AETIOLOGY, DIAGNOSIS, AND TREATMENT OF EARLY VITAMIN-DEFICIENCY STATES

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Vitamins are chemically and structurally heterogeneous organic compounds, and their functions—so far as they are known—differ even more. They are produced either in negligible amounts or not at all in the human body, do not furnish energy, and are not utilized as building units for the structure of the organism; they are able to perform their complicated functions in the transformation of energy and for the regulation of metabolism in minute quantities.

Following the spectacular advance in vitamin research, clinical medicine has not been able to keep pace with the laboratory. For the same reason we know now a larger number of different vitamins than identified human deficiency syndromes. Naturally occurring avitaminosis is mostly due to multiple deficiencies, and therefore controlled animal experiments with deprivation of one single vitamin cannot easily be translated to human beings.

Aetiology of Vitamin-deficiency States

The causes of vitamin-deficiency states are either primary or conditioned.

Primary Deficiency.—Nutritional deficiency states of the tissues may be caused solely by inadequate diet, and this is termed primary deficiency. Primary deficiency states are comparatively rare in this country at present. They are, however, occasionally seen in single old people who are either unable to collect their food or to cook it properly, or in persons with self-imposed restriction of essential food intake (Leitner, 1948a). By "dietary inadequacy" is meant the failure to ingest an essential nutritional factor in sufficient amounts to meet the existing body requirements. "Nutritional inadequacy" means not only the failure to ingest (i.e., dietary inadequacy) but failure to absorb and to utilize essential nutritional factors in sufficient amounts to meet these requirements. "Nutritional failure" occurs when essential nutritional factors fail to reach the tissues and the protective mechanisms of the body are unable to compensate the malnutrition. At that point symptoms begin to appear. The factors responsible for inadequate intake (primary deficiency) are poverty, ignorance, improper cooking and preparation of food, and self-imposed restriction of essential food (faddiness, eccentricity, anxiety).

Secondary or Conditioned Deficiency.—Nutritional deficiency states occurring on adequate dietary intake are known as secondary or conditioned deficiency. The importance of conditioning factors as a cause of deficiency states has not always been sufficiently recognized. Even when gross manifestations of deficiency disease caused by conditioning factors are recognized the findings may lead to one of two errors (Jolliffe, 1942): (1) to consider the lesion a manifestation of the original or conditioning disease unrelated to tissue depletion (e.g., to attribute polyneuropathy to pyloric stenosis); (2) after recognizing the nutritional basis of the secondary manifestation, to attribute the original disease solely to nutritional deficiency (e.g., in the case of a middle-aged edentulous woman to ascribe the symptoms only to malnutrition, disregarding the loss of teeth, the often associated dysphagia, achlorhydria, etc.). The first error ignores the existence of deficiency disease, the second

ascribes most deviations from normal health to malnutrition only.

These conditioning factors are: (a) interference with ingestion; (b) interference with absorption; (c) interference with utilization; (d) increased body requirements; (e) increased excretion; and (f) increased destruction.

Interference with Ingestion

The inclusion of this as a conditioning factor is warranted owing to the frequency with which abnormal conditions and disease may interfere with adequate food intake. For example, in hospitals the food intake is often calculated from the meals served to the patients. It is common knowledge that even convalescent hospital patients consume only a part of the meals as served (DuBois and Chambers, 1942). Our experts similarly calculate an adequate food intake for the population in this country. It is, however, very probable that the monotony of our diet for the last six to seven years, the lack of choice, and the fact that the population's very limited variety in food depends more on the chance of the food available on the world market than on their taste may be considered as a conditioning factor. For a considerable part of the population the relatively low protein and fat and high carbohydrate proportion of our food might be a further aggravating factor.

Gastro-intestinal and psychiatric disorders, causing anorexia, nausea, and vomiting, are clear examples of conditioning; alcohol in place of other food, causing anorexia and chronic gastritis and reducing thiamin intake, also provokes a change from a previously satisfactory diet to something like dry toast, highly seasoned food, coffee, or spirits, which may lead again to any of the deficiency diseases.

Diets prescribed with prolonged restriction of certain essential food factors are occasionally responsible for deficiency states—e.g., in peptic ulcers, obesity, colitis, food allergy, and nephritis. Slimming diets are especially harmful, though their low calorie content gives some measure of protection for a limited time. Even well-planned reducing diets are usually short of B vitamins, and it is advisable to supplement them with brewer's yeast and vitamin A concentrate.

TABLE I.—*Factors Interfering with Ingestion*

Anorexia:
Due to alcohol, operations, debilitating or infectious diseases, congestive heart failure, pregnancy, thiamin deficiency.
Gastro-intestinal disorders:
Gastro-enteritis, vomiting, peptic ulcer, gall-bladder disease, obstructive lesions of the gastro-intestinal tract.
Neuro-psychiatric disorders:
Psychosis, neurosis, migraine, anorexia nervosa, neurological disorders interfering with food intake.
Unsatisfactory denture, loss of teeth.
Therapeutic restriction of essential foods:
Peptic ulcer, obesity, nephritis, allergy, occasionally gall-bladder disease and diabetes.
Monotony and lack of variation in the diet:
Disproportion in the protein, fat, and carbohydrate ratio.

