failure of compensation, as well as the value of diminished salt intake.

4. Another factor of importance in enabling the heart muscle to recover its physiological condition is the circulation through the coronary vessels. In my earlier experiments on the isolated heart-lung preparation I used to put the arterial pressure low, in order—as I thought—to give the heart, under the abnormal conditions of experiment, as little work as possible to do. Many hearts, after the artificial circulation had been established, continued to fail and finally went into delirium or ceased to beat. One day, when the heart was obviously failing, I put up the pressure to 150 mm. Hg, thinking that I should kill the heart outright. Instead of this happening, the heart first dilated widely and beat more forcibly, but as it reacted to the pressure in the arterial system it steadily improved, and both its diastolic and systolic volumes diminished. It continued to beat against this high pressure for hours, so that on all subsequent occasions I have raised the arterial resistance to start with, so that the heart, as soon as it is connected with the artificial system of tubes, has to contract against a high resistance. In my early experiments the arterial pressure had been insufficient to furnish an adequate supply of blood through the coronaries to the heart muscle. As soon as this was supplied by a temporary rise of blood pressure, the heart muscle steadily improved and the heart was able to contract against an abnormally high resistance without undue dilatation, improvement in physiological condition being marked by diminished volume, or as would generally be stated, increased tone of this organ. I am inclined to ascribe the beneficial effects of graduated exercises in heart disease very largely to the improvement of the coronary circulation brought about by the temporary rise of arterial pressure accompanying the exercises. So important is the coronary circulation for the functional capacity of the heart that every medical man should be aware of the manner in which this circulation is regulated. The oxygen usage of the heart is directly proportioned to the work it does, and its oxygen supply must therefore vary within the same limits as its work—i.e., in a healthy heart from 1 to 7 or 10. The most important factor, as is shown by the accompanying table, in determining the amount of blood flowing

Dog, 11 kg.; weight of heart, 107 g.

Time.	Arterial pressure, mm. Hg.	Rate of heart per min.	Total coronary output	Total output.	Output per heart beat, c.cm.	Venous pressure, cm. H ₂ O.	
I.	12.5	84	150	40.80	851.80	5.72	9.6-12.4
	12.8	108	150	50.30	840.30	5.60	8.8-12.0
	12.12	140	150	70.75	840.75	5.60	8.0-11.2
	12.15	170	150	117.40	867.40	5.75	8.0-10.8
	12.18	208	150	260.30	860.30	5.72	12.0-22.0
	12.21	104	150	80.30	840.00	5.60	8.4-10.4
	12.27	104	150	80.30	830.00	5.55	8.0-10.0
12.30	44	150	30.40	820.00	5.45	7.6-10.0	
II.	12.34	60	150	50.30	1452.00	9.70	10.4-12.8
	12.38	100	150	50.30	1350.00	9.00	10.0-12.8
	12.41	128	150	124.90	1346.90	9.00	10.4-12.4
	12.45	166	144	208.00	1386.00	9.65	12.0-14.0
	12.50	190	144	500.00	1310.00	9.20	32.0-34.0

The venous inflow was increased between I. and II.

through the coronary arteries, and therefore the oxygen supply to the heart muscle, is the arterial pressure, so that as the resistance to the heart beat increases, there is a corresponding increase in the flow of blood through the heart muscle. Under extreme conditions of work the flow through the heart muscle may be greater than has been found in any other organ of the body and may amount to 5 c.cm. of blood per minute for every gramme of heart muscle. But the supply of blood and of oxygen is aided by two more circumstances. In the first place, as soon as increased strain is thrown on the heart, or this organ commences to fail, we find an augmented flow through the coronaries out of all proportion to the blood pressure in the aorta. This is not due to the accumulation of

carbonic acid in the blood and must be determined by the formation of metabolites, of which lactic acid may be one, in the labouring muscle fibres. Moreover, the heart has an astounding power of utilisation of the oxygen in the blood. When an isolated heart is fed with blood from an asphyxiated animal, we find that the heart removes the last traces of oxygen from the blood, so that the blood from the coronary sinus does not contain one-half per cent. of oxygen. The enormous range of adjustment in the coronary circulation characteristic of the healthy heart enables us to form some idea of the evil results which must follow impairment of the power of adjustment, such as may occur in consequence of disease of the coronary arteries themselves. We may see how rapidly such a failure of adjustment may act on the heart muscle by repeating Cohnheim's experiment of ligation of one main branch of the coronaries. This is almost invariably followed, within a period varying from a couple of minutes to half an hour, by fibrillation of the ventricles and death of the animal, and a similar result may occur in man as a result of any unequal derangement in the powers of adjustment possessed by different parts of the coronary system.

ON THE FUNCTION OF THE LYMPHOCYTE AND OF LYMPHOID TISSUE IN NUTRITION,

WITH SPECIAL REFERENCE TO THE VITAMIN PROBLEM.

