SYMPTOMS AND SIGNS OF EXPERIMENTALLY INDUCED VITAMIN DEFICIENCIES IN MAN*

BY

S. S. B. GILDER, M.B., B.S., B.Sc.

Assistant Editor of "Abstracts of World Medicine"

A search of the published accounts of experiments designed to induce vitamin deficiencies in man reveals a very uneven distribution of work in relation to the individual accessory food factors. Some vitamins have been the subject of repeated investigations, others have been studied by only one or two investigators, and a few have never received any attention.

There are a number of reasons for these discrepancies. In the first place, it is clear that experiments on human subjects are scarcely justifiable if the results of animal experiment or clinical experience have already suggested that a deficiency entails the development of symptoms dangerous to life or health, or if the changes produced are irreversible. Thus, in the case of vitamin E, animal experiment suggests the possibility that degeneration in the nervous system might result from a deficiency, and it is known that an irreversible sterility is readily induced in male rats by lack of this vitamin. Hence, even supposing that the difficulty of constructing a diet adequate in vitamins A, B, C, and D and lacking in E were overcome, and even allowing for the great variation in signs of deficiency in different species, an experiment on human subjects to test the effects of severe restriction of vitamin E might be disastrous.

Secondly, there is the difficulty of constructing a diet in which only the vitamin under test is deficient. For example, pantothenic acid, as its name implies, is very widespread in foodstuffs, and to eliminate it from an acceptable diet would be almost impossible. Or, again, the diet may be admirable from the research worker's point of view but so unpalatable that even the inhabitants of a mental hospital cannot eat it.

Thirdly, the biochemistry of some of the lesser-known vitamins is so fragmentary that the problem cannot be attacked as yet. In some cases no reliable or simple method of assay of the vitamin has been discovered, so that it is difficult to state in feeding experiments what the subject's intake is, what the concentration in the plasma is, or how much he is excreting.

Fourthly, there is the vexed question of biosynthesis. It is useless to eliminate a vitamin from the diet of an experimental subject if he is capable of synthesizing the substance. It has been shown, for example, that nicotinic acid and vitamin K are synthesized in the intestinal canal by bacterial action. The same is probably true of aneurin, riboflavin, and other vitamins.

Methods of Study

With these difficulties in mind, the experimental methods employable for induction of a vitamin deficiency in man may be considered. The method used in the vast majority of experiments has been to give a diet deficient in only one vitamin and to observe the effects. As a further check on the results it is customary at the conclusion of the

experiment to add the missing vitamin to the diet, when prompt disappearance of any signs and symptoms of deficiency should result. In a few cases an indirect experimental approach has been necessary. Thus Sydenstricker *et al.* (1942) claimed to produce a biotin deficiency by giving a diet containing a prodigious amount of raw egg-white, calculated to contain enough avidin to combine with and inactivate the biotin synthesized in the gut. Again, Ellinger and Shattock (1946) deliberately induced a nicotinic acid deficiency in a woman by giving penicillin orally to kill intestinal bacteria. It is, moreover, probable that as more becomes known about anti-vitamins it may be possible to provoke a vitamin deficiency in a subject on a full diet by giving the appropriate anti-vitamin. This has been suggested by Hawkins and Barsky (1948) in the case of pyridoxin, to which the appropriate anti-vitamin is desoxypyridine.

Studies on experimentally induced vitamin deficiency fall into two groups—those in which the investigator has gone as far as he dare in an attempt to produce more and more symptoms and signs, and those in which the emphasis has been on dietary restriction rather than deprivation and the main object has been to discover the amount of restriction necessary to cause minimal signs and symptoms.