Interference with Absorption

Anatomical, chemical, and physiological changes (Beams *et al.*, 1941) may all interfere with the absorption from the intestinal tract. The reduction of the absorbing surface, hypermotility of the gastro-intestinal tract, and absorbents and lubricants introduced perorally may all be instrumental. In diarrhoeic conditions the reduction of the absorbing surface and

the hypermotility with the rapid passage are causal factors. The clinical importance of diarrhoea in producing pellagra, sprue, riboflavin deficiency, hypocalcaemia, and vitamin A and D deficiency is well known. In the sprue syndrome the hypermotility seems to be reduced by improvement of phosphorylation (Leitner, 1942), by an adequate supply of the B complex in the form of crude liver extract, or even quicker by synthetic folic acid (Spies *et al.*, 1946; Manson-Bahr and Clarke, 1946).

Achlorhydria may interfere with the absorption of ascorbic acid (Alt *et al.*, 1939) and of thiamin (Melnick *et al.*, 1941). In unexplained malnutrition, especially in patients over 40, achlorhydria should always be suspected.

Bile salts play an important part in the absorption of fat and of the fat-soluble vitamins, especially that of vitamin A (Breese and McCoord, 1939) and natural vitamin K (Snell, 1939). The habitual taking of liquid paraffin for bowel regulation also interferes with the absorption of vitamin A (Andersen, 1939) and vitamin K (Elliott *et al.*, 1940). Aluminium hydroxide and kaolin may absorb the water-soluble vitamins from the gut (Bicknell and Prescott, 1946). Resection, short-circuiting operations, and fistulas of the gastro-intestinal tract have long been known to produce macrocytic anaemia and the sprue syndrome (Bennett and Hardwick, 1940). Peripheral neuritis due to interference with absorption in cases of pyloric stenosis, dysphagia, cardiospasm, and neoplasms of the gastro-intestinal tract may respond to parenteral treatment with thiamin (Laurent and Sinclair, 1938).

TABLE II.—*Factors Interfering with Absorption*

Achlorhydria.
Vitamin deficiency (sprue syndrome).
Gastro-intestinal disorders:
Hypermotility, reduction of absorbing surfaces, loss of mucosal integrity (carcinoma of stomach, intestinal tuberculosis, gastro-intestinal fistulae).
Biliary disorders, especially obstructive jaundice.
Therapeutic measures:
Liquid paraffin, colloidal absorbents, gastro-intestinal resections short-circuiting operations, severe catharsis.

Interference with Utilization

The evidence for this is mainly circumstantial, as direct experimental verification is extremely difficult. Provided that the intake is adequate, it is imperative to exclude interference with absorption, increased destruction and excretion, as well as abnormal requirements before defective utilization may be concluded. Carotene has to be converted into vitamin A; thiamin phosphorylated into cocarboxylase; nicotinic acid into coenzymes I and II, etc. These changes may occur in different tissues, but at present most evidence points to the liver as being the main organ for these processes (Moore, 1931; Sydenstricker, 1941), although it was recently suggested that carotene might be converted into vitamin A in the intestine (Glover *et al.*, 1947). In the case of liver dysfunction not only the conversion but also the storage and release of these substances is interfered with. In this way the body becomes dependent on the very variable daily intake, and as storage of the excess is also impaired a deficiency is bound to occur sooner or later.

Vitamin-A deficiency has been established in chronic liver diseases (Haig and Patek, 1942), obstructive jaundice (Stewart and Rourke, 1941), and hypothyroidism (Wohl and Feldman, 1939). Similarly in certain skin conditions, such as Darier's disease, Devergie's disease, and ichthyosis, in which low plasma vitamin-A values were repeatedly observed, impaired liver function could be demonstrated (Leitner, 1946a; Leitner and Moore, 1946). The low plasma vitamin-A levels found in patients with cancer of the gastro-intestinal tract have been attributed to failure in utilization due to hepatic dysfunction (Abels *et al.*, 1941), as in the various nutritional diseases in alcohol addicts (Jolliffe, 1941).

Factors interfering with utilization are: hepatic dysfunction (a liver cirrhosis, chronic hepatitis, alcoholism); hypothyroidism; and malignant diseases of the gastro-intestinal tract.

Increased Body Requirements

In a strict sense adequate nutritional intake should cover increased body requirements. Under certain conditions, however, the metabolic requirements are increased far beyond the average limits, and these exceptions might be considered as conditioning factors. Fever increases the basal metabolism

about 13% for each degree centigrade, strong emotion may also increase the metabolism considerably, while strenuous exercise or very hard work may even raise it to five to fifteen times above the basal level (Best and Taylor, 1943).

