HYPERVITAMINOSIS A AND CAROTENEMIA

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The effect on man of the ingestion of large amounts of carotene has been the subject of many articles in the past twenty years. On the other hand, knowledge of the results of overdosage with vitamin A is almost entirely confined to the effects on rats and mice. The lack of experience with hypervitaminosis in man is easy to understand, since only artificial concentrates contain sufficient vitamin A to be dangerous, and the ability to obtain these is limited. Early recognition of the possible danger of hypervitaminosis has limited the employment of excessive amounts in therapy. Moreover, the zone of safety between an adequate prophylactic dose and a dangerous dose is very large. One safeguard is lacking, that against the zeal of a person who is “sold on” vitamins. We have recently observed a case in which enthusiasm for vitamin therapy was present in a mother and eventually in her child.

REPORT OF A CASE

History.—B. B., a 3 year old boy of Jewish parentage, had appeared well up to the fall of 1938, when he was about 18 months old. At that time his appetite diminished and he seemed to be disinclined to play. Six months later (May 1939) he had a severe attack of tonsillitis, for which he was given sulfanilamide for two days. Two months after this, July 26, 1939, he had a tonsillectomy followed by hemorrhage, after which he received three transfusions. A blood count done after the hemorrhage showed severe anemia and 2,900 white cells per cubic millimeter, of which 44 per cent were neutrophils. The patient’s liver and spleen were found to be enlarged, and clubbing of the fingers was noted. At this time he lost much of his hair, and that which grew back was sparse, dry and coarse.

During the next eight months, the child failed to improve, and because of the enlarging spleen and the continuing anemia he was admitted to the Harriet Lane Home for study with the tentative diagnosis of Gaucher’s disease (March 1940).

Physical Examination.—When the patient entered the hospital in March 1940, his hair was sparse, dry and rather coarse, and eyebrows and fine hair over the body were lacking. The fingers and toes were slightly clubbed. He was pale and sallow, but there was no increase in pigmentation and no jaundice and the scleras were clear. The heart and lungs showed no abnormality. The liver was felt 2 cm. below the costal margin, the edge being sharp and firm. The spleen was enlarged and firm and was palpable 5 cm. below the costal margin. The child’s height was 89 cm. (about normal for his age).

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Laboratory Data.—Most of the laboratory data are summarized in table 1. In addition, a test of dextrose tolerance gave the following results: fasting level, 81 mg. per hundred cubic centimeters of blood; levels after ingestion of dextrose, one-half hour 152 mg., one hour 168 mg., two hours 140 mg. and three hours 111 mg. The results (in milligrams per hundred cubic centimeters of blood) in the levulose tolerance test were: fasting, 91; half-hour, 132; one hour, 131; two hours, 105, and three hours, 102. The erythrocyte sedimentation rate (corrected) was 6 mm. in one hour on one occasion and zero on two others. The bromsulphalein test of hepatic function showed no retention of the drug. Excretion of urobilin was not increased in either the stools or the urine. The Wassermann and tuberculin tests gave negative reactions.

Roentgenograms of the chest and skull showed no abnormalities, but those of the limbs revealed considerable irregularity in cortical structure. In the phalanges and metacarpals the cortex was extremely thin and the medullary cavities appeared to be “vacuolated.” The epiphyses of the upper ends of the humeri and tibias were mottled in appearance, and the distances between epiphyses and diaphyses were greater than normal. There were five carpal centers of ossification, indicating that skeletal development was in advance of the child’s age in years.

A biopsy was done on a piece of bone, but unfortunately the tissue used was from the tibia, in which no change was disclosed by roentgenographic examination; as a result we are unable to say what was the nature of the abnormal process which occurred predominantly in the upper extremities. It is, however, possible to state definitely that the marrow showed no evidence of hypoplasia, nor was there any accumulation of reticuloendothelial cells. The only abnormality was a predominance of the more immature cells of the myeloid series. It was noted that the bones became decalcified in the fixative more rapidly than usual, but there was no evidence from the biopsy of any process that might cause decalcification of the bone.