Sources of Error

In both cases there are many discrepancies in the accounts published, so that the validity of some of the results must be questioned. The first difficulty is to ensure that the changes induced are due to the absence of one and only one vitamin. On this ground some of the earlier publications must be held invalid. Thus the diet used by Sebrell and Butler (1938) to demonstrate ariboflavinosis may have been deficient in other vitamins as well, and the same criticism applies to the study of vitamin-A deficiency by Hecht and Mandelbaum (1940). Moreover, deprivation of one vitamin may affect the action of others and thus bring about a multiple deficiency. For example, Bourquin (1945) noted temporary falls in the ascorbic acid level in the plasma of women who were maintained on a diet low in aneurin, and Mayer and Krehl (1948) have pointed out that rats on a diet low in vitamin A also undergo depletion of vitamin C in liver and blood. This suggests that a "pure" deficiency syndrome may be not only a clinical but also an experimental myth. In the classical "one-man" experiments, such as that of Crandon, there is of course the great disadvantage of lack of controls, but in group experiments many more sources of error may be present. The subjects may be unduly suggestible. If one complains of fatigue, the others may rapidly follow suit. Even where control subjects receiving a vitamin supplement are used and the others receive a placebo, it is important that the investigator himself should not know which members belong to the two groups, lest he unwittingly betray his knowledge.

The duration of a depletion experiment is of great importance. Thus a recent study of vitamin-A deficiency suggests that it takes more than 18 months' absolute deprivation of this vitamin to produce any clinical signs at all, and Elvehjem (1944) cites the case of a monkey on a purified but apparently adequate diet for three years before a change in environment brought out signs of nutritional deficiency.

Other sources of error will be referred to in connexion with the discussion of individual publications. It is now proposed to consider the work that has been done on experimental induction of deficiencies of individual vitamins.

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Vitamin A

The most reliable experiment in vitamin-A deprivation would seem to be that recently described in a Medical Research Council report by the Vitamin Subcommittee (Mellanby *et al.*, 1949). The results differ somewhat from those mentioned in some pioneer studies published in 1939 and 1940, but the British workers planned and conducted their investigations with such great care that one has no hesitation in accepting their conclusions in preference to those of certain German and American investigators. The main facts that emerge from the Medical Research Council study are that it is extremely difficult to produce by dietary restriction signs and symptoms of vitamin-A deficiency in previously healthy adults, and that such signs and symptoms as do appear are few and trivial.

In this experiment 16 volunteers consumed a diet practically devoid of vitamin A for periods varying with the individual up to two years, seven other subjects acting as controls. All were young adults and most were men. No symptoms that could be definitely attributed to vitamin deficiency appeared in any of the 16 at any time. Objectively the only signs found in the subjects under test and not in the controls were a deterioration in the capacity for dark-adaptation and a fall in the vitamin-A concentration in the plasma. Although night vision appeared to be grossly defective on testing in two subjects, neither was really certain that he had greater difficulty in getting about in the black-out (the experiments took place in 1942-3) than previously. The other and more dramatic symptoms and signs described by earlier workers, such as loss of weight, anaemia, and increased fatigability, were absent, and abnormalities such as follicular hyperkeratosis and degenerative changes in the conjunctiva, previously thought on clinical grounds to be associated with vitamin-A deficiency, were either absent or also present in controls.

It would seem that, as Stannus (1945) maintains, follicular hyperkeratosis has nothing to do with vitamin-A deficiency. One may note in passing that Sheard *et al.* (1944) predicted that it would take one to two years to deplete a healthy young adult of his vitamin A reserves. Symptoms complained of more by those on a vitamin-free diet than by controls were dryness of the skin and ocular discomfort, but without corresponding objective signs.

Before publication of the M.R.C. report the classical descriptions of experiments in vitamin-A deprivation were those of Wagner (1940), Hecht and Mandelbaum (1940), and Wald and Steven (1939). Wagner gave a most dramatic description of a syndrome including not only deficient dark-adaptation and changes in sensitivity to various colours but also loss in weight, anaemia, leucopenia, and thrombocytopenia, with appearance in blood films of degenerate forms of red cells and cells of the myeloid series. It must be remembered, however, that his subjects were people who had been under detention in a German penal institution and on a diet nearly devoid of vitamin A for from one year to two years previously. He studied 10 subjects whose diet was restricted for 188 days, the amounts of vitamin A and carotene consumed being negligible, and claimed prompt cure of symptoms by giving 2,000 to 2,500 i.u. of vitamin A at the end of the experiment. It is of course possible that similar changes might have appeared in the British volunteers if their deprivation had been prolonged for another year or so.