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WHEN a rat is kept on a diet completely free from vitamins its growth is at first arrested, then its weight declines, its temperature falls, and eventually the animal dies in a state of complete emaciation. The ordinary white adipose tissue has completely disappeared. The glandular adipose tissue—the “brown fat”—is still present; but microscopic examination shows that most of the cells still contain very small droplets of fatty material, which are, however, much smaller than those found in a normal rat, and in some cells may be quite absent. There is a profound atrophy of the lymphoid tissue, which is obvious to the naked eye. This is most striking in the thymus, which is hardly visible. The Peyer's patches, which stand out very clearly in the intestine of a normal rat, are mostly not visible to the naked eye; after careful search a few can be detected here and there. The spleen is shrunk to a narrow ribbon (see Fig. 1, rat 167). The size of the lymphatic glands in the mesentery and in the groin underneath the skin exhibits such variations, even in normal animals, that it is difficult to appreciate differences in size in animals kept on a vitamin-free diet. Microscopic evidence shows that the lymphoid tissues are empty of lymphocytes. Not only is there a diminished production of lymphocytes in the spleen and lymph glands, but the disintegration of lymphocytes in these organs is also diminished as indicated by the infrequent occurrence of phagocytosis and the relative absence of cellular debris. This change in the lymphoid tissue is reflected in the blood. There is a diminution in the total number of lymphocytes; of these, the small lymphocytes are particularly diminished. This diminution may amount to 50 per cent. when the animal begins to show definite signs of suffering from the lack of vitamins, as indicated by its ruffled fur and by fall of temperature to about 36°, instead of 37°-38° given by a normal animal. In the final stages a fall in the number of lymphocytes from the average figure of 8000 per cmm. of the normal

animal to as low as 1200 has been observed. The polymorphonuclear leucocytes are not affected to the same extent. As a result a differential count gives figures in which the proportions are completely changed. In a normal rat the polymorphonuclear leucocytes constitute about 30 per cent. of the total leucocytes, representing in absolute figures about 2600 cells. As the condition resulting from the deficiency of vitamins progresses the relative propor-

tion of the polymorphs increases, so that in the later stages they may equal in number the lymphocytes and even exceed them (see Fig. 2, rats 161 and 167).

Comparative Effects of Deficiency of A- and B-Vitamins.

When a diet deficient in B-vitamin but containing vitamin A is given, the same general results follow in rats as when both vitamins are absent (see Fig. 3, rats 211 and 212). There is the same initial cessation

FIG. 1.

Shows weights of spleen and thymus altering with changes in the diet. Note that the vitamin-rich diet is an artificial diet, while the vitamin-poor diet is a natural diet—namely, the laboratory diet of bread and water, maize and rice referred to in the text, which is, however, adequate to maintain the animals in good health. The weights are given both calculated per 100 g. of body weight (shaded), and in absolute figures for rats of equal age (not shaded). Atrophy as the result of withholding vitamin B, no atrophy when vitamin A is withheld. Great increase in weight when an abundant supply of vitamins is given.

FIG. 3.

Curves of weights and of temperatures and number of lymphocyte counts of two rats on a diet free from vitamin B alone, but containing an abundant supply of vitamin A. Effect on weight, temperature, and number of lymphocytes of adding the deficient vitamin to the diet of one rat (No. 211).

of growth, followed by a decline in weight and a gradual fall of the temperature. In the final stages of the water-soluble B deficiency the animal presents the same condition of emaciation. This identity of the condition for the specific water-soluble B deficiency with that for the complete vitamin deficiency is

FIG. 2.

TOTAL NUMBER OF LEUCOCYTES.

Refers to the same animals as Fig. 1, and shows absolute number of different types of leucocytes and their relative distribution. Lymphopenia when B is withheld and A is supplied in abundance, no lymphopenia when A is withheld and B is supplied in abundance, increase above the normal when an abundant supply of both vitamins is given. The small lymphocytes are most affected; the polymorphs are not affected at all.

generally recognised. It is usually attributed to the fact that the deficiency of the fat-soluble A-vitamin takes a longer time to produce its effect. The blood picture in an animal kept on a diet free from the water-soluble B-vitamin, but containing an ample supply of the fat-soluble A-vitamin is, like the general condition of the animal, identical with that just described for the complete absence of vitamins; a great reduction in the number of lymphocytes, especially the small lymphocytes, is found. The polymorphs show no change (Fig. 2, rat 212; Fig. 5, rat 211).