Course.—The one outstanding feature of the examination that appeared to point to a possible etiologic factor was the enormously high content of vitamin A in the serum such as would not ordinarily be encountered except four to six hours after ingestion of an excessive dose of vitamin A. On questioning the mother, it was learned that beginning at 2 to 3 months of age the child had received a teaspoonful of halibut liver oil a day (about 240,000 U. S. P. units of vitamin A) up to the present time. Moreover, he had on occasion drunk the oil directly from the bottle in undetermined amounts.

As soon as it was appreciated that the case might be one of hypervitaminosis, the child was discharged with instructions that he should not be given any extra vitamin A. Improvement was immediate. Within two months, the appetite had improved, the patient had gained weight and his hair had begun to grow back normally. By the end of six months his appearance and the composition of his blood were normal and the vitamin A content of the serum was within the upper limit of normality. Certain features remained, however; the phosphatase was still elevated and the serum proteins were still depressed. For a time after he was discharged from the hospital the child showed a desire for
butter and carrots, which led to a considerable though temporary increase in serum carotene and a temporary increase in serum lipids.

Two and a half years after leaving the hospital, the child was back to all appearances normal and of average height and development. He had had no illness except measles, and there was nothing in the mother's account to indicate that any pathologic change was still present. However, his liver was palpable as a firm sharp edge about 2 cm. below the costal margin; the spleen was felt as a large, firm mass occupying the upper left quadrant of the abdomen, and his fingers were still slightly clubbed. The laboratory data were essentially normal except for a slight elevation of the phosphatase content of the blood. The bones appeared normal in structure, but skeletal development was slightly in advance of the chronologic age (7 carpal centers of ossification at 5½ years of age).

In order to understand the significance of the conditions observed in this case, it will be necessary to review in considerable detail what is known concerning overdosage with vitamin A and its precursor, carotene. It has seemed best to carry out the review in the following order: (a) the known results of overdosage with vitamin A and carotene as determined by experiments on animals; (b) carotenemia as it is observed clinically, including the factors influencing the accumulation of carotene in the blood and the clinical effects of carotenemia, (c) hypervitaminosis, (1) the factors leading to accumulation of vitamin A in the blood and (2) the possible mechanisms the body employs to protect itself against the harmful effects of overdosage with vitamin A.

**RESULTS OF OVERDOSAGE WITH VITAMIN A AND CAROTENE IN ANIMALS**

As has been said above, knowledge of hypervitaminosis A is confined to the effects in animals, particularly in rats and mice, which are especially sensitive to the toxic effects of over-dosage with vitamin A. Since different species vary greatly in degree of sensitivity to vitamin A and also possibly in the type of change produced by excessive amounts, one must be cautious in applying the knowledge gained by experimentation with animals to the interpretation of occurrences in the human being. There are, however, certain changes that have occurred in all the species tested, and these should form the basis for an understanding of the effects of intoxication with vitamin A. The following account will be based on the effects of excessive doses of vitamin A on the rat, since that animal has been most extensively studied.

When rats are given toxic doses of vitamin A (over 15,000 units a day), they lose weight almost immediately and may die in a week or ten days. There are certain rather constant...
of the bones of the extremities. Some investigators reported exophthalmos, the cause of which is unknown; others stated specifically that they had never seen this result.

Histologically two features stand out, rarefaction of the bones with extreme thinning of the cortex and increased deposition of fat in the reticuloendothelial cells, especially in the Kupffer cells of the liver and in the spleen. There has been considerable disagreement over the degree of accumulation of fat and the extent of the hyperplasia of the reticuloendothelial cells; some investigators reported almost none, while one author likened the histologic picture to that observed in cases of Schüller-Christian disease.

