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## VITAMIN A AS AN ANTI-INFECTIVE AGENT.

BY

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AND

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THE assigning of names descriptive of some particular function to distinctive vitamins has been a useful, although probably only temporary, step in the development of knowledge of these elusive entities, because their identification has so often depended upon the appearance of definite syndromes in animals whose diets have been deficient in certain respects. The use of the words "antiscorbutic," "antineuritic," and "antirachitic" in describing specific vitamins is an example of this, and from a clinical standpoint the nomenclature has been of great value. Vitamin A has always presented special difficulties to a clinically descriptive term because it has depended to such a large extent on a purely physiological criterion—namely, growth in young animals—for its detection. It is in consequence often referred to as the "growth-promoting" vitamin. Since the recognition of vitamin D (the antirachitic vitamin) as an entity distinct from vitamin A, those with experience of nutritional work have felt that to call vitamin A the "growth-promoting" vitamin is a misnomer, for good growth often takes place in its absence if the diet is otherwise complete. In fact, when growth ceases owing to the single absence of vitamin A from the diet, it often means that the animal is definitely ill—in the sense, as will be seen below, of its having developed some, and often a widespread, infective condition. Indeed, the present paper supplies evidence in favour of the term "anti-infective" being applied to vitamin A.

From the early days of its recognition it has been thought that vitamin A was concerned with resistance to infection, at least of a specific type. This is seen in its description as the "anti-xerophthalmic" vitamin, but this appellation has never become widely adopted, partly because



xerophthalmia in human beings, although related to vitamin A intake as suggested by the observations of Mori<sup>1</sup> and shown by Bloch,<sup>2</sup> is of very rare occurrence, and partly because McCollum, Simmonds, and Becker<sup>3</sup> have shown that this eye condition results from dietetic abnormalities other than vitamin A deficiency.

Several workers, including Drummond,<sup>4</sup> Cramer and Kingsbury,<sup>5</sup> and Steenbock,<sup>6</sup> have commented on the susceptibility to lung infections of animals on vitamin A deficient diets. In the case of dogs E. Mellanby<sup>7</sup> drew attention to the development of broncho-pneumonia in animals living on diets deficient in fat-soluble vitamins. He pointed out that this tendency to broncho-pneumonia was independent of the condition of the bones, which is itself an indication of the vitamin D intake. For instance, when cod-liver oil was present in the diet the bones were well calcified and there was no tendency to broncho-pneumonia or atelectasis of the lungs. When butter-fat was the source of fat-soluble vitamin, the bones under certain experimental conditions were soft and portions of the lungs were often in a collapsed state, probably because of muscular paresis, but there was no broncho-pneumonia or other infective condition. When olive oil replaced butter, badly calcified bones, collapse of portions of the lungs, and broncho-pneumonia were commonly found. These results suggested that protection against infection of the respiratory tract was conferred by vitamin A and not by vitamin D.

Linked up with the problem of xerophthalmia and other infective conditions is that of the changes in epithelium induced by diets deficient in vitamin A. The first to draw attention to these epithelial changes was Mori<sup>8</sup> in 1922, who described them in the larynx, trachea, and ducts of many glands, including the Meibomian, submaxillary, sublingual, and parotid glands of rats. Xerophthalmia he regarded as being due to the drying of the epithelium resulting from the suppression of activity of the lacrymal glands. Wolbach and Howe<sup>9</sup> extended this work of Mori's and described changes in the pancreatic duct and renal pelvis. They gave a detailed description of histological changes in epithelium, and came to the conclusion that infective changes are not responsible for the epithelial hypoplasia and keratinization, but are secondary to them. The diets used by Mori, and those of Wolbach and Howe, were deficient in vitamins C and D as well as A, but these other deficiencies were not regarded by them as affecting the problem.