Quite a different condition is presented by an animal kept on a diet free from the fat-soluble A-vitamin, but containing an ample supply of the water-soluble B. In a typical experiment these animals do not show a gradual fall of the temperature, and even in the last stage do not show the profound emaciation of the water-soluble B deficiency (Fig. 4, rats 208 and 209). There is still a fair amount of fat in the body. A characteristic feature is their great susceptibility to infection, of which xerophthalmia is such a frequent instance that it has been regarded by some observers as a specific result of the absence of the fat-soluble vitamin. Other infections, however, may occur while xerophthalmia is absent. These animals do not show an atrophy of the lymphoid tissue (Fig. 1, rats 208 and 209), nor is the total number of lymphocytes in the blood less than that found in normal animals

FIG. 4.
EFFECT OF FAT SOLUBLE A DEFICIENCY

Curves of weights and of temperatures and number of lymphocytes of two rats kept on a diet free from vitamin A alone, but containing an abundant supply of vitamin B. One of the rats developed xerophthalmia. (Compare with Fig. 3.)

(Fig. 2, rat 208, 209, and 206). Observations on changes on the other elements of the blood are in progress.

For the purpose of this paper we only refer to the typical condition produced by withholding the A-vitamin alone in order to emphasise that it differs entirely from that produced by the absence of the B-vitamin, both as regards the functional activity of the lymphoid tissue and the general nutritive condition of the animal. The two conditions are contrasted in Table I.:

TABLE I.

	Lymphoid tissue.	Number of lymphocytes	Tempera- ture.	State of nutrition.
Absence of— Vitamin A ..	Not atrophied	Normal.	Normal.	No emaci- ation.
Vitamin B ..	Atrophic.	Diminished.	Subnormal.	Emaci- ation.
Vitamins A & B	„	„	„	„

No less striking than the atrophy of the lymphoid tissue, when the water-soluble B-vitamin is withheld, is the recovery of this tissue when this vitamin is added again to the food. Thus in rat 211 (see Fig. 3), which

had been kept on the basal vitamin-free ration and cod-liver oil for five weeks, the total number of lymphocytes had fallen to 4800 at a time when the temperature had become very subnormal (35.6°). The weight was then 80 g. The water-soluble B-vitamin was then added in the form of yeast. Within six days the total number of lymphocytes increased to 8800; after another week it had risen further (see Fig. 5) to

FIG. 5.
TOTAL NUMBER OF LEUCOCYTES.
SMALL LYMPHOCYTES
POLYMORPHS

Total number of leucocytes in vitamin deficiency and recovery after the deficient vitamin has been supplied. Rat 106A had been kept on a diet free from both vitamins A and B for seven weeks until 6/6, when both vitamins were added to the diet. Rat 211 (see Fig. 3) had been kept on a diet containing an ample supply of the fat-soluble A, but deficient in water-soluble B for five weeks until 8/6, when the deficient vitamin was added.

11,800. This rise was accompanied by a complete change in the general appearance of the animal, which rapidly increased in weight to 130 g. in two weeks and had a normal temperature. (Fig. 3.)

In rat 106A (see Fig. 5), which had been kept on a completely vitamin-free basal ration for seven weeks, the total lymphocytes were found to be 5000. Then both vitamins were added and 12 days later the count gave 9900 lymphocytes. There is also a rapid increase in the size of the spleen and thymus, and the Peyer's patches stand out again very prominently. When one considers the extreme degree of atrophy of the thymus in the absence of the B-vitamin, it is astonishing to see the large mass of tissue in an animal which has received the water-soluble vitamin for only a few days (7-10 days). Histologically the various lymphoid tissues show a very active formation of small lymphocytes. Accompanying this change in the lymphoid tissue is the well-known effect on the general nutrition of the animal. It rapidly puts on weight and gets fat, its ordinary adipose tissue getting well loaded with fat.

A Specific Function of the Lymphocyte.

These observations indicate that a specific relationship exists between the water-soluble B-vitamin and lymphoid tissue in the sense that the formation of lymphocytes is impaired in the absence of this vitamin. As a result of our observation the following conception of the mode of action of B-vitamin deficiency has been arrived at: *the lymphocyte has an important and specific function in maintaining the nutrition of the cells of the body, and the disturbances in nutrition which follow the withholding of B-vitamin are secondary to a specific lesion which leads to an interference with the functional activity of the lymphoid tissues.*

This conception will now be considered under the following headings: (A) Observations show that an ample supply of vitamins, as compared with a supply restricted but adequate to enable the animals to grow, to breed, and to maintain them in all respects in normal health, has a favourable effect on the functional activity of the lymphoid tissues and on nutrition,

(B) A consideration of the effects of X radiation upon animals shows that a primary destruction of lymphocytes is followed by disturbances in nutrition identical with those produced by withholding B-vitamin. (C) Other evidence on the relationship between the functional activity of the lymphoid tissues and the nutrition of the body. (D) A criticism of the prevalent conception that vitamins are essential for the life of every cell.