Other histologic changes were noted by various authors, some of which may be of considerable significance if confirmed. Some authors, for instance, found evidence of increased activity of the thyroid gland; one stressed increase in the basophilic cells of the anterior lobe of the hypophysis, and hypertrophy of the island tissue of the pancreas was reported by another.

Although the anatomic studies have usually been made on severely intoxicated animals, certain of the changes, especially those in the reticuloendothelial cells, are known to occur also in animals less severely poisoned. This fact indicates that such changes are the result not of a general intoxication but of a process more specifically associated with excess of vitamin A.

Investigations of the relationship of overdosage with vitamin A to fat metabolism tend to confirm this suggestion. Since this subject has recently been reviewed, it need only be touched on here.

When vitamin A in large but nontoxic daily doses was given to rats, guinea pigs or rabbits, a rise in cholesterol and in total lipids of the serum occurred. This rise was only temporary, however, and tended to disappear after a time, even while the large doses of vitamin A were being given. The same effect was observed in human beings but not in dogs. In rats previous deficiency intensified and prolonged the response, and a similar reaction was seen after pneumonia in infants receiving vitamin A. Apart from this lipid reaction, the effect of vitamin A on physiologic processes has been little studied. No effect was observed on the formation of blood in animals. The serum calcium and phosphorus were not affected, though there was an increase in excretion of calcium, which was attributed to "decalcification" of the bones. The basal metabolic rate was decreased.

An observation of considerable significance, if confirmed, was that function of the liver was at first improved and then depressed by excessive vitamin A. All authors are agreed on the fact that recovery is prompt when the excessive intake of vitamin A is discontinued.

In contrast to the harmful results of overdosage with vitamin A, toxic effects have not been seen in animals after ingestion of excessive amounts of carotene; the animals have not lost weight or died and have not shown any of the outward manifestations of hypervitaminosis. The changes in the metabolism of fat and the histologic changes in the reticuloendothelial "system," especially the increase in the storage of fat, are the same after the ingestion of carotene


11. (a) Josephs. (b) Wendt.


as after large but nontoxic doses of vitamin A. The most obvious reasons for the less pronounced effects with carotene are: (1) carotene is less well absorbed than vitamin A; (2) the effect of carotene is seen only after conversion to vitamin A, and the time taken for this conversion would prevent the flooding of the body with the active vitamin which is necessary for the production of toxic effects. This subject will be more fully discussed in the section devoted to the body's defense against hypervitaminosis.

**CLINICAL CAROTENEMIA**

**Factors Influencing the Carotene Level of the Blood.**—1. Diet: Recognition of the primary importance of diet in carotenemia came as the result of the work of Palmer and van den Bergh and of a large number of clinical observations, most of them on children and persons with diabetes. These studies revealed correlations of xanthosis of the skin with increased content of lipochrome in the blood and with diets rich in lipochromes (carotenoids). Carotenoids are the primary food associated with carotenemia; also important are squash, oranges and egg yolk (egg yolk supplies xanthophyll rather than carotene). Xanthosis of dietary origin is most common in the late summer, and a number of observers have noted that the carotene of the blood is normally at a higher level at this time of the year. In the cases reported in pediatric clinics, young infants appeared to be spared; the condition is observed only in later infancy and early childhood. It is generally recognized that carotenemia and xanthosis are slow to develop, and relatively slow to recede after the high intake of carotene is discontinued. Not every one reacts in the same way to the same diet, and it has been observed that some persons who acquire xanthosis easily do so on a surprisingly small extra amount of carotene. Moreover, the reactions of the same person may vary; it has been noted that a carotene-rich diet may cause xanthosis at first but that the yellow color may later disappear not to return during continuance of the diet.

2. Level of Serum Lipids: The suggestion was made early that the serum lipids might have something to do with the development of carotenemia. The conditions other than ingestion of diets high in carotenoids under which carotenemia occurs in human beings are in general those associated with hyperlipemia—diabetes, nephrosis, and hypothyroidism. In cases of diabetes of the type in which the serum lipids are increased there is also a tendency for carotenemia to develop. Rabinowitch reported


27. (a) Wendt, (b) Josephs, H. W.: Personal observation.