This complication was eliminated by Goldblatt and Benischek,<sup>10</sup> who tested the effect of a simple vitamin A deficiency. By this means they induced metaplasia of columnar, cuboidal, and transitional epithelia to the squamous keratinizing type. When vitamin A was present no changes in the epithelium were observed. In the course of their work they found on making *post-mortem* examina-



tions many cases of infection in animals which had lived on diets deficient either in vitamin A or vitamins A and D. These infective conditions included xerophthalmia, abscess of tongue, abscess of submaxillary glands, broncho-pneumonia, and enteritis. Abscesses beneath the tongue are of interest because of their frequency. They were first described as resulting from a vitamin A deficiency by Sherman and Munsell.<sup>11</sup>

A striking instance of epithelial hypertrophy and keratinization is that described by Fujimaki<sup>12</sup> at the cardiac end of the rat's stomach, induced by diets deficient in fat-soluble vitamin. This hypertrophy he described as cancerous, and certainly, when the centre of the swelling becomes infected, the appearance of the mass is very suggestive of cancer, although, in our experience, microscopic examination does not reveal malignancy.

Another morbid development related to vitamin A deficiency is that of infection of the genito-urinary tract, and the occasional appearance of stones in the bladder and less often of stones in the pelvis of the kidney. The production of stones in the bladder was first described by Osborne and Mendel,<sup>13</sup> and although this was at one time denied by McCollum<sup>14</sup> as being due to vitamin A deficiency, the observation has been confirmed by Fujimaki<sup>15</sup> and Van Leersum.<sup>16</sup> Van Leersum found the stones to be usually composed of calcium phosphate, but occasionally they consisted of calcium oxalate.

McCarrison<sup>17</sup> has also observed stone in the bladder of rats brought up on diets deficient in fat-soluble vitamins. A point of interest about his basal diet is that he included either oatmeal or atta (whole meal) in large quantities among the substances eaten. Since 1922 we<sup>18</sup> have emphasized the special demand on fat-soluble vitamins made by cereals, and especially oatmeal, and this may be another instance of cereal and vitamin antagonism.

In view of the fact that practically all the experimental work except that of Goldblatt and Benischek<sup>19</sup> has been complicated, in that the diets were deficient in both vitamins A and D, and often C, it was felt desirable to repeat the work with the special object of seeing why diets deficient only in vitamin A result in the death of animals eating them. The production of vitamin D by irradiation of ergosterol, as described by Rosenheim and Webster<sup>19</sup> and Windaus and Hess,<sup>20</sup> made it possible to give diets deficient only in vitamin A. The results obtained confirm those above described, but the animals eating these diets were so uniformly attacked and ultimately killed by infective and pyogenic complications as to make the investigation singularly impressive from a medical standpoint. It is, in fact, difficult to avoid the conclusion that an important, and probably the chief, function of vitamin A from a practical standpoint is as an anti-infective agent, and that a large number of common infective conditions are due to a deficiency of this substance in the diet of many people:



## EXPERIMENTAL METHODS AND RESULTS.

The composition of the basal diet used in these experiments was as follows:

Heated casein	...	...	...	...	...	400 grams
Rice starch	...	...	...	...	...	800 "
Salt mixture	...	...	...	...	...	80 "
Cane sugar	...	...	...	...	...	240 "
Marmite	...	...	...	...	...	160 "
Olive oil	...	...	...	...	...	160 c.cm.
Lemon juice	...	...	...	...	...	140 "
Liquid salt mixture	...	...	...	...	...	160 "

The liquid salt mixture had the following composition:

Calcium acid phosphate	...	...	...	...	...	176 grams
Potassium iodide	...	...	...	...	...	10 "
Water	...	...	...	...	...	2,000 c.cm.

The salt mixture was as follows:

Sodium chloride	...	...	...	...	...	92 grams
Magnesium sulphate	...	...	...	...	...	142 "
Sodium phosphate	...	...	...	...	...	185 "
Potassium phosphate	...	...	...	...	...	509 "
Calcium lactate	...	...	...	...	...	694 "
Ferric citrate	...	...	...	...	...	63 "
Sodium fluoride	...	...	...	...	...	1 gram
Manganese sulphate	...	...	...	...	...	4 grams

The casein was heated in an electric oven for thirty-six hours at 120° C. The olive oil varied; in some cases it was omitted from the diet, in others it was given either unheated, or heated and oxygenated for periods of either six or twelve hours at 120° C. As this variable made little or no difference, so far as could be seen, to the outcome of the experiments, it will not be considered further. Vitamin D was given in the diet in the form of irradiated ergosterol (radiostol 1/2 to 1 drop per rat daily). The age of the rats when the diets were started varied between 26 and 35 days, and their weights ranged between 35 and 50 grams.