Hecht and Mandelbaum's study, on 17 individuals, was not prolonged enough to produce gross symptoms, since it lasted for only 124 days. Here again the only abnormal

feature was a deterioration in dark-adaptation, which appeared in from 20 to 45 days. The only unusual finding is that this abnormality took several weeks to correct after a dose of 100,000 i.u. of vitamin A. It is possible that the diet used was deficient in other respects than in vitamin A. The work of Wald and Steven (1939) and of Wald, Brouha, and Johnson (1942) presents no unusual features, but the finding of Booher and Callison (1939) that depletion of vitamin A could be attained by dietary means in 40 days remains as yet unexplained and unconfirmed.

Lastly, it should be pointed out that experimental induction of vitamin-A deficiency, or for that matter of deficiency in any of the vitamins, might be considerably easier if the subjects were pregnant women, and easier still if they were lactating women. Practical testing of this point is of course unlikely.

The Vitamin B Complex

The three best-known members of the vitamin B complex—aneurin, riboflavin, and nicotinic acid—have received a great deal of attention in relation to human nutrition, although it has not been possible to conduct a satisfactory study of experimental human nicotinic acid deficiency, and the data available for riboflavin deprivation are confusing and somewhat contradictory. During the last war many investigations of deficiencies of these three vitamins were carried out in the U.S.A. because it was felt that they were intimately linked with muscle metabolism and therefore any dietary deficiency in them might interfere with the efficiency of the American male in the war effort.

The earliest studies were, however, pre-war ones, but as at first the chemistry of the individual members of the complex was ill understood these studies involved deficiency in the complex as a whole. Nevertheless a comparison of the symptoms produced with the symptoms later recorded as those of aneurin-lack reveals to what an extent the latter dominated the picture.

As a model of such work the findings of Elsom *et al.* (1940) may be considered in detail. They worked with a single volunteer, on whom two experiments in vitamin B deprivation were carried out, in 1933 and in 1938.

The subject was a healthy woman of 60 who in 1933 was maintained for a year on a diet probably deficient in all members of the B complex, and who was again given a diet in 1938 known to be deficient in aneurin and presumed to be inadequate as regards the other vitamin B factors. She received this diet for eight weeks to allow time for symptoms and signs to develop and was then given over successive three-week periods supplements of aneurin, aneurin plus riboflavin, and yeast. The findings are classified as follows:

1. *Cardiovascular*.—After five weeks dyspnoea and palpitation developed, together with a precordial pain not typically anginal. Tachycardia was at first paroxysmal and later continuous. Pulse rate fluctuated greatly, and a soft systolic murmur in the aortic area was occasionally heard. Aneurin administration restored the situation to normal. There were no changes in blood pressure or radiological findings, and, contrary to expectations, the electrocardiogram remained normal. Others had reported electrocardiographic changes said to be typical of aneurin deficiency, but it may be that the signs of the latter are modified in the presence of multiple deficiencies.

2. *Gastro-intestinal*.—After one week anorexia developed, and this increased until there was a complete distaste for all food. Associated with this were increasing nausea and, later, vomiting. These symptoms have constantly been recorded in experiments on aneurin deprivation and have on occasion made it necessary to terminate studies. They were associated in the present case with abdominal discomfort, heartburn, and

constipation, and later with moderately severe generalized abdominal pain. Some soreness of the tongue was occasionally noted. Aneurin administration relieved the pain and anorexia, but in the latter case only temporarily. Radiologically, gastric emptying was found to be delayed and small-bowel motility decreased, but the so-called deficiency pattern in the latter was never seen.

3. *Neurological*.—The first neurological sign to develop was a diminution in electrical excitability of peripheral nerves. Signs of peripheral neuritis then appeared—hypoesthesia and hypoaesthesia, and tenderness along nerves and in muscles. These signs, particularly the muscle-soreness, have been observed frequently in studies of aneurin deficiency; they disappeared promptly on giving this vitamin.

4. *Mental*.—The subject, who before the experiment had seemed to be a sensible, well-balanced individual, complained of irritability, nervousness, depression, and apathy. Memory and capacity for concentration became impaired, and aneurin administration did not altogether cure her mental symptoms.