A. *Effect of a Diet Rich in Vitamins.*—The effect of a diet particularly rich in vitamins has been compared with that of a diet poor in vitamins but containing sufficient to maintain the animals in good health and in a normal condition.

are considered. (See Fig. 1.) The total number of lymphocytes is also higher on the vitamin-rich diet. (Fig. 2.) In rat 201 (see Fig. 6), which grew most rapidly and reached the weight of 210 g. in ten weeks, while in the same time another rat (No. 205) with the same initial weight, but kept on the laboratory diet, had reached only 110 g., the total number of lymphocytes gave the exceptionally high figure of 18,300. That this was not accidental or due to an error was confirmed by another count a few days later, which gave 17,800. It has been noted that rats from the laboratory of the Radium Institute, where a very varied diet is given, grow much more quickly and give lymphocyte counts decidedly higher. These experiments emphasise the importance of the vitamins. Not only is a certain minimum necessary for the healthy vegetative and reproductive life of an animal, but if increased beyond this limit

TABLE II.

Diet.	Rat No.	Weight in g.		Final length in cm.*	Weight in mg. of—		Lymphocytes distribution.				
		Initial.	Final.		Spleen.	Thymus.	Total in 1 c.mm.	Small L.	Large L.	Polym.	Eosinoph.
Vitamin-rich }	198	40	110	15.5	740	330	9,600	71.5 %	8.5 %	17.5 %	2.5 %
	201	60	210	18.5	1060	690	18,300	83.0 %	6.0 %	11.0 %	0.0 %
Vitamin-poor }	202	40	80	14.25	460	185	5,800	67.5 %	11.0 %	15.0 %	6.5 %
	205	50	100	14.5	360	105	8,000	64.5 %	8.5 %	25.5 %	1.5 %

* Nose to root of tail.

The vitamin-rich diet is an artificial food mixture and consisted of the vitamin-free standard basal ration (extracted casein, starch, olive oil, salt mixture) to which dried yeast and cod-liver oil had been added. The vitamin-poor diet is a natural diet. It consisted of a diet of bread soaked in water alternating with boiled rice and maize. This has been for years the usual diet of all the rats of the Imperial Cancer Research Fund laboratory. That this diet maintains them in good health is evident from the fact that they breed on the diet and suffer little from intercurrent disease, epidemics being rare. They put on weight and grow, though slowly. Table II. gives a comparison of two young rats kept on this

the vitamins, in a drug-like action, produce a further effect.

We therefore feel justified in concluding that an ample supply of vitamins A and B stimulates the functional activity of lymphoid tissue and that this is associated with more rapid growth and a general improvement of nutrition.

B. *Effects of Exposure to X Rays or Radium.*—A consideration of the effects of exposure to X radiation or to radium has an important bearing on the thesis.

The first change to be observed is a diminution in the number of circulating lymphocytes; so sensitive is this reaction that an amount of radiation insufficient to be detected photographically will cause an appreciable diminution in the number of circulating lymphocytes within an hour after exposure. Not only do the circulating lymphocytes disappear from the blood, but moderate exposures will sterilise the whole body of lymphoid cells so that an examination of spleen, thymus, or other lymphoid tissues will reveal a more or less complete absence of these cells. If by means of repeated small doses of radiation this lymphopænia be kept up, changes subsequently occur in the animal identical with those resulting from the withholding of B-vitamin. The animal rapidly loses weight, the temperature falls, the testicles present an atrophic condition, adipose tissue disappears, and the animal finally becomes "marasmic" and dies.

The immediate disappearance (within an hour) of circulating lymphocytes following radiation has no decided analogy with the effects of withholding vitamin B; on the other hand, the general and maintained absence of those cells associated with repeated doses of radiation appears to be due to an interference with their production, and a similar want of production is to be observed in the lymphoid tissues of animals starved of vitamin B. In this respect, also, the two effects would seem to have common ground. The regeneration of the lymphoid tissues, which follows the atrophy due to radiation when exposure is discontinued, is strikingly similar to that observed in vitamin experiments when the deficient vitamin B is added to the diet. The spleen, thymus, and other lymphoid tissues increase in size and present abundant production of lymphocytes; the blood content passes from exhibiting a lymphopænia to a lymphocytosis, which may sometimes far exceed the normal limit; and the general condition of the animal then becomes normal. Fig. 7 gives the results of an experiment especially designed to illustrate these effects of radiation, which since their discovery 15 years ago, have been extensively studied, both in this country and in the United States. The observations were made on eight rats, of which four were subjected intermittently to exposures of radium over a period of 21 days, while the other four animals were kept as controls. The amount of radiation applied was measured. By the use of screens, and by varying the amount of radium bromide, the exposure to radium was varied on different days. The maximal exposure given at one time was 0.29 rads and was given on the first two days and on the last day. The intermediate exposures were smaller and varied from 0.02 rads to 0.04 rads. The total exposure given over the whole period amounted to 1.25 rads,

FIG. 6.

