbert⁴⁰; Stephenson⁹⁵). A marked feature is reduced sensitivity of the coverings of the eyeball, and Stephenson draws particular attention to the apparently small amount of pain associated with keratomalacia, and the comparative ease with which the physician can consequently examine the eye, a feature which he says should immediately suggest the nature of the condition. In advanced cases the sensitivity of the cornea may be 100 times below normal, and that of the conjunctiva perhaps 4 times below normal as demonstrated by John⁴⁶. This diminished sensitivity has been found to persist after months of treatment, and long after the xerotic changes have disappeared.

It is of interest that Kreiker⁵¹ has shown that at an early stage of the eye disease, before any macroscopic eye changes have occurred, there are already epithelial changes which can be detected in microscopic sections, and no doubt it is this epithelial change which predisposes to infection.

In the dark skinned and yellow races slaty pigmentation of the conjunctiva may be an early symptom⁴⁰, but up to now no such pigmentary change appears to have been reported in white patients⁸⁰.

Pillat⁷⁹, who gives a full account of these eye changes, states that they can best be studied in adults in whom the disease is less rapid. Because the disease is more severe and more rapid in the infant than in the older child, keratomalacia is most often found in infants, whereas children of school age may suffer for months from night blindness and xerophthalmia without the disease progressing as far as keratomalacia. Hence the younger the child the greater the risk of blindness. If adequate treatment is given in the earlier stages of the disease, the cure of the eye symptoms is rapid and complete; but it is obvious that if the corneal changes are advanced blindness must result. Vitamin A deficiency was recently found to be the commonest cause of blindness in Denmark, and Blegvad³ stated that only 14 per cent. of the Danish children who survived the disease had fairly good vision. Mori⁷⁴ reported that a large number of the children who survived the disease in Japan were blind, and Pillat finds it to be a common cause of blindness in North China. Wright¹¹¹, as previously stated, concludes that it is 'the chief cause of preventable blindness in the Indian empire.'

CHANGES IN THE SKIN AND HAIR.—Skin symptoms probably precede the eye symptoms in many cases, and this seems of special interest in view of the author's finding regarding the lower incidence of skin infections in babies given a supplement of vitamin A (see Part II). De Gouvêa¹⁹ described in 1883 the dry, scurfy-looking skin with diminished sensitivity, and falling out of the hair often associated with this disease, features mentioned by many subsequent observers as will be seen below. Mori⁷⁴ in Japan, Stephenson⁹⁵ in England, Bloch⁷ in Denmark, Kirkpatrick⁴⁹ in India, all were struck with the skin changes, and most of them noted also changes in the hair, including occasional 'bleaching.' Their patients were nearly all children. Pillat⁷⁹, describing the disease in adults in China, devoted much attention to the skin, which he describes as becoming greyish and later yellowish, due to an increase in pigment in the basal cell layer of the epidermis⁸⁰. This pigmentary change, like the similar pigmentary change in the conjunctiva, does not appear to have been recorded in members of white races suffering from vitamin A deficiency. In mild cases, he says the skin looks pasty and puffy; in severe cases the fat disappears and the skin become lined and wrinkled. It feels dry, and there is marked reduction in sweating, and comedones may form. In severe cases the skin is covered with scurf and feels as if it had been powdered with flour, and sometimes larger scales form which adhere more firmly. The hair in severe cases becomes dry and dull and falls out, and the nails may be dry and lustreless and even chalky. Frazier and Hu²⁸ in China state that several weeks before the onset of eye symptoms in their patients (adults), the skin was dry and slightly rough; subsequently 'spinous keratinized papules' (presumably the 'comedones' mentioned by Pillat) appeared at the sites of hair follicles on the limbs and trunk; there was an absence of visible sweating and some wrinkling of the skin and dryness of the hair. Most of these general statements are borne out by individual case histories recorded by other observers, who repeatedly note the dryness of the skin.

Two interesting reports concerning skin lesions in this disease have come from East Africa^{71, 30}. There were many cases of night blindness and xerophthalmia in a prison in Uganda⁷¹, and 81 prisoners were segregated for observation; of these 71 suffered from night blindness, 45 had xerophthalmia, and 74 an 'acne-form eruption.'