5. *Blood Changes*.—These were indefinite. There was a suggestion of a hyperchromic anaemia such as has elsewhere been described as part of the aneurin-deficiency syndrome, but this persisted long after the experiment ended.

6. *Miscellaneous*.—The woman complained of tiring easily. Her skin became pale and flabby, and oedema of the arms and legs became progressively greater though weight was lost. Aneurin temporarily improved these symptoms, riboflavin did not help, and only administration of whole yeast cured her. The syndrome did not greatly differ from that induced in the same subject in 1933, save that glossitis and neurological disturbances were more prominent and anaemia, mental changes, and cardiovascular manifestations less prominent in the earlier study.

To this pilot study other investigations involving induced deficiency in more than one member of the vitamin B complex have not added a great deal. The mental changes were worked out in greater detail by O'Shea and Elsom (1942) in an experiment involving three elderly women and four controls. Foresight and judgment were shown to be definitely impaired, and were only partially improved by aneurin administration. Guetzkow and Brozek (1946) showed that, whereas a restriction of B complex in young men for over five months caused no intellectual deterioration, a further *total* deprivation for three weeks interfered with those mental functions in which speed plays a part.

The question of physical fitness in relation to deprivation of the vitamin B complex has been investigated in young men by Egaña *et al.* (1942), who produced undue fatigue and loss of efficiency in seven healthy doctors in three to four weeks (but no other symptoms), and by Johnson *et al.* (1942), who found that physical fitness deteriorated most if aneurin was withdrawn from the diet, in which case deterioration was associated with muscle and joint pains. Johnson's results have, however, been severely criticized by Keys *et al.* (1944), who state, as a result of short-term experiments on eight volunteers, that young men do not undergo physical deterioration rapidly when placed on a diet deficient in vitamin B complex. This latter paper gives evidence of careful work and must command respect, although Johnson in a reply points out the considerable difference in conditions between the two experiments. Keys (1945) later published results of a very cleverly designed experiment in which volunteers, after 161 days on a diet restricted in aneurin, riboflavin, and nicotinic acid which produced no significant results, took a diet almost devoid of vitamin B complex for 33 days. An elaborate system of cross-controls showed that aneurin was the important factor in producing anorexia, nausea, loss of endurance and physical fitness, as well as apathy and depression.

Aneurin

The earliest studies in which only aneurin deficiency was induced were those of Jolliffe *et al.* (1939) and Williams *et al.* (1939). Jolliffe used five normal volunteers and induced symptoms within four days, afterwards abolishing them within three to six days by giving an aneurin supplement. The only constant symptom was fatigue. Other symptoms included anorexia, dyspnoea on slight exertion, precordial pain, burning feet, and muscle cramps. Hyperaesthesia of the feet developed in four subjects and tenderness of the calves in one. In Lead III of the electrocardiogram an inverted T-wave was observed in two volunteers. Williams *et al.* gave four young women a diet containing less than 0.1 mg. of aneurin daily and found that symptoms appeared at a much later date, taking four to five weeks to develop. In addition to those features mentioned by Jolliffe, they observed constipation and achlorhydria and noted changes in the T-wave in Lead IV F of the electrocardiogram. Symptoms and signs disappeared within 12 days when 4 mg. of aneurin was given parenterally. In a second study Williams *et al.* (1940) extended their observations and improved on their experimental diet. They stress the point that withdrawal of aneurin alone from the diet does not produce beriberi. Neither oedema nor severe neuritis was ever seen, nor was cardiac dilatation ever detected. Radiologically the slow gastric emptying and sluggish intestinal motility mentioned in Elsom's experiment were observed. The experiment was prolonged up to 111 days and a state of extreme debility resembling neurasthenia was produced.

In a third experiment Williams *et al.* (1942) gave 11 women a diet less restricted in aneurin than in previous studies; they again emphasize the state of emotional instability and impaired physical efficiency previously noted. Holt (1944) has criticized these publications of Williams *et al.*, and thinks that they lay too much stress on neurasthenic symptoms, which have been observed in other experiments in which aneurin deficiency could not possibly play a part. Holt quite rightly mentions the fact that in the Netherlands Indies, where beriberi is rife, Dutch physicians are constantly on the look-out for signs of vitamin-B deficiency and yet know nothing of the syndrome of so-called "subclinical aneurin deficiency." Najjar and Holt (1940) produced no symptoms in subjects deprived of aneurin for 40 days. Other experiments on aneurin deficiency, such as those of Wang and Yudkin (1940), Archdeacon and Murlin (1944), Foltz *et al.* (1944), and Daum *et al.* (1948), have not added anything of significance to the basic picture described above.