In the control experiments where a source of vitamin A was included in the food, 0.5 gram of dried cabbage (dried at a temperature of 70° to 80° C. for twenty hours) was generally added; and in other cases either butter (0.1 gram daily) or cod-liver oil (5 to 10 mg. daily) was used as a source of vitamin A. In a few experiments which belong to another investigation other substances deficient in vitamin A have been fed to the rats, and the results are recorded in the tables. These included vegetable margarine, heated wheat germ, and ergot. The amount of vitamin A in these substances in the quantities given is negligible, but, as we have recently shown, ergot is a rich source of vitamin D.<sup>24</sup>


I.—*Post-mortem Findings in Animals Fed on  
Vitamin A Deficient Diets.*

In the accompanying tables infection is indicated by +. The extent and intensity of infection in the case of

TABLE I (a).—A-Deficiency; Basal + Vitamin D (Irradiated Cholesterol or Itadistol).

Rat No.	Sex	Days on Diet.	Xerophthalmia.	Tongue Abscess.	Alimentary Infection.	Kidney Infection.	Bladder Stone.	Bladder Infection.	Other Sites of Infection.
28		128	++	++	+	+	+		Lung.
27		141	+	+	+	+	+		Gland of neck, submaxillary glands, thyroids, testes, seminal vesicles, lung, Mesentery.
64	F.	169	+	+	+	+	+	+	Lung, prostate glands, nasal sinuses, middle ear.
279	F.	94	+	++	+	+	+	+	Lung, trachea.
280	M.	96	++	++					Nasal sinuses.
289	F.	75	+	+	+	+	+	+	Nasal sinuses, middle ear.
283	F.	64	+++	+					Nasal sinuses, middle ear.
319	F.	107	+	+					Prostate glands, Fallopian tube, rectal wall, nasal sinuses.
286	M.	78	++	+					Nasal sinuses, middle ear.
355	M.	81	++	++	+				Prostate.
291	F.	79	+	++					Cervical and submaxillary glands, nasal sinuses.
329	F.	83	+	++					Cervical glands.
315	M.	74	+++	+					Nasal sinuses, middle ear.
290	F.	83	+++	+++				+	Prostate.
346	F.	78	+++	+++				+	
281	M.	87	+	+++				+	
313		79		+				+	
418	F.	62		+++				+	
415	M.	63		+++				+	
282	M.	90	+++	+++				+	
419	F.	60		++					
345	M.	108		+++					
284	F.	97		+++				+	
352	F.	100		+++				+	
286	M.	79		+++				+	
292	F.	104	+++	+++	+			+	
287	M.	108	+	+	+			+	
421	M.	82	+++	+++	+			+	
389	F.	92	++	+++	+			+	
296	F.	111	++	+					
453	F.	69	++	++					
420	F.	80	+	++				+	
288	M.	111	+	+++	+			+	
297	F.	91	+	+	+			+	
456	F.	70		+				+	
479	M.	58		++				+	
450	M.	74	+++	+++	+			+	
387	F.	93	+	+	+			+	
285	M.	116	+++	+	+			+	
481	F.	63	+	+	+			+	
480	F.	63	+	+	+			+	
388	M.	107	++	++				+	
451	F.	83	++	++				+	
555	F.	49	++	++				+	
389	M.	115	+	+++	+			+	

Nasal sinuses, ureters, seminal vesicles.



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xerophthalmia and tongue only are indicated by the number of + marks in each case.