No local treatment was given. The diet was unchanged, except that one ounce of cod-liver oil daily was given to each man. After 9 weeks the percentage of cures was:—night blindness 100 per cent.; xerophthalmia 100 per cent.; dermatoses 98·6 per cent. Thus it will be seen that if we accept this eruption as a symptom of vitamin A deficiency, it was much more common, and an earlier manifestation of the disease, than any objective eye change. The dermatosis is described as 'a dryness of the whole skin with the exception of the face, associated with a papular eruption, most apparent on the extensor surfaces. The papules are smooth, black and extremely irritable. Histologically, these papules are found to have as their nucleus an altered pilo-sebaceous follicle, which is sealed with a comedo, and shows more or less evidence of perifolliculitis.' Pustulation was rare. Sequieri³⁰ shortly afterwards examined patients at a mental hospital with similar eruptions as well as ocular manifestations of vitamin A deficiency. He says of the skin that 'as a rule the lesions are small, some little bigger than the head of a large pin, others about the size of a millet seed. They are in the form of blunt cones, and the lens shows that they are about the orifices of the hair follicles.' He said that he had seen this condition of the skin not infrequently in Kikuyus both on the farms and in hospital.

Besides changes in the texture of the skin, skin infections, often preceding eye symptoms, are recorded and emphasized by many writers. Lesions frequently mentioned are: furunculosis, pyodermia and ulcers, and sometimes impetigo. The following notes give some indication of the observations of different writers:—

Mori⁷⁴ says the xerophthalmia is frequently preceded by a long period of skin sepsis with furunculosis and chronic scalp abscesses, Stephenson⁹⁵ noted 'acute bedsores' in his babies with keratomalacia and states that four other writers had already drawn attention to them. In school children with xerosis of the eyes, he found⁹⁴ relapsing pustular eruptions common. Bloch⁸ found pyodermia common, and Pillat⁷⁹ records the presence of furunculosis and styes, and describes one case with what he calls 'dermolacia' or 'decaying hollows' in the skin. Frazier and Hu²⁸ found a marked tendency to pustulation in one third of their cases, and they speak also of ulcers. Spence⁹² found the incidence of skin sepsis, including boils and impetigo, high among his cases. Ross⁸⁵ and others mention furunculosis. Aykroyd¹ describes the frequency of 'salt water boils' on the wrist and forearms of fishermen on the Labrador coasts where vitamin A deficiency is common. These boils originate from the rubbing of wet garments, but Aykroyd is doubtful whether they are due to a food deficiency, though it is tempting to assume a similar aetiology in these cases and in the infants described in Part II, in whom local irritation of the skin apparently allowed local organisms to set up dermatitis. The rapid improvement in local skin sepsis following cod-liver oil or similar medication is noted by Pillat⁷⁹, Frazier and Hu²⁸, and Spence⁹², and the last three writers state that this improvement occurs without any local treatment of the skin lesions. Forest and Wolff²⁶ state that those babies in their series who developed eczema showed evidence of xerosis more rapidly than those without eczema; in view of other records, it seems fair to assume that this eczema was, at any rate in part, the direct result of vitamin A deficiency. Even Hippocrates apparently mentioned eruptions of boils in connection with night blindness (see Stephenson⁹⁴).

It would seem from these descriptions that there is no one type of skin infection particularly characteristic of vitamin A deficiency, but that a variety of skin infections, often chronic or relapsing in character, may occur. From the investigations described in Part II of this paper it would seem that vitamin A deficiency favours infections with local organisms at any site of skin irritation from external causes.

CHANGES IN THE RESPIRATORY TRACT.—Dryness of the mouth and hoarseness (corresponding presumably with the epithelial changes noted in the larynx and trachea of rats by S. Mori⁷⁵, and in their tongues by Tyson and Smith¹⁰²), are described as early symptoms of vitamin A deficiency in man by Herbert³⁹ and by Lossouarn⁵⁸; the latter noted hoarseness in more than half his cases and stated that it often preceded the appearance of night blindness. Pillat⁷⁹ also noted some cases with hoarseness which disappeared with improved nourishment. Respiratory infections are common in most of the recorded groups of cases, but here it seems impossible to guess to what extent the bronchitis and pneumonia are attributable to the vitamin A deficiency. In no large group of cases, so far as the writer can ascertain, are we told that the administration of vitamin A exerted any marked effect on the cure of respiratory infections, and the probable influence of other dietetic deficiencies must be borne in mind, since pneumonia is known to be a common terminal infection in many infants in poor general condition. Blegvad⁵ found pneumonia to be the commonest cause of death in the Danish infants who were mostly under one year old and suffered from a variety of deficiencies (including iron deficiency and vitamin C deficiency, either of which might increase the incidence of respiratory infections), and he states that of 60 fatal cases, 46 had pneumonia. In Chinese children with xerophthalmia Pillat⁷⁹ found pneumonia the second most common cause of death, and drew attention to the presence of 'obstinate bronchitis' with the disease both in adults and children. On the other hand, in some large series, such as M. Mori's⁷⁴ in Japan, pneumonia was not recorded as common, though he says that bronchitis was not infrequent. In the description by Wilson and Du Bois¹⁰⁵ of the post-mortem findings in a child dying of xerophthalmia, it is of interest that the respiratory infection present was not the common bronchopneumonia of babies, but bronchiectatic cavities with abscess formation, resulting presumably from local epithelial changes.