28. (a) Wendt, (b) Umber. (c) Labbé, M.: Presse méd. 33:17, 1925. (d) Rabinowitch, I. M.: Canad. M. A. J. 18:527, 1928; (e) Carotenemia and
that those patients with the highest levels of serum carotene tended in general to have the highest levels of lipid. If a large enough number of cases is studied to obtain the extreme variations in values which are encountered only under pathologic conditions, it can be shown that a correlation does exist. However, the lack of demonstrable correlation in small series and under normal conditions has led several observers to deny that the lipids have any significance in carotenemia.

In a recent study, it was found that during and after pneumonia, the levels of carotene and of lipid could be correlated when account was taken of the ingestion of carotenoids and the time required after ingestion for accumulation of the carotenoids in the blood. When carotene was given by mouth the rate of accumulation in the blood stream depended in general on the level of lipid during the period of ingestion. In a recent study of hypothyroidism the values of serum carotene were found to be dependent on those of the serum lipid. A close relationship between carotene and cholesterol has been stressed, and it has been claimed that the yellow color of the nodules present in xanthoma is due to their content of carotene.

3. Other Factors: The fact that when carotenoids are removed from the diet the carotene of the serum falls to an extremely low level suggests that the stores of carotene in the fat depots are only to a minimal extent available for maintenance of the level in the blood. Moreover, it has been found that thin people have a higher concentration of carotene in the fatty tissue than well nourished persons, which indicates that even when fat is mobilized from depots in the tissues, carotene remains behind. The fate of the carotene which disappears from the blood is not entirely known. Some of it is evidently deposited in the fatty tissues. A large part is removed from the circulation in the liver, where it undergoes conversion to vitamin A. Some of it is undoubtedly oxidized. Whether or not it has any function other than as a precursor of vitamin A is unknown.

The increase in the activity of the reticuloendothelial cells after the ingestion of excess carotene may explain why the high initial carotenemia tends to disappear later; the rate at which removal is accomplished is at first exceeded by the rate of intake but later increases to take care of the excess carotene. It has been suggested that hypothyroidism and diabetes interfere specifically with the conversion of carotene to vitamin A, but it is hard to see how this would lead to accumulation of carotene in the blood unless the mechanism of removal were also impaired. Several investigators have advanced the hypothesis that failure of oxidation of carotene is the determining factor, especially in diabetes and hypothyroidism. Until more is known concerning the part that oxidative processes play in the removal of carotene from the blood in the living organism, and not merely in vitro, this hypothesis can hardly be proved or disproved.

Carotenemia has been noted among Europeans living in the tropics, and Castellani and Chalmers mentioned a condition which they called ochridermatosis, which occurred only at sea level and disappeared when the patients were removed to higher altitudes. The diet was not mentioned. Sequeira saw what he considered a similar case in Africa apparently not dependent on diet and without hypercholesteremia. Improvement occurred only after the patient was given small amounts of thyroid. Bouin and Lévinson reported carotenemia in a group of patients with chronic malaria who had been inadequately treated.

Effects of Carotenemia.—Xanthosis Cutis: Carotenemia has been considered completely harmless, its only symptom being the development of the characteristic yellow color of the skin which generally disappears as soon as the responsible conditions have been corrected. Usually the yellow color varies with the level of carotene in the blood, but a close parallelism is not always present. A striking exception to the general rule is the absence of xanthosis cutis in persons with carotenemia with nephrosis.

(Clausen and McCord29k and personal observations). Histologic examination shows that the carotene is found mostly in the superficial horny layer of the skin and that its concentration becomes less the deeper one goes.40 The fact that it is present in sweat and sebaceous material has led to the hypothesis that its presence in the skin is dependent on this excretion and the subsequent rubbing of the carotene into the horny layer. Its predominant occurrence in those areas in which the horny layer is particularly thick or in which sweating is most marked (palms and soles, forehead, nasolabial folds, axillas and groins) would tend to bear out this theory.