The influence of sunshine in the provocation of deficiency symptoms is well known. Its precipitating effect in pellagra ("mal di sole") is partly ascribed to its traumatic action (Smith and Ruffin, 1937) and partly to the excretion of the B vitamins in sweat (Cornbleet *et al.*, 1943).

A conditioned deficiency may be produced by thyroid, dinitrophenol, and fever therapy, which increases the whole metabolism, or by high carbohydrate diet, insulin-shock therapy, and parenteral administration of large amount of glucose, which increase the demand for coenzymes (Spies *et al.*, 1938). The water-soluble vitamin-B group, especially thiamin, may easily be washed out of the tissues and used up by repeated glucose infusions (e.g., after operations). The resulting "water-logging" (Sydenstricker, 1941) after excessive parenteral administration of glucose is a manifestation of thiamin deficiency.

Pregnancy and lactation have long been known to provoke symptoms of vitamin deficiency. Nixon *et al.* (1942), utilizing his material in Hong Kong and in this country, found besides pregnancy neuritis, already described in this country (Theobald, 1936), conditions allied to toxæmia and beriberi in undernourished pregnant women. It is not yet clear whether these symptoms are due only to increased requirements. Damage of the liver from pregnancy toxæmia may also lead to impaired liver function interfering with the utilization and storage of thiamin, choline, and other members of the vitamin-B group.

The importance of large doses of a single synthesized vitamin as a conditioning factor is still insufficiently recognized. Since Spies, Bean, and Ashe (1939) and Sydenstricker *et al.* (1940) first noticed that symptoms of thiamin and riboflavin deficiency became more pronounced in pellagrins after nicotinic acid treatment similar occurrences have been repeatedly recorded in clinical medicine. Lehmann and Nielsen (1939), Braendstrup (1940), and Salvesen (1940) described signs of pellagra after large parenteral doses of thiamin. Bichel and Meulengracht (1941) reported the development of pellagra after treatment with riboflavin; Leitner (1945) described signs of riboflavin deficiency after large parenteral doses of thiamin. Repeated attempts to produce imbalance of the vitamin-B factors experimentally have been unsuccessful, but Richards (1945) was able to induce fits in rats kept on pyridoxin-poor diet after large doses of thiamin, whilst the fits (characteristic of pyridoxin deficiency) could be entirely prevented if small doses of pyridoxin were given before the thiamin. Richards also suggested that one of the two types of thiamin toxicity described previously by Leitner (1943) which resembled thyroid overdosage might well be considered a vitamin deficiency induced by excess of the single vitamin.

Apart from the comparatively small number of verified descriptions of this syndrome, one encounters in hospital and private practice many partly abortive cases which often appear after repeated parenteral doses of one single vitamin—mainly thiamin.

A woman admitted to hospital with menopausal arthritis and gross adiposity was given a routine slimming diet, mersalyl, and thyroid. After having lost about 1 st. (6.35 kg.) in weight she still complained of shortness of breath; there were no signs of organic heart disease, and it was suggested that the shortness of breath was due to thiamin deficiency. Daily parenteral injections of 25 mg. of thiamin improved the breathlessness within five days, but painful cracks developed at the angles of the mouth, followed by crust formation and cheilosis.

Leitner (1946b, 1947a, 1947b) emphasized again that sub-clinical latent deficiencies within the vitamin-B group may often become manifest after energetic treatment of the obvious deficiency. Farrar (1947) found that administration of large doses of thiamin in inadequately nourished cases of pernicious anaemia aggravated the glossitis and caused diarrhoea and pellagrous dermatitis, but no pellagra-provoking effect of thiamin could be observed in the same patients when adequate diet had been given. He also found that haematological relapse appeared quicker when nicotinic acid was administered after stopping liver treatment. Davidson and Girdwood (1948) observed in two cases of pernicious anaemia and three cases of sprue the appearance, during treatment with folic acid, of

vitamin-B complex deficiency, consisting mainly of peripheral neuritis, cord involvement, angular stomatitis, cheilosis, and pellagrous dermatitis with depression. Whilst administration of purified vitamins was of little avail, potent liver extract always brought about an improvement. As the liver extract, containing only traces of the vitamin-B complex, produced the most dramatic effect on a wide variety of vitamin-deficiency symptoms, Davidson and Girdwood suggest that liver extract may contain a factor which liberates members of the vitamin B complex from their inactive form or facilitates their absorption or utilization. Leitner (1948b) subsequently put forward again the explanation that large doses of one purified vitamin (i.e., one single enzyme system) may easily upset the balance in deficiency states or may exert an inhibitory effect on other enzyme groups which at that particular time are present in abnormally low amount. The well-balanced multiple enzyme systems present in potent liver extracts may restore the disturbed equilibrium without containing large doses of any of the known purified vitamins.