CHANGES IN THE GASTRO-INTESTINAL TRACT.—The great majority of writers who pay attention to the general symptoms associated with xerophthalmia, emphasize diarrhoea as an early symptom, especially in childhood. It is mentioned, for example, by: Thalberg⁹⁸, Herbert³⁹, Mori⁷⁴, Stephenson⁹⁵, Yarr¹¹², Monrad⁷², Bloch⁷, Blegvad⁵, Ross⁸⁵, Schwartz⁸⁶, Pillat⁷⁹, Kirkpatrick⁴⁹, Lossouarn⁵⁸. It is, moreover, a common cause of death in this condition (Mori⁷⁴, Stephenson⁹⁵, Blegvad⁵, Pillat⁷⁹). Mori⁷⁴ points out that the fortuitous presence of diarrhoea might cause the appearance of xerophthalmia in a border-line case as a result of lessened fat absorption. On the other hand, the rapid cure of diarrhoea which he frequently obtained with cod-liver oil, strongly suggests that these intestinal symptoms, like the eye and the skin symptoms, are generally a consequence and not a cause, and were primarily due to the epithelial changes set up by the vitamin A deficiency. The infecting organism would probably in some cases be a local inhabitant of the intestinal tract, and in some a virulent organism gaining entrance from outside, just as happens apparently in other cases of gastro-enteritis in infancy. Pillat⁷⁹ drew attention to cases in which typhoid and

dysentery preceded the appearance of eye symptoms, and other cases in which no infective origin could be found for the diarrhoea. Like Mori he found that in the latter type the diarrhoea would usually disappear with treatment with animal fat, including cod-liver oil. He states that similar cases of diarrhoea occur in China without eye symptoms, and are probably also due to vitamin A deficiency. He notes that constipation also may sometimes occur with keratomalacia.

Two other symptoms mentioned by Mori⁷⁴, which rapidly disappeared when cod-liver oil was given (apparently with no other treatment), were voracious appetite, which he says appears at some stage of the disease in nearly every case, and abdominal distension. In later stages, however, the appetite might be poor. De Gouvêa¹⁹ and Stephenson⁹⁵ were also impressed with the voracious appetite. One is naturally inclined to attribute these two symptoms to a deficiency made good by the oil, and as voracious appetite is not a symptom of rickets, vitamin A deficiency would seem the probable cause. As against this, is the fact that many writers associate poor appetite with xerophthalmia. It is interesting in this connection to recall certain symptoms in a group of kittens fed by the present author⁶⁰ on skimmed milk, vegetable oil, orange juice and marmite, and suffering presumably from vitamin A deficiency. These animals showed ballooning of the abdomen and great eagerness for food, beginning all meals with apparently voracious hunger, though the actual intake of food (which was provided *ad libitum*) was small. This eagerness for food, but small intake, may explain the fact that some writers stress voracious appetite and some poor appetite in children.

CHANGES IN THE URINARY TRACT.—Leber⁵⁴ in 1883 described in a post-mortem case desquamation of renal epithelium corresponding to the epithelial desquamation found in the eye with xerophthalmia. Such desquamation shows itself in life, and the presence of large quantities of desquamated epithelium in the urine is emphasized by Herbert^{40a} as occurring 'in every severe case' he had seen. He found it was often accompanied by pus cells in the urine. Spence⁹², in his series, found the same condition in 'the more severe cases,' and it persisted till vitamin A treatment was given. Pillat⁷⁹ mentions it in one case. Bloch⁸ found pyelitis in 27 out of 86 children with xerophthalmia, but is unable to provide information concerning the presence of desquamated epithelium in his cases.

As yet there appears to be no clear evidence showing that renal calculi in man may be the result of vitamin A deficiency, though this has been suggested as a possible cause of such calculi in India.

PYREXIA.—In many cases of vitamin A deficiency, pyrexia occurs which is apparently not due to the presence of infection. De Gouvêa¹⁹ noted this pyrexia in 1883 and Herbert³⁹, Mori⁷⁴, Hsu⁴³, and Wright¹¹⁰ have all recorded it as frequent. Forest and Wolff²⁶ say the pyrexia does not appear until after the onset of eye symptoms. Pillat⁷⁹ said he had observed pyrexia associated with diminished sweating, and in 6 severe cases of adult

keratomalacia he found that this disappeared with a few days cod-liver oil treatment. Temporarily after the institution of such treatment, there might even be excessive sweating. It seems probable, therefore, that in some cases at least the pyrexia is the result of diminished heat loss associated with the skin changes.