Riboflavin

With this vitamin we are on much more controversial ground than with aneurin. The classical papers on experimentally induced ariboflavinosis are those of Sebrell and Butler (1938, 1939), but some doubt has been cast on their work. The diet given to their experimental subjects—18 women—was thought to be deficient only in riboflavin, but it may have been also deficient in other members of the B complex, such as pyridoxin, which has been said to heal the lesions of so-called ariboflavinosis. Be that as it may, 10 out of the 18 women developed a cheilosis after 94 to 130 days on the deficient diet. The first sign was a pallor of the lip mucosa near the angles of the mouth. Lesions became macerated and then fissured, the fissures occurring symmetrically at the angles of the mouth and extending somewhat downward. The lesions were moist and covered with a superficial crust, and sometimes extended on to the

skin. Along the line of closure there was loss of superficial lip mucosa. In addition a fine greasy desquamation on a mildly erythematous base was seen in the naso-labial folds, on the alae nasi, in the nasal vestibule, and on the ears. Lesions responded to synthetic crystalline riboflavin and not to nicotinic acid, and are therefore considered to be due to lack of the former; but the evidence is not entirely convincing, since lesions did not always disappear with dramatic suddenness.

Of the women who did not develop cheilosis, four received riboflavin supplements after the 139th day and no symptoms developed by the 365th day, while cheilosis developed in three of the other four who continued with the experimental diet. It is interesting to speculate on the reason for the comparative "resistance" of some of the women to riboflavin depletion, since all were inmates of a mental hospital and had presumably subsisted on a fairly standard diet before the experiment. Possibly the lesions were not entirely due to lack of riboflavin; there is, however, the possibility of biosynthesis of the vitamin, as suggested by Najjar *et al.* (1944) in a study of 12 adolescent boys given for three months a diet deficient only in riboflavin. They remained in excellent health, and the amount of riboflavin excreted in the urine rose after a preliminary fall to ten times the amount ingested.

When four subjects received a diet restricted in riboflavin alone to an amount approximating to half the suggested daily requirement, no signs of deficiency appeared during a period of 288 days, according to Williams *et al.* (1943).

It has been suggested that riboflavin deficiency is associated with ocular lesions such as corneal vascularization, but direct experimental proof of this is lacking. Thus when Boehrer *et al.* (1943) gave three individuals a diet deficient in riboflavin the only evidence of corneal vascularization was found in a control subject, and this did not respond to a large daily riboflavin supplement. Keys and his colleagues (1944) published an impressive paper on the effects of riboflavin restriction on six normal young men. These men probably received about twice as much riboflavin daily as did the patients studied by Sebrell and Butler. Although the experimental period amounted to 152 days in three instances, not the slightest clinical evidence of a deficiency was obtained. Lastly, it should be noted that Machella and McDonald (1943) have strongly challenged the statement that riboflavin deprivation leads to cheilosis. To sum up, the burden of proof must still rest on those who support the contentions of Sebrell and Butler.

Nicotinic Acid

Nobody has as yet given a direct demonstration of clinical effects caused by withholding nicotinic acid alone from a dietary. There are two points for consideration here. First, a great body of evidence points to the occurrence of synthesis of this vitamin on an appreciable scale in the intestine. Secondly, although Goldberger and Wheeler (1915) produced classical pellagra by dietary restriction nearly 30 years ago, it is still by no means certain that this disease always appears as a result of severe nicotinic acid deficiency. For example, Briggs *et al.* (1945) admitted to hospital two patients who still had mild lesions of an old pellagra and gave them a diet containing only 3 mg. of nicotinic acid daily, for 42 and 9 weeks respectively. No change occurred in the severity of the lesions.