TABLE III.—*Factors Increasing Body Requirements*

Increased activity:
Strenuous and prolonged physical efforts, psychosis, delirium.
Certain environmental influences:
Certain manufacturing processes and industries, excessive winds, light glare (snow).
Fever.
Pregnancy and lactation.
Hyperthyroidism.
Therapeutic measures:
Thyroid, alpha-dinitrophenol, parenteral dextrose, or excessive continuous fluid intake as in urinary infections, high carbohydrate diets, fever therapy, large doses of a single pure vitamin.

Increased Excretion

Increased excretion of vitamins may secondarily lead to malnutrition, but there are very few substantiated observations to this effect. Lactation, polyuria, or forced water-intake (Cowgill *et al.*, 1930) may cause increased excretion of vitamins (e.g., in urinary infections, sulphonamide treatment). The occasional observation of a mild gestational polyneuropathy with rapid development of symptoms and signs during the first few weeks of lactation might be an example of increased excretion. Excessive perspiration in the Tropics might condition a deficiency of the water-soluble B vitamins, as some of them appear in sweat in a considerable concentration after heavy physical exercise (Cornbleet *et al.*, 1943).

The main factors that increase excretion of vitamins are: (1) polyuria (diabetes mellitus, after excessive intake like urinary infections, sulphonamide therapy); (2) lactation; (3) excessive perspiration.

Increased Destruction

Induced vitamin deficiency in animals has long been known. Generalized erythematous scaly dermatitis with pruritus, arrest of growth, spastic gait, and abnormal posture could be produced by feeding raw egg-white in animals (Boas, 1927) and man (Sydenstricker *et al.*, 1942). The cause of this syndrome is a biotin deficiency. The glycoprotein (avidin) contained in the raw egg-white forms a complex in the gastro-intestinal tract with biotin, and this complex cannot be broken down. Cooked egg-white, on the other hand, does not inactivate biotin. Another severe deficiency is chaste paralysis in silver foxes fed on raw fish. It consists of anorexia, hyperaesthesia, ataxia, and death, with cerebral lesions similar to Wernicke's encephalopathy, and it is due to thiamin destruction caused by the thiaminase in raw fish (Melnick *et al.*, 1945). It is prevented by injection of vitamin B, (Evans *et al.*, 1942) or by cooking the fish. Although both conditions are very probably not due to simple destruction of the vitamin, it is perhaps pertinent to mention them here—"antivitamins," "inhibitors" (Woolley, 1944).

Factors leading to increased destruction of vitamins are: (1) achlorhydria; (2) alkalis, sulphonamides; (3) toxic doses with lead? arsenicals? gold?

Achlorhydria seems to interfere with the assimilation of ascorbic acid. Alt *et al.* (1939) have shown 65% destruction of ascorbic acid in three hours at a pH of 7.95, and Melnick *et al.* (1941) found that thiamin is stable in acid gastric juice (pH 1.5 to 8) during an incubation of 16 hours, but if antacids were added thiamin was completely destroyed. Bile and pancreatic juice also destroyed a considerable part of thiamin.

It has been claimed that vitamins, especially vitamin C, are often destroyed owing to their "detoxifying" actions—e.g., by arsenicals, gold, lead, sulphonamides, barbiturates, T.N.T., etc.—but the evidence is conflicting (Bicknell and Prescott, 1946).

The discovery of biosynthesis of vitamins by the intestinal flora focused some attention on sulphonamide therapy. It was known for some time that sulphonamides reduced the therapeutic action of nicotinic acid. Whilst there could be competition for the same enzyme system (Wood, 1940) between sulphydryl and nicotinic acid, the explanation did not hold good for sulphonamides not containing the pyridine ring. Later it could be shown in man that, after giving sulpha-guanidine or sulphasuxidine, the vitamin biosynthesis—e.g., that of thiamin (Najjar and Holt, 1943), riboflavin (Najjar *et al.*, 1944), nicotinic acid (Ellinger *et al.*, 1944)—in the intestines was substantially reduced or perhaps completely inhibited. As the extent of the biosynthesis is at present unknown the loss of this function may be considered from a practical point of view equivalent to destruction.

Diagnosis

Diagnosis of early vitamin-deficiency states is exceedingly difficult. The deficiency should be diagnosed at a time when symptoms have not yet been developed into the textbook description of deficiency disease; in the latter case the patient would be severely ill. The early symptoms are often non-specific, and laboratory methods are usually of little help at this stage, and to recognize the condition reliance has to be placed on the patient's dietary history, on indefinite symptoms and signs found on physical examination, and on a balanced clinical judgment. Complete nutritional failure is a rare condition in this country, but different degrees of deficiency state with a host of vague symptoms are frequent enough to warrant serious concern. In the earlier stages of vitamin research there was an inclination to attribute definite symptoms to a particular vitamin, but clinical experience has taught us that with greater frequency it takes the form of borderline states of ill-health owing to multiple deficiencies, often with vague symptoms which might easily be attributed to other causes.