SUSCEPTIBILITY TO INFECTION.—Some mention of infection associated with vitamin A deficiency has already been made. In most clinical accounts of xerophthalmia one is struck by the associated infections. Thus Bloch⁸ found in his series of 86 infants and young children that 80 per cent. suffered from an infection: 12 had bronchitis, 15 pneumonia, 13 otitis media, 27 pyelitis and 14 pyoderma. The direct association between vitamin A deficiency and skin infections has already been discussed; what of the other infections? Bloch contrasts his xerophthalmia cases with a series of 32 scorbutic children, with 30 per cent. showing infections, as against 80 per cent. in the xerophthalmia series. But the comparison does not seem fair since vitamin C deficiency is often an isolated deficiency in an otherwise adequate diet, and may occur in the diet of an artificially-fed baby of parents in comfortable circumstances, whereas Bloch's cases of vitamin A deficiency occurred in babies and young children of the poorest classes and the diets were obviously deficient in a number of constituents. Hence it is impossible to determine whether the associated infections were the result of vitamin A deficiency or whether a number of different dietetic defects all played their part.

A contrasting, though very much smaller, group of cases are those studied by Spence⁹² in Newcastle. These were older, varying from 2 years to 54 years old, and Spence found, apart from skin infections, no evidence of increased incidence of infective disease among them, or among other members of their families who were presumably for the most part also consuming inadequate diets. Moreover, there seems no evidence in the published descriptions of xerophthalmia to show that vitamin A deficiency predisposes to any of the infectious fevers. On the other hand, should severe vitamin A deficiency exist, it seems likely that the local epithelial changes occurring in mucous membranes would provide a favourable condition for the entrance of infections of various sorts, and, by analogy with vitamin A deficiency in animals, one would expect infections, largely by local organisms, to occur in children with vitamin A deficiency. However, there seems at present no way of establishing that, for example, pneumonia recorded as having occurred in a vitamin A deficient child was due to the vitamin A deficiency rather than, let us say, to a deficiency of vitamin D and C or of iron. There is one type of infection which is frequently recorded on vitamin A deficient diets on which Hess⁴¹ lays stress, namely infestation with intestinal parasites.

Xerophthalmia associated with disease of the liver.—Blegvad⁵ draws attention to the occasional occurrence of keratomalacia in persons who are suffering from hepatic disease, and suggests that this is due to poor fat absorption in such cases. In the light of evidence now existing to show that the liver is the main storehouse of vitamin A in the body, it is probable that both deficient absorption and deficient storage of the vitamin has occurred in such cases, and this suggests the need for paying particular attention to the vitamin A intake in persons with disease of the liver. Wright¹¹¹ stresses the association of keratomalacia with liver disease in India, where infantile biliary cirrhosis is relatively common.

Skin lesions associated with idiopathic steatorrhoea (Gee's disease).—

The so-called coeliac disease of children, or idiopathic steatorrhoea of adults, is a disease with nutritional disturbances associated with defective absorption of various foodstuffs, important among which is fat. These patients are extremely liable to symptoms of deficiency of one of the fat soluble vitamins, vitamin D, and can be cured of the symptoms of rickets and tetany by increasing the vitamin D available to the body. Are they also liable to symptoms of vitamin A deficiency? Parsons^{77a}, in a masterly account of coeliac disease in a recent text book, states that with this disease xerophthalmia 'is rarely seen, although an instance is reported by Schick.' Bennett, Hunter and Vaughan^{78a}, in their account of 15 cases of steatorrhoea in adults and adolescents, say that 'the frequent occurrence of skin lesions in the present series appears too striking to be mere coincidence. They were noted in seven cases and described by the dermatologists as psoriasis, eczematous or pustular dermatitis.' They suggest that deficiency of the vitamin B complex may be responsible for the skin lesions in some cases, but it is certainly tempting to suppose that some of the skin lesions were associated with vitamin A deficiency, more especially as at least one of their cases suffered from loss of hair. What part, if any, vitamin A deficiency may play in other symptoms of coeliac disease, for example the abdominal distension, attacks of diarrhoea, stunted growth and occasional apparent voracious appetite, it is impossible to say. It is probable that many of these symptoms are of mixed origin as the nutritional deficiencies are multiple, but vitamin A deficiency may well be one factor.

Mortality.—The mortality with xerophthalmia and keratomalacia shows wide variations; as one might expect, it is highest in infants and diminishes during childhood. In Blegvad's series, the majority of whom were infants with keratomalacia, that is were very young and also suffering from fairly advanced disease, he estimated the mortality to be 21.5 per cent.: of those under 3 months old 39 per cent died, and of those over 12 months old only 11 per cent. Bloch⁸, in Denmark, studying cases of a similar type thought that probably one-third of the cases died before they reached 8 years of age, and that the mortality was highest in babies under 6 months old. On the other hand, Mori⁷⁴, although unable to give figures for the mortality, since his cases were out-patients, thought that among those adequately treated few died. His cases, however, were older, mostly between 2 and 5 years old, and in the great majority the eye changes were at an earlier stage than in Blegvad's series. Nevertheless, Mori stated that in Japan thousands of children died yearly from the diarrhoea (which at that time he attributed to insufficient animal fat) or recovered blinded from xerophthalmia. Stephenson⁹³ says that to his knowledge nearly half his babies with keratomalacia (average age $4\frac{1}{2}$ months) died, but most of his cases did not receive the dietetic treatment now known to be necessary. On the other hand, most of the school children he examined with xerosis he considered in tolerably good general health⁹⁴: hence presumably the mortality among them was small.