Reference has already been made to the induction of what seems to have been a nicotinic acid deficiency by the indirect method of sterilizing the interior of the intestine and so killing the bacteria responsible for nicotinic acid synthesis. Thus Hardwick (1946) records the development

of stomatitis and acute dermatitis with ulceration at the angles of the mouth in a woman given sulphaguanidine, and cure of the lesions by nicotinic acid. Ellinger and Shattock (1946) gave penicillin orally to a woman, with the intention of producing deficiencies, and observed the appearance of dark-brown patches on the tongue within a few days. In addition the patient complained of malaise, lassitude, difficulty in concentration, slight physical incoordination, and a redness of the feet. Nicotinic acid cured her promptly. The trap in these experiments is of course that antibiotics or sulphonamides may interfere with biosyntheses of other vitamins.

Biotin

Here again indirect means must be used to induce a vitamin deficiency experimentally. The only study available is that of Sydenstricker *et al.* (1942), who attacked the problem by giving to four volunteers the raw white of 80 eggs a day, so as to render unavailable the biotin in the diet and synthesized in the gut. Obviously this freak diet bears no relation to everyday life and the experiment is purely of academic interest. After three to four weeks a greyish pallor of the skin was observed; this was unrelated to the blood picture. Later the skin became dry and desquamated, and the lingual papillae became atrophic, while general symptoms resembling those of aneurin deficiency appeared. Injection of a small amount of biotin sufficed to restore the patient to normal. Other observers have not as yet recorded a similar experiment.

Pyridoxin

Hawkins and Barsky (1948) attempted to induce a pyridoxin deficiency in one of them (Hawkins) by taking a purified diet with addition of all the necessary known vitamins except pyridoxin for 54 days, after which he received a supplement of 10 mg. of pyridoxin daily for seven days. Findings during the period of deprivation were indefinite, but lack of the vitamin may have been related to the development of albuminuria (though Hawkins had an old history of renal colic), to some depression and mental confusion which disappeared on adding pyridoxin to the diet, and to a lymphocytosis which also disappeared with resumption of a normal diet.

Vitamin C

The first work on experimentally induced vitamin-C deficiency in man was done in Germany in 1939, and was soon followed by an important paper published by Crandon and his associates (1940). Although several carefully conducted experiments have been carried out since, little has been added to the clinical picture described by the pioneer workers.

The first work was done by Rietschel and Mensching (1939) in Würzburg. Mensching subsisted for 100 days on a diet thought to be free from vitamin C, all food containing this substance being thoroughly cooked with soda to destroy the vitamin. No signs or symptoms appeared, and the only reason for discontinuing the experiment was that Mensching doubted his ability to keep to the diet when he went home for Christmas. In a second paper Rietschel and Schick (1939) described an attempt by Schick to induce signs of deficiency in himself during a 160-day period on the diet used by Mensching. Again no signs of deficiency appeared, although Schick undertook a strenuous skiing expedition during the experiment. A few hypertrophied red papillae appeared on the gums, but these were ascribed to the effect of recent dental fillings. It is of interest that a previously troublesome bronchitis cleared up during the experiment.

In 1940 an American observer (Crandon) at last succeeded in inducing signs and symptoms of vitamin-C deficiency in himself (Crandon *et al.*, 1940). He showed that Rietschel's colleagues had discontinued their experiments too soon, since in his case there were no physical findings for the first four months. Crandon put himself for six months on a diet free from vitamin C but supplemented by all the other known dietary constituents. In the later stages of the experiment Crandon lost weight, but this may have been due to the type of diet rather than to a vitamin deficiency, since giving vitamin C did not result in increase in weight. Like Schick, he found that he was remarkably free from respiratory infection, to which he had been subject in other winters.

The first definite signs presumably due to vitamin-C deficiency appeared in the skin after 134 days on the diet. They took the form of small perifollicular hyperkeratotic papules on the buttocks and calves. Each papule contained an ingrowing hair, and the hairs tended to become fragmented. The skin, particularly on the extensor surfaces of the limbs, became dry, and the backs of the hands became rough. After 161 days small perifollicular haemorrhages or petechiae appeared on the legs below the knees, and were more numerous after prolonged standing. The relation of the skin lesions to vitamin-C deficiency was confirmed by their disappearance on giving the vitamin.