Personal and Dietary History

The U.S. Public Health Service states that nutritional diseases constitute their greatest medical problem, not from a point of view of death but from that of disability and economic loss (Wohl, 1945). The fact that no similar statement has been made by public health authorities in this country does not by any means imply that the problem is non-existent here.

Grossly inadequate diet can be recognized without difficulty. Particular consideration should be given to patients on any special diet—e.g., those with obesity, peptic ulcer, dyspepsia, diabetes, etc. Detailed attention should be paid to dietary history in cases of psychoneurosis.

Clinical Examination

As manifold deficiency symptoms usually occur simultaneously, a wide variety of vague and interwoven symptoms are met with. The earliest symptoms consist of such general complaints as anorexia, fatigue, loss of weight, restlessness, irritability, paraesthesias, cramp in the muscles, burning of the eyes, photophobia, dimness of vision, impairment of memory, etc. These vague symptoms may be caused by different deficiencies, and they become pronounced with advancing disease.

In a vitamin-A deficiency clinical signs are detectable only when the process is moderately advanced. Perhaps the earliest change is xerosis conjunctivae, which can be observed if the eyelid of the patient is kept open for a few minutes; the lustre is lost owing to the rapid drying of the conjunctiva. This is due to metaplasia and thickening of the conjunctival epithelium, which reduces the secretion. It may be the earliest sign of vitamin-A deficiency. Like night-blindness—another symptom of vitamin-A deficiency—it is not specific, and both might have several other aetiological causes. Xerosis conjunctivae may later develop into Bitot's spots, which may or may not be

associated with night-blindness. Burning of the eyes, lacrimation, photophobia, and discharge are further early eye symptoms. More advanced changes of vitamin-A deficiency are to be seen in the skin, which becomes dry, scaly, and horny, with sharp oval-shaped papules around the follicles. Late stages of vitamin-A deficiency are connected with more pronounced damage of epithelial structures, mainly of the mucous membranes.

In a survey of 195 hospital and private patients with complaints not expected to interfere with the vitamin-A level, normal blood carotene and vitamin-A values were found (Leitner and Moore, 1948a). No signs of vitamin-A deficiency could be detected in any of these cases clinically. We found, however, low vitamin-A values in certain rare skin diseases (Leitner and Moore, 1946, 1948b) with characteristic skin lesions (Leitner, 1947c).

The early changes of *vitamin-B deficiency* are the most frequently met with in practice. It has been mentioned that the various members of the vitamin-B complex are grouped together more by virtue of their association in nature than by any structural similarity. Owing to their close association deficiency symptoms of the various members of the group overlap even more than would at first be expected.

The earliest signs of thiamin deficiency are generally ill-defined, and they are due most probably to deficiency of the entire B complex. The prodromal period may be described as a period of ill-health lasting for a long time. As thiamin is mainly concerned with metabolism of the nervous tissue, early deficiency symptoms chiefly connected with the abnormal function of the nervous tissues, such as anorexia, fatigue, irritability, dizziness, apprehension, etc., might be expected to form part of the clinical picture. But these symptoms are absolutely unspecific, like many of the early symptoms of other vitamin deficiencies, and the laboratory methods available are not sensitive enough to determine their origin. It may be argued that ill-health is the earliest symptom of many of the slowly developing pathological conditions, the specific symptoms and signs developing much later. It has, indeed, been my experience that more definite symptoms and signs follow if the symptoms mentioned remain untreated, and therapeutic tests corroborate this assumption. Though these early symptoms attributed to deficiencies are often encountered, properly controlled large-scale surveys have never been carried out.

Anorexia, fatigue, loss of weight, inability to concentrate, nervousness, transient digestive disturbances, intermittent pain and burning sensation, soreness at the corners of the mouth, burning pains in the eyes with visual disturbances, headache, dizziness, insomnia, and depression are early signs attributed to riboflavin deficiency. Sebrell and Butler (1938) differentiated by feeding experiments the well-known symptoms which later were termed hyporiboflavinosis (Stannus, 1944): paleness of the lips and angles, followed by maceration and bilateral superficial fissures. The macerated lesion becomes subsequently dry, a crust forms at the angles (angular stomatitis); the lips remain pale, red, denuded, cracked, and crusted with transverse markings (cheilosis). The tongue is clean, the papillae are flattened, with patchy denudation and congestion of the capillary loops leading to magenta colour in contrast to the shiny, atrophic, often painful scarlet-red tongue in pellagra. A fine scaly, somewhat "branny" desquamation on an erythematous base on the alae nasi, on the naso-labial folds, eyelids, ears, occasionally the hands, vulva, and perineum, are other early signs (Sebrell and Butler, 1938). Ocular disturbances (Spies, Vilter, and Ashe, 1939) such as conjunctivitis, burning, photophobia, pruritus, sensation of sand, and corneal vascularization leading later to punctate opacities are regarded by some authorities as the earliest signs of hyporiboflavinosis (Sydenstricker *et al.*, 1940).