The commonest cause of death varies in different localities: diarrhoea would appear to be the most common, but pneumonia, as already shown, is mentioned by many writers.

Post-mortem findings in the human subject.—As in the rat, guinea pig, and monkey, so in the human subject dying from vitamin A deficiency,

characteristic epithelial changes are found. One of the fullest descriptions of post-mortem findings is that of Wilson and Du Bois¹⁰⁵, who made a post-mortem examination on a 5 months old baby dying with keratomalacia.

The infant was emaciated, the skin was dry and felt waxy, and the corneae were cloudy. The characteristic epithelial changes already described were present in the trachea, bronchi, lungs, renal pelvis, uterus, pancreatic ducts, submaxillary ducts and other parts, and these changes were associated with local inflammations. There were inflammatory changes in the lachrymal and salivary glands (the latter an extremely common site of abscess in the rat); cyst-like cavities with fibrosis and inflammation in the pancreas, and emphysema and bronchiectatic cavities with abscess formation in the lungs. Thus the pathological changes found in the human subject closely corresponded with those found in experimental animals.

The eye signs also arise from changes in the character of the epithelium. The epithelium of the conjunctiva may become a stratified epithelium many rows deep. Kreiker⁵¹ says that in the first stage of xerosis the goblet cells of the conjunctiva disappear and gradually the conjunctival epithelium loses its normal character and becomes more like epidermis. Later, the superficial layers of epithelial cells undergo hyaline degeneration, and below these 'cornification' occurs. The appearance of Bitôt's spots is due to the casting off of stratified epithelial cells, the hyaline degeneration giving the 'oily' appearance mentioned by some writers. The changes which occur in the cornea are of the same type.

Response to treatment with vitamin A.—As already shown, the use of liver or liver oil in night blindness and keratomalacia is both ancient and widespread. Nearly sixty years ago Snell⁹¹ was systematically using cod-liver oil for the eye disease in this country. Some clinical writers, as for example, M. Mori⁷⁴, came as near fixing upon the curative agent as was possible before the existence of fat soluble vitamins was recognized. Mori knew deficiency of animal fats brought about the disease, and that certain oils, for example, cod-liver oil, were potent therapeutic agents. Once vitamin A was postulated from animal work and its association with eye changes in the rat was established, the eye lesions in the rat were quickly recognized as corresponding with the eye changes carefully described in the human subject so many years before.

As a result of the animal investigations, however, the means of cure has been put upon a scientific basis, and for this reason is already much more systematically used for the human disease.

It is generally agreed that unless the disease is very advanced, treatment with vitamin A causes steady improvement. The eye symptoms respond well, and night blindness, occurring without objective eye changes, may be cured in as short a time as 12 hours¹ up to 2 to 3 days: a single large dose of cod-liver oil will abolish this symptom at least temporarily. Spence⁹² found that Bitôt's spots were diminished within a week of beginning regular treatment with cod-liver oil, and disappeared in the worst cases by the fifth to sixth week. Xerosis disappeared in another 10 to 15 days, and in his cases all signs disappeared within 2 months. Mori⁷⁴ states that in Japan, where there is a well-marked seasonal incidence, the slighter cases improve

without active treatment in the late autumn and in winter, but may relapse again the following year. Xerophthalmia has been cured in breast-fed infants by giving the mother cod-liver oil (Shiele, quoted by Blegvad⁵), though it would seem unwise in such a serious disease to trust to this indirect method of medication.

Under treatment with cod-liver oil, the skin rapidly becomes moister; pyrexia disappears; skin lesions heal or disappear; the abdomen, if enlarged, becomes smaller; diarrhoea probably clears up; and if there has been an excess of epithelial cells in the urine, these disappear. Weight usually improves, and there is a steady improvement in activity and health.

Studies of the effect of vitamin A administration either prophylactically or in acute infections.

So far we have considered the disease 'vitamin A deficiency' as revealed in the records of persons suffering from night blindness, xerophthalmia or keratomalacia, and have suggested that these eye changes are far from being the earliest changes in the disease. It is, therefore, interesting to consider what light has been thrown by other types of investigation on the symptomatology of vitamin A deficiency in man.