TABLE I (b).  
*A-Deficiency ; Basal Diet + Vitamin D + Vegetable Margarine.*

Rat No.	Sex.	Days on Diet.	Xeroph.	Tongue Abscess.	Alimentary Infection.	Other Sites of Infection.
151	M.	66 Margarine			+	
316	F.	70 Margarine		+		
341	F.	41			+	
305	M.	86 Margarine			+	Nasal sinuses.
337	F.	69 Margarine	+		+	
348	M.	76 Margarine		++		
329	F.	113 Margarine	+	++		Middle ear, nasal sinuses.

There was no kidney infection, bladder stone, or bladder infection in any of the animals in this group.

II.—*Post-mortem Findings in Animals Living on Diets Deficient in Vitamins A and D.*

TABLE II (a).—*A-Deficiency ; Basal (no Vitamins A or D).*

Rat No.	Sex.	Days on diet.	Xeroph.	Tongue Abscess.	Alimentary Infection	Kidney Infection.	Bladder Stone.	Bladder Infection.	Other Sites of Infection.
RO.				+	+				
RO.				+					
RO.									Lungs.
RO.		41		+	+		+		
RO.		43							
RO.		45							Lungs
RO.									
RO.			+		+	+			Lungs.
RO.									Lungs.
300	F.	96	++	+++		+	+	+	Prostate glands.
298	F.	100	+++	+	+		+		Nasal sinuses.
289	F.	74							
288	M.	93			+				
267	M.	91	+	+		+		+	
299	F.	115	++	++	+	+		+	Prostate glands, middle ear, nasal sinuses.



TABLE II (b).—*A*-Deficiency; Basal (No Vitamins *A* or *D*) + other Substances.

Rat No.	Sex.	Days on Diet.	Xeroph.	Tongue Abscess.	Alimentary Infection.	Kidney Infection.	Bladder Stone.	Bladder Infection.
285	M.	69 Heated wheat germ		+				
287	F.	89 Heated wheat germ		+	+		+	+
281	F.	88 Fat-extracted wheat germ						
268	M.	47 Ergot (50 mg.)				Stone		
266	F.	55 Ergot (50 mg.)	+++		+	Stone	+	
271	M.	57 Fat-extracted ergot (100 mg.)						
272	F.	83 Fat-extracted ergot (100 mg.)		++		Stone		

The wheat germ used in experiments 286 and 287 was heated for twelve hours at 120°C. Ergot used in 268 and 266 contained vitamin D, but the fat-extracted ergot of experiments 271 and 272 was free from vitamin D. The nasal sinuses were infected in rat No. 281.

The regularity with which stone in the pelvis of the kidney appears in animals whose diets contain ergot suggests that this substance plays some part in the development of the condition. It will be noticed that, without ergot, although infection of the kidney is common, stone in the kidney is rare. In other experiments, besides those given above, stones or gravel have been found in the renal pelvis when ergot has been a diet constituent.

#### ADDITIONAL DETAILS OF POST-MORTEM EXAMINATIONS OF A FEW OF THE RATS ON VITAMIN A DEFICIENT DIETS.

*Rat 313.*—Tongue. Left kidney twice normal size. Medulla replaced by pus so that only a thin strip of cortex remains. Left ureter extremely dilated, being almost a quarter of an inch wide at its junction with the pelvis; stone impacted at lower end. Right kidney enlarged; numerous necrotic areas in cortex; advanced pyelonephritis. Large quantities of necrotic epithelial debris in bladder.

*Rat 284.*—Abscess of tongue involves most of tongue and has perforated on to the upper surface. Larynx contains a little pus. Kidneys slightly enlarged (more so left); white mottling of cortex, particularly marked in left kidney; slight pyelonephritis in both kidneys. Abscess in prostate glands. Large quantity of pus in both middle ears.