Nicotinic acid deficiency is also introduced by a long period of "deficiency development time" characterized by loss of appetite and weight, disturbances of the alimentary tract, general muscular weakness, lassitude, irritability, insomnia, depression, inability to concentrate, vertigo, numbness, palpitation, flight of ideas, anxieties, loss of memory, and confusion. At this stage no physical signs are present and the diagnosis of malingering, neurasthenia, or anxiety neurosis is easily made. The characteristic mucous membrane and dermal lesions appear

much later. Hyperaesthesia of the tongue may precede the swelling, redness, and indentation caused by the teeth. Desquamation of the superficial layer causes a scarlet-red, dry, smooth, beefy tongue which is often painful. Secondary infection with monilia and Vincent's organisms over the fissures and aphthous ulcers occurs frequently, and the inflammatory process often extends to the neighbouring mucous membranes. The associated angular stomatitis and cheilosis might respond to riboflavin treatment. (Angular stomatitis may also be caused by ill-fitting dentures, dribbling, chewing-gum, and lipstick.) The characteristic skin lesions may sometimes be missed (pellagra sine pellagra). They are more often than not symmetrical, and may be precipitated by sunlight or other irritation. Hands, face, neck, knees, feet, and perineal regions are favourite places, but the sunburn-like, erythematous, pigmented, often hyperkeratotic, and distinctly demarcated lesions may appear anywhere. Mental symptoms such as emotional instability, depression, and confusion may be precipitated suddenly (Gottlieb, 1944), or within a few days in persons on deficient diet.

A woman, aged 64, who lived for 10 years on a restricted diet developed pulmonary tuberculosis. She was admitted to a sanatorium and improved greatly on a full diet. After eight months' sanatorium treatment she suddenly developed diarrhoea accompanied by anorexia. Within a few days changes occurred in the oral mucous membrane, followed by depression and confusion, and the skin and eye changes characteristic of pellagra were fully developed (Rimington and Leitner, 1945).

It would exceed the scope of this paper to discuss the possible relationship of macrocytic and microcytic anaemias to vitamin and nutritional deficiencies. It is perhaps sufficient to refer to the results achieved with another B vitamin—folic acid—in macrocytic anaemia, in the sprue syndrome, and in allied conditions.

Early *vitamin-C deficiency* is another widespread condition. Owing to the scarcity of citrus and other fruit and fresh vegetables for many years, congested, swollen, purple-red, easily bleeding gums occur comparatively often. I have also seen florid scurvy on five occasions during recent years, mainly in old single men who normally cooked only once a week for themselves and lived predominantly on warmed-up, overcooked meals. Fatigue, weakness, and anaemia are often early unspecific signs of vitamin-C deficiency, together with localized follicular keratosis. Petechial haemorrhages are usually moderately advanced signs, and although increased capillary fragility is more and more attributed to vitamin-P deficiency (Scarborough, 1940), the two substances appear to be associated in nature.

Laboratory Tests

These are of little help in early vitamin-deficiency states. Urinalysis is usually normal. The blood picture may or may not show a moderate microcytic or normocytic anaemia. Blood sedimentation rate, total serum proteins, and albumin globulin ratio are usually within normal limits. The fractional test meal often shows an achlorhydria, but this is neither pathognomonic nor characteristic. It is said that oesophagoscopy and gastroscopy usually reveal the same changes as are found in the buccal cavity. The "deficiency pattern" of the small intestine, found on x-ray examination with abnormal segmentation, pooling, disappearance of herringbone structure, obliteration and coarsening of the mucosal folds (Golden, 1941), although not always characteristic, may offer some indication of a B-complex deficiency.

During the last few years exact laboratory tests have been worked out for the determination of a given vitamin in the blood; saturation and excretion tests were also introduced. The assessment of the vitamin status, especially in the case of early deficiency, is, however, not simple. While the results of saturation tests as shown recently by Ellinger and Hardwick (1947) for nicotinamide may be affected by unknown mechanisms, low vitamin values in the blood and urine may, on the other hand, be found without depletion of stores in the organs; these findings are at times singularly uncharacteristic in cases of early deficiencies, and can be used only with great caution in the assessment of physiological deficiency. Moreover, it is essential that the laboratory data should be carefully correlated with the clinical findings. Within these limits, however, it is obvious that exact laboratory tests can

substantially contribute to the detection of subclinical deficiency states. For vitamin A the chemical estimation of the vitamin in plasma and the estimation of the dark-adaptation, for thiamin and riboflavin the determination of the excretion of vitamin B₁ and B₂, are the routine laboratory tests. Saturation tests are used for the assessment of nicotinic acid and ascorbic acid; some also rely on the vitamin-C estimation in the white cell layer, on the determination of capillary fragility, and on x-ray changes in the bones. The great difficulty with these procedures is that they nearly always require specialized laboratory technique.