Contrary to expectations, the gums and teeth remained practically normal, apart from a little bogginess. Biopsy specimens revealed normal structure. Radiographs of teeth showed occasional interruption of the lamina dura. It would seem that the gum changes in classical scurvy are due to an infective factor in addition to a vitamin deficiency.

The subject first observed fatigue and weakness after three months, and this was progressive. Capacity for walking and running, for instance, was particularly impaired. Within 24 hours of receiving a dose of vitamin C lassitude was said to be less. The healing of wounds was investigated. Although after three months it appeared to be normal, there were definite signs of deficient healing in the depths of a wound surgically inflicted after 182 days. In 1940, Fox *et al.* published the results of a study on native mine-workers which serves as a corollary to Crandon's experiments. Their investigation was based on the opposite principle to that of Crandon. They found a community of individuals who were existing on a diet probably deficient in vitamin C, and separated them into two groups, to one of which they gave a daily supplement of 40 mg. of ascorbic acid. Apart from an increased incidence of scurvy in the group not receiving a supplement, no differences were detected between the two groups after seven months. As it is admitted that the exact intake of vitamin C in the two groups, and therefore presumably the intake of other vitamins, was not known, the investigation is of limited value.

Pi Joan and Lozner (1944) conducted an experiment on six volunteers, who after a short period of saturation with vitamin C received a diet free from this vitamin until symptoms appeared. Results were very similar to those of Crandon, for no symptoms appeared for five to six months. The first signs of impending scurvy were lassitude, fatigue, and irritability, and two weeks later petechial and perifollicular haemorrhages appeared. Only one subject had gingival bleeding.

Johnson *et al.* (1945) confirmed the maintenance of physical efficiency in the early weeks of deprivation of vitamin C in a study of 24 volunteers who received a diet

devoid of vitamin C for eight weeks. Farmer's (1944) findings in an experiment involving 12 young men did not differ greatly from those of Crandon. He stresses, however, a marked tendency to infection of experimental wounds as well as the previously observed slowness of healing. His subjects also underwent psychological tests, and it was found that the choice reaction time increased after the third to fifth months on a deficient diet. There was also loss of interest and of motivation. Characteristics such as aggressiveness or submissiveness became exaggerated.

The latest investigation to be published is that arranged by the Vitamin Subcommittee of the Medical Research Council (Peters *et al.*, 1948). The main points in Crandon's experiment were confirmed in a very carefully arranged and controlled study on 19 young men and women which continued for over a year. The observers agree with Crandon that the first sign of a deficiency is enlargement and keratosis of hair follicles, but do not think that the skin changes are pathognomonic of vitamin-C deficiency. This first appeared after 17 weeks and was present in all test subjects by the end of the sixth month. Follicles were plugged with a horny material in which a hair lay coiled. The main areas affected were the upper arms, back, buttocks, backs of thighs, calves, and shins. After a few weeks the follicles became red and, later, haemorrhagic. An acne present in five subjects at the beginning of the experiment became worse.

Gum changes appeared after six months in the form of tiny interdental haemorrhages with swelling. In two cases gingivitis became really severe and necrosis and gross bleeding occurred, but the volunteers had had some gum disease before the experiment. There was evidence of increased fatigue, but in contrast to the findings of earlier workers no psychological changes were observed. The fact that no weight was lost must be attributed to the more careful choice of diet. The observers do not confirm Farmer's findings of an increased tendency to wound infection, and emphasize that wound healing was delayed only after scurvy had developed. The dryness of skin mentioned by Crandon was not seen. The volunteers did not complain of weakness.

A curious feature is the occurrence of anginal attacks in two volunteers with some electrocardiographic evidence of heart-block.

Other Vitamins

The above are the only vitamins deficiency of which has so far been induced experimentally in man. In the case of the lesser-known members of the B complex, such as pantothenic acid, folic acid, *p*-aminobenzoic acid, choline, and inositol, and of vitamins D, E, K, and P, either insufficient is known to plan an experiment or the attendant risks are thought to be too great.

Summary

The symptoms and signs of experimentally induced deficiency of vitamins A and C and of aneurin, riboflavin, nicotinic acid, biotin, and pyridoxin are discussed.