*Rat 292.*—Tongue abscess. Marked xerophthalmia; pus in the anterior chamber of the right eye. Stomach contains dark brown blood. Pyloric mucosa inflamed. Both kidneys much enlarged, lower pole of right kidney almost reaching brim of pelvis; cortices mottled, particularly marked in right kidney; great distension of the pelvis, which contain white necrotic material. Ureters grossly dilated (size of large intestine); fine sand at the lower ends, the right being inflamed and containing a blood-stained effusion. Pelvis intensely congested. Coils of small intestine adherent to



the right Fallopian tube and bladder. Intestine acutely inflamed and contains blood-stained serum. Right side of pelvic floor inflamed, being a mass of necrosed friable tissue with an abscess cavity extending down to bone. Fallopian tubes show small white areas (similar to those seen in the kidneys, and probably necrotic) scattered on the outer surface. Right tube inflamed and adherent to the pelvic floor and intestine. Spleen enlarged. This rat had haematuria prior to death.

*Rat 287.*—Stomach full of blood. Pyloric mucosa injected and showing haemorrhage into it. Left kidney slightly enlarged with semipurulent fluid in pelvis. Left ureter dilated. A large number of small stones and much epithelial debris at base of bladder. Two sessile red projections springing from bladder mucosa (granulomata or papillomata). Very large abscess in right submaxillary gland extending to level of first rib and upwards to the mandible. Chain of enlarged longitudinal glands on left side, some commencing to suppurate. Small abscess in either thyroid. Pus from abscess shows in film numerous Gram-positive diplococci, Gram-negative bacilli, and a few staphylococci and streptococci.

*Rat 421.*—Large abscess of tongue extending almost to the tip and communicating with another large abscess underlying the left mandible. The tongue abscess has perforated and there is pus in the larynx. Stomach full of altered blood; mucosa injected with numerous streaky haemorrhages; petechial haemorrhages on outer surface of cardiac portion, and cardiac epithelium shows a curious circumscribed rugosity at the upper pole. Bladder small and full of a bright yellow sandy deposit (showing chiefly calcium oxalate crystals). Spleen shows on its surface numerous circular white foci (similar to those often seen in the kidney). Right epididymis intensely inflamed.

*Rat 288.*—Severe enteritis (chiefly of jejunum). Small amount of altered blood in stomach. Pelvis of left kidney much dilated. Left ureter enormously dilated, the distal end being inflamed and filled with the same type of necrotic material as is found in the bladder. Right ureter moderately dilated. Bladder grossly inflamed; mucosa covered with shaggy masses of granulation tissue and necrosed cells which are very adherent, whilst papillomatous-like masses are numerous. Abscess at base of tongue has perforated and formed an abscess in the mid-line of neck overlying the larynx, and communicates with an external sinus. Left seminal vesicle enlarged and appears caseous. Abscess in left prostate. Nasal sinuses full of pus.

### III.—Control Animals—Basal Diet+Vitamin D (Irradiated Ergosterol) + Some Source of Vitamin A (Dried Cabbage or Butter or Cod-liver Oil).

Fifty rats of the same age and weight were kept for longer periods than the foregoing on diets which, while made up in the same way as those of the other experimental animals, contained some source of vitamin A, generally dried cabbage, but in some cases butter or cod-liver oil. No gross infective lesion was found in any of these animals, the only pathological findings discovered being three cases of hepatic cyst of parasitic origin.

### DISCUSSION OF RESULTS.

The fact that in practically all of the rats on a vitamin A deficient diet upon which a detailed *post-mortem* examination has been made some and generally many organs have been found to be infected by micro-organisms,



is a most striking result. Under these conditions the animals live for fairly long periods, varying in the foregoing cases from 58 to 169 days. During most of the time they eat their food well and show moderate growth. It is only during the last week or so of the experiment that they fail to eat up their ration and lose weight in consequence. It appears as if they continue in fair health until the infective process gets the better of their general condition, and brings about loss of appetite and weight, and ultimately death. The evidence for infection was in every case macroscopic, being based either upon the presence of definite pus or of an acute inflammatory process. This meets the objection to deductions made only on the basis of histological observation, pointed out by Gross.<sup>6</sup> Sometimes microscopic examinations of the tissues were made. In those cases in which bacteriological examinations of infected tissues and of pus were made no specific micro-organism was found, this result agreeing with that of other investigators. Gram-positive diplococci were often found, but these were usually associated with streptococci, staphylococci, and Gram-positive and Gram-negative bacilli. Occasionally the pus from infected glands of the neck showed a few chains of streptococci and no other organisms.