Differential Diagnosis of Early Symptoms

As naturally occurring deficiency is always multiple, the associated symptoms are, especially in the early stages, often interwoven, and this makes the diagnosis of a deficiency of a specific chemical substance most difficult. Vague, ill-defined, waxing and waning complaints, prominent among them being fatigue, weakness, loss of appetite, loss of initiative, irritability, personality changes—in fact, all the common symptoms of neurasthenia—are frequently encountered. The patients are neurasthenics, indeed, and it is often difficult to separate these two conditions, particularly as neurasthenics are liable to eat an inadequate diet. Weir Mitchell long ago established that some neurasthenics benefited by a properly balanced forced diet combined with rest; and after careful study of the modern version of Weir Mitchell's method—the modified insulin treatment in neurotics (Sargent and Slater, 1944)—one wonders whether seclusion and reassurance or proper food are more important for their cure.

TABLE IV.—Symptoms described as Manifestations of Early Vitamin Deficiency (after Cayer, 1946)

Fatigue*	Paraesthesia*	Depression*	Weakness*
Insomnia*	Palpitation*	Abdominal discomfort	Lassitude*
Anorexia*	Nervousness*	Muscular weakness*	Muscle pain
Vertigo*	Irritability*	Backache	Lack of concentration*
Headache	Dyspepsia*	Apprehension*	Anxiety
			Confusion
			Decreased output of work

*Symptoms given as symptoms of neurasthenia in the textbooks of medicine.

Table IV may facilitate the appreciation of the overlapping between symptoms of early vitamin-deficiency states and neurasthenia (Cayer, 1946). This overlapping unfortunately led to the indiscriminate use of vitamin preparations all over the world. All evidence, however, shows that administration of vitamins without underlying deficiencies does nothing to improve the patient.

The difficulty in the assessment of early deficiency states warrants the occasional administration of vitamins as a therapeutic test. If the quick disappearance of symptoms is followed by general well-being the suspected diagnosis might have been right. Great care, however, has to be exercised, as slight improvement often follows any therapeutic trial.

Treatment

The underlying principle of the treatment of early vitamin-deficiency states is to deal with the conditioning factors and to supplement the tissue deficiencies. The degree of depletion of the various food factors varies in different patients, and, whilst often only one deficiency symptom predominates in the clinical picture, it has to be borne in mind that other deficiencies are also likely to be present. Food contains many still unknown factors certainly necessary for proper nutrition, and these are not present in synthesized vitamin preparations. The basis of treatment consists accordingly in securing an adequate diet.

It is quite evident that provision of the average daily requirements is not sufficient to make up for past losses. Although some of the patients showing early vitamin deficiencies may appear obese and overnourished, an investigation of their food intake will show that they have an imbalanced diet. The intake in these cases ought to be at least 3,500 calories, containing 120–130 g. of proteins (calculated for a person of 11 st.—70 kg.). This diet cannot be given easily to patients in this country at present;

our rations, even with additional foods for invalids, cannot provide either the necessary calories or the suggested protein intake. It is to be hoped, however, that the world food situation will soon enable the food policy of this country to be altered, at least for those who are in special need. Table V indicates the foods rich in different vitamins.

TABLE V.—Food Rich in Vitamins

Vitamin A	Thiamin	Riboflavin	Nicotinic Acid	Ascorbic Acid
Butter	Wholemeal	Wholemeal	Bran	Blackcurrant
Milk	Oatmeal	Bran	Peanuts	Rose-hip
Cheese	Beans	Nuts	Chicken	Lemon
Eggs	Peas	Beans	Pork	Orange
Carrots	Beans	Peas	Beef	Lime
Broccoli	Lentils	Broccoli	Liver	Grapefruit
Lettuce	Parsnip	Endive	Kidney	Strawberries
Spinach	Nuts	Spinach	Heart	Tomatoes
Tomatoes	Milk	Mushrooms	Meat extracts	Green pepper
Liver	Eggs	Milk	Salmon	Red pepper
Eel	Fish-roe	Cheese	Mackerel	(paprika)
Carp	Pork	Eggs	Brewer's yeast	Potatoes
Fish-liver oils	Veal	Fish-roe		Cabbage
	Beef	Kidney		Sprouts
	Brewer's yeast	Liver		Cauliflower
		Meat extracts		Turnips
		Brewer's yeast		Parsley
				Spinach
				Dandelion