Curves of weight and of temperature and number of lymphocytes of three rats kept on an artificial diet rich in vitamins, on a natural diet poor in vitamins, and on a completely vitamin-free diet respectively. Also recovery of rat 195 kept on the vitamin-free diet when vitamins are added again.

laboratory diet for ten weeks with two rats of equal age kept on the vitamin-rich diet. The latter put on weight and grow in size much more rapidly although the diet is artificial. There is no difference in the temperature, but there is a distinct difference in the development of the lymphoid tissue. The weight of the thymus of rats of equal age is much greater on the vitamin-rich diet; it is heavier even when calculated for 100 g. of body-weight. (See Fig. 1.) The spleen also tends to be heavier on the vitamin-rich diet if calculated per 100 g. of body-weight, and is much heavier when the absolute figures, comparing animals of equal age,

the difference in the length of the arrows giving an approximate indication of the amount of exposure in rads applied on different days. All the four rats exposed to radium reacted in the same way: cessation of growth, fall of temperature, and lymphopænia. When killed the animals showed macroscopically atrophy of the lymphoid tissues; the Peyer's patches were difficult to identify, the thymus had disappeared almost completely, the spleens were very small; in three of the animals the splenic weight was determined and found to be 40 mg., 90 mg., and 110 mg. respectively. Microscopically these tissues were depleted of lymphocytes, and cell division of the plasmoidocytes is infrequent. The figure illustrates the effects of radiation on growth, temperature, and number of lymphocytes with reference to two of the rats, and demonstrates clearly the great similarity to the condition presented by animals in which the lymphoid tissue is undergoing atrophy as the result of withholding the water-soluble vitamin B.

FIG. 7.

Effect of exposure to radium on the body-weight, temperature, and number of lymphocytes. The amount of exposure to radium measured in rads is indicated approximately by the length of the arrows.

C. Function of Lymphoid Tissue with Relation to Nutrition.—What is the nature of the function of the lymphoid tissue in relation to nutrition? Unfortunately our knowledge of the function of the lymphoid tissue has hitherto been very obscure in spite of the large amount of work that has been devoted to it. We know very little concerning the condition determining the formation of lymphocytes. The problem of the fate of the lymphocytes is also not yet solved.

From observations on the number of lymphocytes entering the blood stream by the thoracic duct Davis and Carlson⁶ conclude that many more lymphocytes enter the blood with the lymph in the course of 24 hours than can be found in the blood at any given time. Bunting and Houston¹ have confirmed this conclusion. They calculate that 3,300,000,000 cells enter the blood stream during 24 hours. Since the number of lymphocytes in the circulating blood remains approximately normal, lymphocytes must either constantly be undergoing disintegration within the body or leave the blood stream. It is probable that both these processes take place. Lymphocytes may temporarily leave the blood stream and return to it by the thoracic duct. Another fraction may leave the body altogether, as Bunting and Houston suggest, by passing through the intestinal mucous membrane into the lumen of the intestine. It is certain from histological evidence that a disintegration of lymphocytes takes place in the lymphoid tissue. But what determines the disintegration of lymphocytes, and what relation there is between disintegration and new formation of lymphocytes, are questions to which no certain answer can as yet be given.

There is evidence that the lymphocytes take a part in the absorption of food from the intestinal canal, where they are present in large numbers in the villi. Fatty substances on account of their specific staining reactions can be shown to be absorbed by lymphocytes.²⁴ Such histological evidence cannot at present be brought for the nitrogenous constituents of the intestinal contents. But chemical evidence to that effect was furnished by one of us, who showed that during digestion the corpuscular elements of the blood are richer in non-coagulable nitrogen than during fasting.⁴ This and observations on the absorption of protein introduced parenterally led to the conclusion that

the leucocytes take a part in the absorption of the nitrogenous food materials.³ There are, therefore, two channels by which food material is absorbed and utilised; it is carried partly in solution in the fluids of the blood and partly it is ingested and carried by the cellular elements, presumably the lymphocytes. The passage along the path represented by the lymphocytes is impeded when a lymphopænia has been established either by withholding the water-soluble B-vitamin or by exposure to radiation, and disturbances in nutrition leading to marasmus ensue. There is evidence that the absorption of food is impaired in yet a different manner, when the water-soluble B-vitamin is withheld. Rats kept on the vitamin-free basal ration show, when killed four hours after the food has been given, a stomach distended with food. The intestine is more flaccid and more dilated than in an animal which has received the same ration with the addition of the water-soluble vitamin, and the peristaltic movements are less powerful. The blood-vessels in the pyloric portion of the stomach and in the intestine are not so dilated. This effect on the intestinal tract is an immediate one and occurs at once when the water-soluble vitamin is withheld. The explanation of this apparent general paresis of the intestinal tract requires further investigations. It accounts, perhaps, for the reduced intake of food which, as several observers have noticed, occurs when the water-soluble vitamin is withheld and which so far has received no satisfactory explanation. As shown by the well-filled stomach, the animal does not decline to take food when the water-soluble vitamin is withheld, but the intestinal tract appears to be unable to deal with the food as efficiently as when the vitamin has been given; therefore the capacity to take food is limited. Our attention has been drawn recently to a paper by Lumière,¹⁶ who describes a similar effect in pigeons as the result of feeding on polished rice.