It will be noticed that the addition of vitamin D makes no great difference to the experimental results under discussion, for whether vitamin A only or both vitamins A and D are deficient the animals die with well-defined infective lesions. In fact, it often appeared that the addition of vitamin D in the absence of vitamin A hastened the onset of the infective condition. The reason for this is probably that the presence of vitamin D stimulated the rate of growth, and thereby made a greater call on the vitamin A stores of the body, thus hastening the diminution of resistance. There is no doubt that the stores of vitamin A in animals living on a diet devoid of this substance rapidly disappear. Evidence of this is seen in the tests made on the livers of deceased animals for the presence of vitamin A by the method described by Wilson<sup>22</sup>—a method involving the use of the colour test of Rosenheim and Drummond<sup>21</sup> as modified by Carr.<sup>23</sup> Even in the case of rats dying at an early stage, and before any great pathological change had occurred, liver extracts gave negative results, indicating the rapid using up of the initial stores of vitamin A in these rats. The control animals which received vitamin A in their food remained free from infection, and all gave evidence, by the same test, of abundant quantities of the vitamin in the liver.

As regards the infective lesions that developed, it will be noticed that xerophthalmia was not so common as might be expected, only 38 per cent. of the animals developing this lesion. It is, indeed, worthy of note that advanced lesions, even in old animals, were occasionally found at necropsy, although the animals showed no clinical signs of xerophthalmia.



In the 93 A-deficient animals examined the most characteristic condition was the lack of adipose tissue and the general visceral atrophy, but almost as prominent was the evidence of infection in some site, only two animals of the 93 seeming to escape this.

Abscess at the base of the tongue, arising in the accessory salivary glands, was found in 72 per cent. of the animals. In animals surviving for longer periods this figure rose to 90 per cent. These abscesses varied much in size, some being small caseous foci in the centre of the gland, while others involved almost the whole tongue, infiltrating it almost to the tip. Perforation of a tongue abscess was not uncommon. In one case a sinus communicated with the skin of the anterior surface of the neck, and in another perforation into a large artery resulted in death from haemorrhage. Associated with the tongue abscesses, suppuration occasionally occurred in the submaxillary glands and in the lymphatic glands of the neck. In some cases a chain of suppurating lymphatic glands was seen in the neck, the glands being usually quite discrete. The thyroids were involved in the suppuration in one animal.

Infection of the lungs was noticeably rare, only 9 per cent. showing any definite signs, which were chiefly of a septic broncho-pneumonia. These cases all occurred during the winter months, though the temperature of the rat room was kept constant.

Infection of the alimentary tract was quite common, though in most cases it appeared as a terminal event, there being no clinical evidence of its occurrence. An acute inflammation of the small or large intestine occurred in 21 per cent. of the rats. Many of these cases arose during an epidemic of enteritis in the rat room when, as previously mentioned, the vitamin A deficient animals proved to be very susceptible to the infection. In quite a number of animals an acute enteritis involving the duodenum and jejunum appeared to be the immediate cause of death. The intestine was grossly injected and filled with a copious haemorrhagic exudate. Usually there were signs of recent haemorrhage into the pyloric portion of the stomach.

Lesions of the urinary tract often dominated the scene in the abdomen. The occurrence of calculi—usually in the bladder, rarely in the kidney—was fully confirmed, but infection occurred independently of their presence or absence; 44 per cent. showed evidence of infection either in the kidney or bladder, but the incidence was considerably higher in those rats surviving longer periods. The infection took the form of a pyelonephritis or cystitis, and sometimes pus was found in the kidney substance. The infection was usually associated with such conditions as hydronephrosis, extremely dilated ureters, and a distended bladder. Multiple small white necrotic foci in the cortex of the kidney were often found, but their exact origin



has not yet been determined. Similar foci have also been observed in the spleen on two occasions.