2. Increased Serum Lipids: Anderson and Soley41 noted an increase in serum lipids and pronounced fall in basal metabolic rate in several California farmers who had eaten vegetables in large amounts. The liver was enlarged in 4 of the 9 patients. An increase in serum lipid was noted by two other observers42 but, in general, little attention has been paid to the blood lipids in carotenemia.

3. Harmful Effects: Some recent work throws doubt on the generally accepted harmfulness of carotenemia. Sequeira39 reported weakness, loss of weight and low blood pressure. He was speaking, however, of cases observed in the tropics in which diet was apparently not a factor; hence it is possible that the carotenemia was secondary to some underlying factor responsible for the whole condition. Anderson and Soley reported that the liver was enlarged in about half of their patients and that the removal of rose bengal from the blood was slower than normal.

A more certain example of harmfulness is furnished by a case recently reported by Henschen.43 A woman of 49 acquired a pica-like craving for carrots during an attempt to cure “anemia” with a vegetable diet. She ate 2 to 3 bushels a month (about 2 pounds [0.9 Kg.] a day), mostly raw, for six months, and a generalized xanthosis cutis developed. She also complained of paresthesias of the hands and feet. She was thin, pale, rather easily fatigued and subject to dyspnea. The liver and spleen were enlarged. The yellow color was general over the body, but the scleras were clear. Examination of the blood gave the follow-

ing data: The hemoglobin content was 57 per cent. Erythrocytes numbered 3,400,000 per cubic millimeter and leukocytes 5,300, with neutrophils 62 per cent, lymphocytes 28 per cent and monocytes 4 per cent. There was poor clot formation, but no estimation of the number of platelets was made. There was 0.347 mg. of carotene per hundred cubic centimeters of serum (normal 0.07 to 0.19). Serum xanthophyll was not increased. When carrots were removed from her diet, the patient slowly improved, though the number of white cells remained low. Later cataracts developed.

Reports of Earlier Cases of Dietary Carotenemia.—In the records of the Johns Hopkins Hospital there are 6 cases of carotenemia in which the diet alone either was or might have been responsible. This series is exclusive of cases of carotenemia occurring in the course of diabetes or nephrosis or of hypothyroidism, in which the low thyroid function is definitely the primary factor. They are included at this point because they have a bearing on the discussion of hypervitaminosis and because they confirm the hypothesis that carotenemia may not be as harmless as heretofore pictured.

Case 1.—The patient was a child of 16 months, who had recently come from California, where she had been indulged in oranges, the only source of carotene that she could be ascertained to have received in significant amount. She recovered promptly, and at no time did untoward symptoms develop.

Case 2.—The serum of this patient, also a child, was received for diagnosis. All that I can ascertain is that no harm resulted from the carotenemia and that the clinical diagnosis was made from the yellow color of the skin. It is unusual to see xanthosis cutis with the serum carotene as low as it was in this case.

Case 3.—Carotenemia was diagnosed in a well-to-do, asthmatic man who enjoyed vegetables in large quantities. No special studies were made, and the case is included only as one in which the patient was not harmed by the carotenemia.

Case 4.—A 38 year old clergymen had as his only complaints yellowness of the skin and loss of weight. He had been supplementing his diet with carrots and carrot juice for about seven years. When carrots were removed from his diet, he recovered rapidly.

Case 5.—This patient, a colored farmer who had lived largely on vegetables, especially spinach, was extremely undernourished. Low blood pressure, emaciation and extreme muscular weakness led to a first impression of hypopituitary cachexia (Simmond's disease). Later, hypothyroidism was suggested on the bases of the high serum cholesterol and low basal metabolic rate. On a diet of high caloric value he improved extraordinarily rapidly.