It might be held that the reduced intake of food is in itself an adequate explanation of the condition of marasmus, which is the result of the deficiency of the water-soluble vitamin. This possibility has been considered by Hopkins and later by Drummond,² and they are agreed that the reduced food intake is not in itself an adequate explanation of the decline in health which the animals undergo. This view has received confirmation recently by the observations of Karr¹⁴ on dogs. These animals also showed a reduced food intake when the water-soluble vitamin was withheld. But one dog exceptionally maintained its normal food intake. Nevertheless, it, too, passed into the same abnormal condition as the other dogs with a reduced food intake.

Jolly¹² and his collaborators¹³ have made an extensive study of the effect of acute and chronic starvation on the lymphoid tissue. They found an atrophy of this tissue, especially of the spleen and thymus, accompanied by a great rarefaction of lymphocytes; in fact, a condition similar to that occurring after radiation and after withholding vitamin B. They also state that chronic underfeeding produces a more intense atrophy than acute starvation. They do not appear to have examined the circulating blood for a lymphopænia. As a result of his observations Jolly¹² looks upon the lymphoid tissue "comme un tissu renfermant des réserves précieuses, d'une grande noblesse au point de vue de la constitution chimique auxquelles l'animal peut faire appel à certains moments. . . . Le tissu lymphoïde nous apparaît ainsi à la fois, comme une réserve de cellules sanguines et comme une réserve de constituants nucléaires." Further observations are necessary to determine whether starvation alone produces as marked a lymphopænia as the withholding of the B-vitamin. In man observations have been made only with reference to the total number of leucocytes, and the effects are apparently not constant. Von Noorden²¹ states that in his clinics low numbers—3000 to 4000 total leucocytes—were frequently found in persons emaciated from underfeeding. But he also quoted other observers who have obtained nearly normal figures in such cases. Different results were also obtained on one and the same man, the fasting man Succi; Luciani¹⁵ records a fall from 14,530 to 861 per c.mm. between the first and seventh day. Then they rose to 1530 per c.mm. and remained there throughout his 30 days' fast. In Vienna, however, Tauszk²⁷ recorded on the same person on another occasion a more gradual diminution from 9600 on the third day to 4200 on the thirtieth and last day of the fast.

Human pathology furnishes further evidence in support of the intimate relation of the lymphoid tissue to nutrition. The blood of infants and young children is particularly rich in lymphocytes, and during the first year gives figures as high as 8000–10,000 per c.mm.^{7 11} The lymphocytes then gradually diminish in number, but the level of 2000 per c.mm. which persists throughout adult life is not reached until the sixth year. The fact that disturbances of the adenoid tissue are of special significance in childhood and are frequently associated with disturbances in nutrition¹¹ is well known. There are, moreover, in infants conditions of marasmus which cannot be ascribed to neglect or deficient

feeding, and in which the only lesion found so far has been atrophy of the thymus.²³ We have not been able to find in the literature systematic observations on the condition of the lymphoid tissue generally in this condition. Dr. D. H. Paterson²² has kindly informed us that in his observations on post-mortem examinations of cases of malnutrition and marasmus carried out in the Hospital for Sick Children, Great Ormond-street, he has always found an atrophy of the spleen associated with an atrophied thymus, and that the Peyer's patches were so atrophic that they could not readily be made out. We have not been able to find in the literature observations on the lymphocytes in the different conditions of malnutrition and marasmus.

D. Necessity of Vitamins for Individual Cell Life.—Are vitamins necessary for the life of the individual cell or for the life of the animal as a whole? The fundamental assumption has been made—and is now generally accepted—that every living animal cell requires not only foodstuffs but also vitamins: life cannot exist without vitamins. That is, in fact, the definition of vitamins.

MacCarrison¹⁷ suggests as an explanation the analogy that "vitamins are as the spark which ignites the fuel mixture of a petrol-driven engine, liberating its energy. The spark is of no use without the fuel, nor the fuel without the spark." Although the animal continues to take in food, its cells cannot utilise the food and starvation results. We may remark in passing that this generalisation does not apply either to the C-vitamin—since rats do not suffer in health if this vitamin is withheld—nor to the A-vitamin, since starvation does not, as a rule, result when this vitamin is withheld. The generalisation was, in fact, established on the basis of the earlier experiments on pigeons and rats before the existence of several vitamins had been recognised and when either the B-vitamin was withheld alone or when a complete absence of vitamins had been established. This in itself weakens the conception of vitamins as substances essential to the life of all cells. But we shall argue here as if this conception applied to the B-vitamin alone. In our preliminary note⁵ we have already criticised this conception. But it is of such fundamental importance that it may not be out of place to repeat and extend our criticisms.