Of late years much attention has been focussed on the possible part played by vitamin A deficiency in increasing susceptibility to infection, and it has been suggested that reduced immunity due to vitamin A deficiency is widespread or that vitamin A is a special 'anti-infective agent.' An attempt is, therefore, made below to give a very brief survey of the subject from this aspect. No increased immunity to infections has been demonstrated as the result of giving an excess of vitamin A to persons already getting an adequate supply either in a good general diet or in the form of a cod-liver oil supplement.

Thus Wright, Frosst, Puchel and Lawrence¹⁰⁹ in the Montreal Foundling and Baby Hospital, found no reduction in the common upper respiratory infections in a group of babies given vitamin A concentrate in addition to the cod-liver oil which was given to all infants as a routine measure. Again, lads in a Royal Air Force technical school, getting a good diet, who were given a large daily dose of vitamin A, suffered from a roughly similar incidence of minor respiratory infections to those noted in the controls (actually the vitamin A group showed a very slight advantage, but the difference was not statistically significant⁶⁵).

Vitamin A as a purely prophylactic agent has also been studied in groups of persons who, it was thought, might have received an inadequate supply of the vitamin in their diet.

For example Barenberg and Lewis³ compared the incidence of respiratory infections in babies receiving partly skimmed milk (a diet which one would suppose might well be deficient in vitamin A), with other groups of babies in the same institution getting either extra vitamin D or extra vitamin A and D combined, and found no significant difference between the groups. The groups, however, were fairly small.

The interpretation of the work of Green, Pindar, Davis and Mellanby³⁴, in connection with puerperal infection, is complicated by the simultaneous administration of vitamins A and D. They gave extra vitamins A and D combined to a large group of pregnant women and reported a greatly reduced incidence of puerperal pyrexia in women so treated as compared with controls. On the other

hand, Burton and Balmain¹⁰ carried out Dick tests on pregnant women and on patients convalescent from scarlet fever, both groups being treated with vitamins A and D combined, and also carried out Dick tests on controls, but failed to reveal any influence of these vitamins on the result of the Dick reaction.

Hence none of these observations can be regarded as establishing the existence of any widespread vitamin A deficiency, nor the value of vitamin A as a prophylactic agent against general infections, since all positive results may be ascribed to the action of either vitamin A or vitamin D or both, or else numbers are too small to establish any conclusions. The prophylactic administration of vitamin A to babies described in Part II suggests that among infants slight vitamin A deficiency is not uncommon and that extra vitamin A diminishes the incidence of skin infections. In other words, susceptibility to skin infections is probably the first sign of vitamin A deficiency in infants. If this be so, then more information concerning the prevalence of vitamin A deficiency should be obtainable by using this vitamin in the treatment of skin infections.

To some extent this has already been attempted. Thus Kuipers⁵², van Gulik¹⁰³ and Prakken⁸³ have each treated the eczema seborrhoicum of infants with vitamin A, with or without an acid in addition. The two first writers claim benefit from this treatment, but Prakken failed to confirm their results. The present author is now engaged at the Queen's Hospital for Children on work concerning the value of vitamin A in the treatment of skin infections.

Vitamin A has been given as a therapeutic agent during the course of acute infections, for example, in puerperal septicaemia, pneumonia, measles and scarlet fever. Unfortunately in most of these observations vitamins A and D have been given together, which makes it impossible when beneficial results have been claimed to assess the part played by either separately.

The extensive observations of Orenstein⁷⁶ and his colleagues on pneumonia in South Africa are not open to this objection. Their investigations appear to have been thoroughly controlled, and are clear cut. They used a vitamin A concentrate alone, without added vitamin D, for the treatment of native mine workers with pneumonia, because it had been suggested that the diet of these workers was deficient in vitamin A. However, it was proved that extra vitamin A did not affect the mortality rate, length of stay in hospital, or the complications and sequelae in their patients. Donaldson and Tasker²⁰ had previously carried out observations, on a smaller scale, on pneumonia cases and considered their results favourable, but they had apparently employed beef liver and a combination of vitamins A and D, so that a clear interpretation of their results is not possible. In 1929 Mellanby and Green⁶⁹ suggested, as a result of a small series of observations on cases of puerperal septicaemia, that vitamin A was of value in the treatment of this condition. However, their observations also were complicated by the simultaneous administration of vitamins A and D, and, as far as the author is aware, the value of vitamin A in such cases has not yet been confirmed.