Case 6.—A well-to-do woman of 45, because of imagined idiosyncrasies to meat, eggs, milk and starchy foods, had lived largely on vegetables and fruits for a number of years. In addition to having carotenemia, she was markedly underweight, with low blood pressure.
and asthenia. Hypothyroidism was diagnosed on two occasions when she was in the hospital. She was greatly improved by a diet high in calories, given in the hospital.

The patients in the first 3 of these cases were symptomless and entirely unharmed by the carotenemia. In case 1, however, the serum lipids were well above the normal. The last 2 cases considered by themselves would be hard to evaluate; in case 5 the extremely inadequate diet might have caused the entire clinical picture, and in case 6 the impression of hypothyroidism was particularly strong and in addition the diet was inadequate. Certainly the cases in which there is evidence of harm were those in which the patient had taken the carotene-containing foods for a long time or had lived largely on diet may have caused the low blood pressure, and in case 4 the blood pressure was not excessively low. The high values for blood lipid and cholesterol and the low basal metabolic rate are definitely part of the picture of carotenemia, occurring as they did in Anderson and Soley's cases as well as in 3 of the 4 cases reported here in which the lipids were determined. A tendency to leukopenia also appears to be a characteristic, but one that may be absent; in the series I have reported it occurred in 2 of the 3 cases with symptoms (4 and 6), and it was present in Henschen's case. Anderson and Soley merely stated that the blood was normal, without reporting the actual counts.

Perhaps the most confusing aspect is the relationship of carotenemia to hypothyroidism.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, Sex</th>
<th>Source of Carotene</th>
<th>Date</th>
<th>Serum Carotene, Micrograms/100 Cc.</th>
<th>Serum Lipids, Mg./100 Cc.</th>
<th>Basal Metabolic Rate</th>
<th>Loss of Weight</th>
<th>Weakness</th>
<th>Hypo-ten-sion, Leukocytes, No./C.mm.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16 mo. F</td>
<td>Oranges</td>
<td>2/38</td>
<td>610</td>
<td>60</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Child</td>
<td>Unknown</td>
<td>Jan. 39</td>
<td>220</td>
<td>55</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>37 yr. M</td>
<td>Carrots</td>
<td>Oct. 36</td>
<td>...</td>
<td>...</td>
<td></td>
<td>0</td>
<td>0</td>
<td>8,500</td>
<td>Diagnosis made on appearance of skin</td>
</tr>
<tr>
<td>4</td>
<td>36 yr. M</td>
<td>Carrots and carrot juice for 7 years</td>
<td>9/32</td>
<td>600</td>
<td>60</td>
<td>441</td>
<td>-19</td>
<td>+</td>
<td>Symptomatic improvement on discontinuation of carrots and carrot juice</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>18 yr. M</td>
<td>Vegetables, especially spinach, principal source of food for 5 years</td>
<td>12/10</td>
<td>550</td>
<td>55</td>
<td>429</td>
<td>-45</td>
<td>++</td>
<td>8,500</td>
<td>Rapid improvement on high calory diet</td>
</tr>
<tr>
<td>6</td>
<td>47 yr. F</td>
<td>Vegetables and fruit principal source of food for 4 years</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>Elevated</td>
<td>-45</td>
<td>++</td>
<td>Considered to be hypothyroid on 2 occasions, but improved rapidly on high calory diet</td>
<td></td>
</tr>
</tbody>
</table>

Every symptom that has been mentioned as occurring with carotenemia except the loss of weight could occur in hypothyroidism. Only consideration of the fact that the diet came first and the symptoms followed will allow a correct evaluation to be made. A possible explanation of this similarity lies in the reported antagonism between carotene or vitamin A and thyroxin. According to this theory the symptoms of hypothyroidism may exist not only as the result of diminished activity of the thyroid gland, but as the result of "neutralization" of thyroxin by carotene or vitamin A.