The prostate glands and seminal vesicles were frequent sites of suppuration, whilst occasionally the epididymis was acutely inflamed or suppurating. A purulent exudate was seen in the Fallopian tubes on one occasion.

Pus was found in the nasal sinuses or in the middle ear on eighteen occasions, an incidence of 20 per cent. In one isolated case a small but definite abscess was found projecting from the wall of the left ventricle of the heart.

The control animals received the basal diet *ad lib.*, plus some source of vitamin D, with the addition of a source of vitamin A either in the form of dried cabbage or cod-liver oil or butter. Fifty rats fed under these conditions over periods as long as, or longer than, those which the deficient rats survived have been killed and examined. In no single case was evidence of gross infection found corresponding with that found in the vitamin A deficient rats. The only pathological findings were three cysts of the liver, of parasitic origin. Otherwise all the tissues appeared perfectly healthy.

On the basis of these facts we suggest that vitamin A plays a significant part in raising the bodily resistance to infection. Perhaps this effect is solely due to the favourable medium which obstruction by desquamated keratinized cells provides for bacterial growth. At any rate, this must be a factor. Possibly it is the combination of the keratinizing process and a diminished resistance which makes animals with vitamin A deficiency so prone to infection.

The question arises as to what extent the part played by vitamin A as an anti-infective agent is specific. Would, for instance, the absence of any essential dietetic factor result in the infective and pyogenic conditions met with in this experimental work? We can offer no definite evidence that this is not the case, but an extensive experience of nutritional work suggests that vitamin A is more directly related to resistance to infection than any other food factor of which we are aware. In a series of several hundreds of rats which have had adequate amounts of vitamin A and little or no vitamin D only two cases of gross infection have been found, both septic bronchopneumonias associated with definite rickets. Experience with scurvy in man and animals does not lead to the belief that vitamin C is concerned with infection in the same sense as vitamin A. Although, therefore, the specificity of vitamin A and infection is not settled, the evidence obtained is in its favour. We are endeavouring to obtain additional evidence on this point by experiments in which infective material is injected into animals on A-deficient and control diets.

Another point of importance is whether lack of vitamin A has any relation to the common suppurative processes found in man. Is it possible to relate inflammatory processes



of the nasal sinuses, middle-ear disease, pneumonia, ulcerative conditions of mouth and eyes, to this dietetic deficiency? This question also cannot be answered definitely. It is certainly possible that there is a close relationship, since it is generally agreed that a deficient intake of vitamin A is a common fault among civilized man. We rely almost entirely on milk, butter, egg-yolk, and green vegetables for our supply of this substance, and the consumption of these, especially among the poor, is notoriously low.

We feel that, until further knowledge is gained, the experimental results are sufficiently impressive to warrant the assumption that vitamin A plays an important part in conferring resistance to many types of infection. We think that the study of the etiology of some infective conditions cannot be complete without including the consideration of this dietetic factor. We suggest, for instance, that the problem of puerperal septicaemia, and even that of acute rheumatism, might be considered in relation to the vitamin A intake. The importance of vitamin D has attracted great attention recently, and it has even been suggested that preparations of vitamin D can be safely substituted for cod-liver oil in medical treatment. The work above described shows that this teaching is erroneous, and that, although vitamin D controls, probably absolutely, the calcification of bones and teeth, it has no direct power to promote resistance to infection in the same way as vitamin A. If a substitute for cod-liver oil is given it ought to be at least as powerful as this oil in its content of both vitamins A and D.

#### SUMMARY.

In an extensive study of animals brought up on a diet deficient in vitamin A it is shown that practically all die with some infective or pyogenic lesions. In the control animals receiving vitamin A these lesions are absent. The presence of vitamin D does not prevent the development of these morbid conditions, and this vitamin seems to be unrelated to resistance to infection.

The lesions produced in animals by diets deficient in vitamin A are commonly found in man, and it is desirable that this fact should be borne in mind in the study and treatment of these and other infective and pyogenic conditions.

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