Another disease on which some interesting work has been done is measles. Ellison²² treated 300 cases with vitamins A and D combined, and compared them with 300 control cases. Control and treated cases appear to have been well matched, and whereas the death rate in the control group was 8.7 per cent. that in the treated group was only 3.7 per cent. These figures seem to indicate that the vitamin treatment was of considerable value, but they leave unsettled the question whether vitamin A or vitamin D, or both, were material factors. Since the maximum seasonal incidence of both measles and rickets is in the late winter and early spring months, it seems likely that many of these patients from poor homes may have suffered from vitamin D deficiency, in which case the results described might be entirely due to the extra vitamin D given. A curious point is that although the mortality rate was

less than half in the vitamin treated group, yet the incidence of otitis media was just about the same in the two groups. Sutliff, Place and Segool⁹⁶ carried out similar observations on cases of scarlet fever, their object being to compare the incidence of otitis media in cases given extra vitamins A and D and in those not so treated. They arrived at the conclusion that the vitamin supplements were ineffective in reducing the incidence of otitis.

If vitamin A deficiency is playing an important part in increasing susceptibility to severe infections which may cause death, then careful post-mortem examination, with particular attention to the presence or absence of the epithelial changes characteristic of vitamin A deficiency should go a long way towards settling the question. Certainly existing knowledge would seem to indicate that infections occurring in vitamin A deficient animals are the direct result of pathological changes in the epithelium. Hence if at a human post-mortem examination these changes are definitely absent, then one might legitimately assume that the infection was not the result of vitamin A deficiency. It is, however, obvious that very extensive examination would be necessary to establish such a negative result.

Studies of the vitamin A content of the human liver and blood.

Four different workers: Wolff¹⁰⁷ in Holland, both Moore⁷³ and Green^{35a} in England, and Fox²⁷ in South Africa, have approached the question of vitamin A deficiency from another standpoint. They have estimated colorimetrically the vitamin A value of the livers of persons dying from different causes, hoping in this way to find some correlation between the cause of death in different groups of cases and the amount of vitamin A in the liver. The figures obtained varied enormously. In persons dying of accidents, and supposed to be otherwise healthy, the values obtained varied from 0 to 1,210 blue units per gramme of liver (Wolff¹⁰⁷). Even in a supposedly homogenous group of adult males, all on the same ration, and all dying as the result of accident, Fox found the blue value varying from 12 to 988. The values obtained by Fox for persons dying of accident (12 to 988) and for those dying from pneumonia (0 to 483) who had also been on the ration, showed a wide overlap, though the pneumonia cases showed a lower average value. In the present state of our knowledge, it seems likely that if the same series had been estimated biologically (an impossibly large undertaking), the two methods would have often given discrepant results. Nevertheless, certain considerations of great interest emerge from these studies. They strongly suggest that persons with liver disease, or degeneration of liver cells, have a deficient storage capacity for the vitamin^{35a}. Other features of interest are that persons dying of organic heart disease, bronchitis, kidney disease and septicaemia, as well as new-born infants, give low average values; on the other hand, diabetics, presumably on account of the nature of the diet prescribed, have high average values. At present it is impossible from these observations to draw any general conclusions as to whether or not widespread vitamin A deficiency exists in the countries where the work has been done, or to assess the part played by vitamin A deficiency in lowering resistance to infection.

Clausen¹³ in a preliminary report on 'carotinemia and resistance to infections,' concludes, from a statistical analysis of the diets and respiratory infections of 700 children under 3 years old, that vitamin A deficiency may account for some severe infections. He found that carotene is present in the blood at birth, and rises by 2 years old to an average of 0.075–0.100 mgm. per 100 c.c. in the plasma. The average values for healthy children were low in the winter months, namely, December to February.

Summary.

This paper attempts to construct from the literature on the subject a clinical account of the disease 'vitamin A deficiency,' with special reference to children.

Incidence.—The disease is stated to be common in India, China, and the Far East, as well as in some parts of Central America and Labrador. In Europe it is probably much less common now than it was during the last century; in this country cases of sufficient severity to give rise to keratomalacia, or even to xerosis of the conjunctiva, are apparently comparatively rare. Since, however, in many cases eye changes are clearly not the earliest symptoms, it is possible that the disease is present in many areas where it has passed unrecognized. Whether or no vitamin A deficiency of slight grade is frequent in this country is a debatable point: the evidence submitted in Part II suggests that it is common in infants. Persons of any age may be affected, but children are more susceptible than adults, and the younger the child the greater the susceptibility. The deficiency is most likely to occur in the poorest sections of the population. There exists no satisfactory evidence to show that vitamin A deficiency is a common cause of any of the usual respiratory or intestinal infections occurring in children in this country.

Diets deficient in vitamin A.—The eye symptoms produced by vitamin A deficiency have usually occurred on high carbohydrate diets, or sometimes on a diet of skimmed milk. The dietaries have usually contained little or no eggs, meat, animal fat, or green vegetables, and have consequently been deficient in more factors than one. No quantitative knowledge exists as to the vitamin A requirements of children. A breast-milk diet may, under some circumstances, provide insufficient vitamin A for a baby.