The evidence on which the conclusion is based is derived entirely from experiments on highly differentiated animals—viz., mammals and birds. If the conclusion is correct it should apply to all forms of life. Numerous attempts have in fact been made to show that it applies to even the lowest forms of life: yeasts, bacteria, and plants. The case of yeast is of special interest because it is particularly rich in the water-soluble B-vitamin. It must therefore either be capable of synthesising this vitamin or it must be dependent on a pre-formed supply. The recent work of Nelson, Fulmer, and Cessna²⁶ has shown quite clearly that yeast is capable of synthesising the water-soluble B-vitamin, and Harden and Zilva⁸ have independently arrived at the same conclusion. Since this paper was written Coward and Drummond² have published observations which prove that plants can synthesise the fat-soluble A-vitamin, and that apparently this synthesis may be effected from inorganic salts. The experimental evidence on which the claim of the indispensability of vitamins for the lower forms of life was based has been subjected to a critical review and experimental test by Lumière,¹⁶ who showed that these experiments quite clearly established the facts that the lower forms of life can live and grow in the absence of vitamins. The addition of material containing vitamins had merely a stimulating effect on the growth of these cells, and it was not even clear whether this effect was due to the addition of the vitamins or to other organic material.

The generalisation that life cannot be maintained in the absence of vitamins, even in its limited form as applying to the B-vitamin, does not necessarily follow from the experimentally established facts. These facts are that a highly differentiated animal—a bird or a mammal—dies in a condition of starvation when the B-vitamin is absent. But although a highly differentiated animal as a whole requires vitamins in order to maintain its life, it does not follow that all the cells of such a highly differentiated animal require the vitamin. If such animals presented a definite lesion in some organ or tissue essential to life, and if such a lesion would account for the condition of emaciation and the eventual death of the animal, then the generalisation that all cells require vitamins, or even this particular vitamin, would have to be abandoned. In the past such a lesion has not been found. The functional atrophy of the lymphoid tissue throughout the body had not been noticed and the importance of the function of this tissue in relation to nutrition was not recognised. Starvation was looked upon as the primary effect caused by the absence of B-vitamin, and the atrophy of spleen and thymus which has been repeatedly noticed by several authors was regarded as the result of the chronic starvation.

That the absence of the B-vitamin ultimately leads to a condition of emaciation similar to that produced by the complete absence of food is beyond doubt. To the view that this is due to the failure of the cells of the body to utilise the food absorbed from the intestine in the absence of the B-vitamin we oppose the conclusion that it is due to a specific lesion which leads to a functional atrophy of the lymphoid tissue. Such an atrophy of the lymphoid tissue, whether it is brought about by withholding the B-vitamin or by exposure to radiation, or by any other agency such as a toxin, produces a condition of marasmus.

Therapeutic Considerations.

This conclusion suggests the possibility of therapeutic applications apart from the obvious one in conditions of marasmus associated with a lymphopænia. We have seen that an abundant supply of the water-soluble B-vitamin stimulates the functional activity of the lymphoid tissue and increases the number of lymphocytes in the circulating blood. The administration of this vitamin may therefore have a favourable influence in the course of infections in which the defence depends on the activity of the lymphocytes. The old-fashioned administration of yeast to persons suffering from boils is perhaps an empirical application. Conversely it may be possible to inhibit the excessive production of lymphocytes in lymphatic leukaemias by withholding this vitamin. Another more obvious application which would appear to follow is that persons undergoing treatment by X rays or radium, or working with these radiations should receive an ample supply of this vitamin in their diet. We are at present investigating whether the resistance of animals to radium can be increased by an abundant supply of vitamins.

Summary and Conclusions.

Absence of the water-soluble B-vitamin from the diet leads in rats and mice to an atrophy of the lymphoid tissue throughout the body and to a lymphopænia in the circulating blood. The polymorphonuclear leucocytes are not affected. Absence of the fat-soluble A-vitamin does not lead to an atrophy of the lymphoid tissue and there is no lymphopænia.

Absence of the water-soluble B-vitamin leads to characteristic nutritional disturbances such as loss of weight, emaciation, subnormal temperature which may be designated by the term "marasmus." No such marasmus results from withholding the fat-soluble A-vitamin.

The lymphopænia established by withholding the water-soluble B-vitamin is rapidly abolished by the administration of the water-soluble B-vitamin and, *pari passu* with it, the concomitant marasmus. A permanent lymphopænia, and associated with it an atrophy of the lymphoid tissue throughout the body, can also be induced by exposure of rats to sufficient doses of X rays or radium. Such animals then also develop a condition of marasmus similar to that observed when the water-soluble B-vitamin is withheld. Since the functional disturbances in the lymphoid tissue produced by two such widely different agencies lead to the same nutritional disturbances it is concluded that the lymphocytes play a part of fundamental importance in the nutrition of the body. Other evidence points to the conclusion that they are concerned in the absorption and assimilation of food from the intestine.