Vitamin A deficiency is difficult to induce in healthy adults, and the signs and symptoms are trivial.

The most striking features of experimentally induced aneurin deficiency are fatigue, anorexia associated with nausea and vomiting, peripheral neuritis, mental changes, and cardiovascular changes. Riboflavin deficiency may lead to cheilosis, but this is not certain. The exact results of nicotinic acid deficiency are not yet known. Biotin deficiency may lead to a dermatitis with pallor of the skin. Pyridoxin deficiency may be associated with albuminuria, mental changes, and lymphocytosis.

Experimental induction of vitamin-C deficiency leads after an interval of several months to perifollicular hyperkeratosis and later to petechial and perifollicular skin haemorrhages. Gum changes are slight.

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The *Danish Foreign Office Journal* (No. 3, 1949) contains an illustrated account of recently invented Danish scientific apparatus. The country that gave the world the Finsen lamp has raised the construction and design of these lamps to an extremely high standard. A new haemometer gives a direct reading on an electrically controlled scale of the haemoglobin in any sample of blood which is compared with a standard colour in an illuminated observation window. The lighting is adjusted until the tints of the two are identical. A new audiometer, with a frequency range of 20 to 20,000 kilocycles, has a built-in microphone and masking oscillator, and two insulated loud-speakers mounted on an adjustable stand. A new all-purpose electric water-bath, heated by an infra-red lamp, can be raised to a temperature of 400° C.

DISABILITY PRODUCED BY EXPOSURE OF SKIN TO MUSTARD-GAS VAPOUR

BY

D. C. SINCLAIR, M.A., M.D.

(From the Department of Anatomy, University of Oxford)

For a period after the introduction of mustard gas (2,2'-dichlorodiethyl sulphide) in the 1914-18 war "casualties" were produced as a result of ocular and respiratory lesions. Later, when adequate measures were taken to protect the eyes and respiratory tract, the skin burns came into increasing prominence as a cause of disability. The introduction of effective respirators and good gas discipline also had a considerable effect in reducing the incidence of disabling systemic poisoning.

In the interval between the wars the disability produced by the action of mustard gas on human volunteers was studied by various workers, and these investigations were intensified during the 1939-45 war, particularly with respect to tropical conditions. There was, however, no generally accepted classification of this disability, and, further, in most cases no practical test was applied to its assessment, which therefore depended solely upon the personal opinion of the investigator. In 1944 a system for the practical evaluation of disability in terms of the results of standard physical performance tests was evolved in Australia by Ennor, Gorrill, Legge, and Sinclair. In an attempt to evaluate the factors concerned in the production of disability in the field a modification of this system* has been applied to the analysis of disability in men exposed to mustard-gas vapour in the Tropics.

Material and Methods

Over a period of two years 179 men were under observation following exposure to various dosages of mustard-gas vapour under tropical conditions. All the subjects wore fully effective respirators throughout exposure; 147 wore ordinary tropical Australian battle-dress and 32 wore additional clothing which denied access of mustard vapour to the genitalia and buttocks.

On each day after exposure a standard physical performance test was carried out, consisting of two runs over a specially constructed assault course and a six-mile (9.6-km.) march in full equipment. In certain cases the capacity of the subject to defend himself by firing an automatic weapon was assessed. On the basis of his performance in these tests every man was placed each day in one or other of five categories. Table I sets out these

TABLE I.—Classification of Disability

Category	Criteria for Inclusion
1. Unaffected	No objective sign of exposure
2. Injured, without disability	Performance test satisfactory; no treatment required
3. Injured, requiring treatment	Performance test satisfactory; treatment required
4. Partially disabled	Failure on any part of performance test
5. Totally disabled	Failure on any part of performance test, plus inability to use any weapon in self-defence by reason of: severe burns of the hands, loss of vision, gross systemic intoxication, or pain requiring morphine

categories, together with the criteria for inclusion in each. (The subsequent use of the terms "disability," "disabled," etc., without qualification, should be taken to refer to categories 4 and 5 of Table I taken together.) So long as

*The Ministry of Supply wishes me to make it clear that this system has not been officially accepted by the Medical Directorates of the British Armed Forces.