The clinical picture of vitamin A deficiency.—If we imagine a case of established vitamin A deficiency in a child, we would probably picture a child of very poor parents, thin, undersized and apathetic and suffering from a variety of dietetic defects and very probably also from complicating infections. If the patient is a baby, he will probably be marasmic and have keratomalacia; if a school child, he may be well grown or undersized and eye symptoms are likely to be less severe. Severe vitamin A deficiency rarely, if ever, occurs alone. If we nevertheless try to imagine a child suffering from the effects of vitamin A deficiency alone, the following

seems the probable clinical course (the order of onset of the different symptoms varying from case to case):—

A child, otherwise apparently in good health, develops an increased susceptibility to infections of the skin; he may have boils, sores, impetigo, or napkin rash or other evidence of skin sepsis, and this susceptibility continues throughout the disease, the lesions often being chronic. In the next stage, the texture of the skin itself undergoes a change and becomes dryer than normal, and may show desquamation. The dryness will probably not affect the skin of the face. A papular or 'acne-form' eruption may be present on extensor surfaces. There are usually periods of looseness of the bowels, sometimes a chronic diarrhoea sets in, occasionally constipation appears, and the rate of growth is retarded. The child loses the alertness of health and may be very lethargic. The hair loses its normal gloss, and if the child belongs to a dark skinned or yellow race, some slaty pigmentation of the conjunctiva and skin will probably appear. The voice may become hoarse and there may be bronchitis. The child may show great eagerness for food, and a large abdomen. By this time, if the patient is old enough and he is watched when playing in the dusk, evidence of night blindness will probably be present; it is apparently invariably present before there is xerosis of the conjunctiva. The first objective eye change in a white skinned child may be either conjunctivitis, or dryness of the conjunctiva with the formation of Bitôt's foam spots; and by the time these have appeared the weight will probably be stationary. There is often irregular pyrexia, which is more likely to be noted in hot climates as it probably results from diminished sweating and consequent diminished heat loss. If the case is still untreated and the deficiency severe, the child will grow thinner, subcutaneous fat is lost, the skin becomes shrivelled, there is powdery and flaky desquamation of the skin, the hair falls out and the eye changes progress with involvement of the cornea. In an advanced case there is marked wasting, with shrivelled, dry, desquamating skin, large numbers of epithelial cells in the urine, pyrexia, loss of appetite, extreme apathy; and corneal changes which frequently produce blindness, together with infections of both skin and eye. If there has been exposure to strong sunlight there may be some bleaching of the hair. Death occurs most often from diarrhoea or from pneumonia. In an older child the disease runs a slower course, in a young infant a much more rapid course, and the younger the child the worse the prognosis. The order of appearance of symptoms varies: in some cases one group of symptoms, and in other cases another will predominate, but by the time objective eye changes are present it is probable that evidence of change in other epithelial tissues will also be present, for in most cases it seems that they precede the eye changes.

Mortality.—The mortality for established cases of vitamin A deficiency varies greatly. With adequate treatment, even in advanced cases, it is probably small, unless the child is acutely ill with an infection. Without specific vitamin A treatment the mortality among babies is very large; among older children much smaller.

Post-mortem changes.—The characteristic post-mortem changes are in the epithelium and occur simultaneously at many sites; cuboidal or columnar epithelium is transformed into epithelium of a squamous type, and squamous epithelium becomes keratinized. Infections apparently gain entrance as a direct result of this epithelial change.

Treatment.—If treated early with adequate doses of vitamin A, for example in the form of cod-liver oil, the prognosis at all ages is good; and without other treatment, eye changes, skin changes, hoarseness, diarrhoea, voracious appetite and pyrexia all diminish and disappear. If treatment is begun late, though life may be saved, vision will probably be lost.

Conclusion.

It is hoped that this attempt to summarize our clinical knowledge of vitamin A deficiency may lead to the collection of more evidence regarding its incidence. If the syndrome described is borne in mind, it is hoped that clinicians may recognize the disease at an earlier stage, and in some cases at least establish its identity by the therapeutic test of giving vitamin A without other forms of medication. If pathologists will keep the condition in mind, and examine for the characteristic epithelial changes, evidence should be forthcoming as to whether or not vitamin A deficiency is a common cause of infections bringing about death. Apart from these fatal infections, evidence is required as to whether or not vitamin A deficiency is an important factor predisposing to skin infections, and on this subject further investigations are in progress. It is possible that the much higher incidence of skin infections in the lower social strata than in the higher, is more a matter of diet than of soap and water.

Up to now no satisfactory evidence is available proving the value of vitamin A administration (without other therapeutic measures) either in the prophylaxis or the cure of any of the common acute infections present in this country.

The possibility that vitamin A deficiency plays a part in certain common diseases of the central nervous system has been suggested, but clinical work bearing on this problem is not at present available.

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