In addition to a rich and well-balanced diet, vitamins should be administered in deficiency states. Parenteral administration of vitamins should be restricted to emergencies and to those cases in which there is obvious interference with absorption. As indicated earlier, large doses of parenterally given pure vitamins, especially those of the B group, may provoke a serious imbalance, and even if there is a deficiency of the administered vitamin they sometimes cause more harm than good. This point should be specially stressed, as there are indications that latent deficiencies without obvious clinical signs and symptoms are much more widespread than is realized. In early vitamin deficiencies something like five to ten times the daily minimal requirement should be given—e.g., thiamin and riboflavin 10–15 mg., nicotinamide 100–200 mg., ascorbic acid 150–300 mg., in divided doses three times a day. Fat-soluble vitamins should be given in larger doses, and my practice is to give 50,000 to 100,000 i.u. of vitamin A daily. As vitamin-A deficiency is often connected with disturbance of liver function, simultaneous parenteral application of liver extract seems, in my experience, to reduce the time needed for correction of the deficiency (Hoagland, 1945). Vitamins D and K are outside the scope of this paper, and no therapeutic suggestion is therefore given for deficiency of these.

In cases of deficiency of one of the vitamins of the B group it is advisable to give, instead of the most obviously lacking factor, a mixture of thiamin, riboflavin, nicotinamide, and possibly folic acid, together with brewer's yeast, 1–1½ oz. (28–42 g.), or liquid liver extract, 1 oz. (28 ml.), daily. Injection of the less refined liver extracts may also be tried. Symptoms usually begin to improve after two to four weeks, but as the depletion may be of long standing it is advisable to continue giving smaller doses for a longer period, particularly as dietary treatment alone in this country is bound to be ineffective for some time to come.

Summary

Deficiency states may be caused solely by the failure to ingest an adequate diet, or may be conditioned by factors which interfere with ingestion, absorption, and utilization, or by conditions which increase the requirements for vitamins and their excretion or destruction. The physiological and pathological aspects, and the therapeutic measures that may result in a conditioned deficiency state, are briefly discussed.

The clinical diagnosis of early deficiency states is exceedingly difficult, as the deficiencies tend to be multiple and the symptoms in many instances are non-specific. Physical signs are often

absent, and laboratory findings may not be characteristic in the early stages. Diagnosis should not be made on the basis of symptoms alone; careful evaluation of the dietary history, symptoms and signs, the available laboratory data, and response to specific therapy may help to establish the cause.

Not only a number of diseases but also some of the therapeutic measures used to combat them may precipitate a deficiency state, and the imbalance of vitamin-B factors is particularly stressed. The treatment of early vitamin-deficiency states is in every case an individual medical problem requiring exact diagnosis and properly planned therapeutic measures.

I am greatly indebted to Drs. F. J. Bentley, W. I. Card, T. Moore, and Prof. H. A. Krebs for much help, advice, and valuable criticism.

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THE TREATMENT OF NEUROSYPHILIS WITH PENICILLIN*

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The powers of penicillin have excited the whole world, but penicillin was introduced as an antibacterial remedy and it was not to be expected that it would be potent against the protozoal infection of syphilis. Moreover, it was soon discovered that penicillin given intramuscularly did not find its way into the cerebrospinal fluid; it did not, it was said, pass the blood-brain barrier; and so it was inherently improbable that it would have much effect on syphilis of the nervous system. We knew also that nowhere did the spirochaete entrench itself more strongly than in the brain; we knew that general paralysis especially was a hard nut to crack. It was therefore right and natural that the first rumours that penicillin was in some degree effective in cases of neurosyphilis, and even in cases of general paralysis, should be received with a certain amount of incredulity; and this attitude is apparent in most of the reports on the trials of penicillin in neurosyphilis, because nearly all observers, finding some clinical improvement but little immediate change in the cerebrospinal fluid and blood, have gone on to treat their patients with malaria. General paralysis is a progressive and inexorable disease that allows, no temporizing, and one must have good reason for withholding the well-tried standard, if desperate and often inadequate, remedy.

My own attitude at the beginning was the same. Early in 1945 some penicillin became available for civilian hospital use in diseases for which it was known to be appropriate, and just at that time I had admitted to the National Hospital under my care a man of 50 suffering from taboparesis.

This patient was euphoric and fatuous, and had recently lost his position as a secretary-accountant because of his inability to carry out his duties. He was pursuing allotment gardening in a hypomanic way, and had undertaken several allotments though he was a small weak man. At home he was restless, irritable, obstinate, and sometimes tearful. He had some tremor of his lips and tongue and a tremulous dysarthria, and also some tremor of his hands. His pupils were inactive to light, his knee-jerks and ankle-jerks were absent, and his plantar reflexes were weakly extensor. His cerebrospinal fluid showed typical parietic characteristics and his blood Wassermann reaction was strongly positive. I decided to try the effect of penicillin, and we were able to obtain the required amount. The reports which had come from America had at first suggested that over a million units might be necessary, but by the time treatment was started on this patient it was being said that even two million units were required, and he was given a course

*A paper read to the Society for the Study of Venereal Diseases on Jan. 24 (abbreviated).