Further evidence of the existence of an intimate relationship between the functional activity of the lymphoid tissue and the general nutrition of the organism is afforded by the fact that an abundant supply of the water-soluble B-vitamin has a favourable effect on the development of lymphoid tissue and the number of lymphocytes, and associated with it on the general nutrition of the animal. There is, further, the clinical experience that disturbances of lymphoid tissue are of special significance in infancy and are there frequently associated with nutritional disturbances.

The conception that vitamins—and the B-vitamin in particular—are necessary for the life of every individual cell is criticised. This vitamin is necessary for the maintenance of life of a highly differentiated

animal, not because its presence is necessary for the life of all the cells of such an animal, but because its presence is necessary for the normal functioning of lymphoid tissue. In other words, the term "deficiency diseases" is, like the term "vitamin," a misnomer. These diseases have their origin, like other diseases, in specific lesions. These lesions may be induced by different agencies of which a deficiency in vitamins is only one.

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THE EFFECT OF B-VITAMIN ON THE APPETITE.

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YOUNG rats fed on diets deficient in vitamin B lose weight after varying periods of time and finally die in a condition of emaciation. It was thought interesting to determine whether diminished food intake was a contributory factor in this loss of weight. Young rats from the same litter were employed. All the animals were fed for the first two weeks on a basal ration containing vitamin A and B in the form of cod-liver oil and marmite respectively. The basal ration was the one usually employed by workers in this field and contained purified caseinogen, starch, and a salt mixture. As a source of fat containing no vitamin A a specially prepared form of palm-kernel oil was used. It consisted of an edible quality of palm-kernel oil which had been heated for four hours at 160° C., and subsequently treated with superheated steam at 230° C. Experiments (unpublished) have been carried out with this substance, which show that palm-kernel oil, after such treatment, is quite free from the fat-soluble A vitamin.

Method of Experiment.

The rats were kept in metabolism cages in a warm room. The food—placed in beakers which were firmly fixed in the cage so that no spilling could occur—was presented twice a day, in the morning and

evening, and on each occasion was allowed to remain in for a period of one hour. The average daily intake of each animal on such a diet was thus determined. After two weeks both vitamins were removed from the diet of certain of the rats. The others were kept on the diet rich in vitamins, and served as normal controls. At once, within 24 hours, the animals receiving the vitamin-free diet showed a considerable fall in their food intake. The level of intake remains low throughout the period that this diet was maintained. At the same time there was also a steady decline in the weights of the animals. Thus, one of the rats which had been consuming on an average 9.37 g. daily now only took 5.64 g.; during this period, too, its weight fell from 55 g. to 43 g. The control animal fed on a diet rich in vitamins maintained a daily intake of 14.20 g. and its weight rose from 72 g. to 110 g. (Table I.)

TABLE I.

Week of experiment.	R 1.			R 2.		
	Diet.	Average daily intake.	Weight 36 g.	Diet.	Average daily intake.	Weight 39 g.
1	Normal	g. 8.95	g. 48	Normal	g. 12.6	g. 57
2		9.79	55		13.1	72
3	Vitamin-free	4.8	53		11.98	83
4		6.41	46		13.7	99
5		5.73	43		15.94	110

A trace of marmite was now added to the diet of the vitamin-free animals. It was administered separately in the mornings about two hours before the first feed. The marmite was eagerly consumed by the animals. The intake of the basal ration at once rose and at the same time the weights began to improve. The improvement in intake was as rapid in onset as the fall had been after the removal of the vitamins. In the case of the above-mentioned animal the intake rose from 5.73 g. to 8.66 g. daily. The weight rose from 43 g. to 59 g. in a period of three weeks. It should be noted that the intake never reached the level attained during the period when both vitamins were administered. (Table II.)

TABLE II.

Week of experiment.	R 1.			R 2.		
	Diet.	Intake.	Weight.	Diet.	Intake.	Weight.
6	Vitamin-free and trace of marmite	g. 10.22	g. 51	Normal	g. 14.6	g. 115
7		7.66	55		13.8	120
8		8.22	59		14.2	123

Previous Experiments Summarised.

The literature on the subject is not very extensive. Drummond¹ has investigated the protein metabolism in rats fed on diets containing no vitamin B. He was unable to detect any abnormality sufficient to account for the inability to maintain weight. During the course of these experiments he noted that the food-consumption of the rats fed on the diet deficient in vitamin B was reduced. Increased consumption could be brought about by the addition of flavouring agents to the diet. The same effect was produced by the addition of water-soluble vitamin B. Only when the vitamin was added, however, was there any resumption of growth. Drummond² has also shown that there is no disturbance of fat absorption in the absence of the fat-soluble vitamin A from the diet. Karr³ carried out experiments on dogs, in which weighed quantity of food deficient in water-soluble vitamin B was presented to the animals. At first the portion was completely consumed. Subsequently most of the animals refused to take a part, and ultimately failed to eat any. The desire to eat could be restored on addition of vitamin B. The same result was obtained if the vitamin was presented apart from the food. In the case of one animal, although the intake remained normal, the usual symptoms produced by the vitamin deficiency made their appearance.