Another point that must be emphasized is that it is the abnormal intake of carotene rather than the amount in the blood that is the cause of trouble. In conditions such as diabetes and nephrosis, in which carotenemia may occur without excessive intake, none of the symptoms cited are present. Apparently under ordinary condi-
tions carotene must be ingested in excessive amount for a long time or must form the major part of the diet to the exclusion of other constituents in order to be harmful.

**CLINICAL HYPERVITAMINOSIS**

*Factors Influencing Vitamin A of the Blood.*—Little is known of the factors leading to the increase of vitamin A in the serum, and that little has come principally from experimentation on animals.

1. **Diet:** Increasing the dietary intake of vitamin A beyond a certain optimum will increase the amount stored, but it is usually not possible to push the level of vitamin A in the blood above what might be called a normal maximum, except for a few hours after administration of a large dose. A child of 4 years who was given per comorph liver oil in large doses for resistant rickets received about 120,000 U. S. P. units of vitamin A every day for a month with no more than a minimal effect on her serum vitamin A, determined twenty-four hours after the last dose. Two infants were given 200,000 U. S. P. units of vitamin A a day for several weeks. There was a slight temporary rise in vitamin A in the blood, lasting about a week. Likewise, in rats ingestion of 2,500 U. S. P. units a day raised the level of vitamin A from 1 unit per cubic centimeter of serum to about 2 units, and, although a large amount was stored in the liver, the serum vitamin A fell to nearly its former level within two or three days after the high ingestion of the vitamin was discontinued. 44

2. **Level of Serum Lipids:** The conditions in which hyperlipemia occurs tend to be associated with increases in vitamin A as well as with carotenemia. Also, as in the case of carotenemia, the relationship is of a general nature and one must utilize pathologic extremes to be able to demonstrate it. 41 An important difference lies in the far more rapid removal of excessive vitamin A than of carotene from the blood. The postabsorptive curve of vitamin A is influenced by the level of serum lipid just as is that of carotene 42 but the specific removal of vitamin A in the liver effectively prevents prolonged accumulation in the blood, while the slower removal of carotene permits an accumulation which is also aided by the relatively higher solubility of the latter substance in the blood lipids. It seems likely also that the solubility in lipids is a less important factor in the case of vitamin A than of carotene. If vitamin A and lipids tend to vary together, it is because they are subject to similar influences. 45

The highest values for vitamin A seen in over 700 cases did not exceed 2.5 units per cubic centimeter except immediately after ingestion, even though the series included some cases with high levels of lipid (cases of nephrosis and 1 of myx edema). Following pneumonia there was a tendency for hyperlipemia to develop in some of the children observed; under these circumstances the vitamin A might temporarily reach a value of 3.5 units per cubic centimeter of serum (patients not receiving supplementary vitamin A). These levels were the highest seen with the exception of those in the case of vitaminosis reported here.

*Protection Against Hypervitaminosis.*—A factor of safety for the animals that rely on carotene for their source of vitamin A is the relative harmlessness of carotene. Also any damage which it does cause is apparently not permanent, and rapid and complete recovery is to be expected as soon as the excessive intake of carotene is stopped.

The facts just reviewed point to the existence of a mechanism for the maintenance of the level of vitamin A in the blood within certain limits. It seems highly significant that this mechanism exists in the case of the vitamin, which can produce toxic effects, and not in the case of its precursor, carotene, which appears to be relatively harmless. It is interesting that the dog, which apparently lacks this mechanism for the limitation of the level of serum vitamin A (personal observation), is the one animal thus far studied in which none of the toxic effects from vitamin A have been elicited. 106

Another protective mechanism is the storage of vitamin A in the liver, where it appears to be harmless. It is not the total amount of vitamin in the body that determines the presence of toxic symptoms but the ingestion of amounts large enough to overwhelm the ability of the liver to remove it from the circulation. 46 Seemingly it is possible to push the storage in the liver without limit, and no symptoms of intoxication are produced unless the daily dose is raised above the "toxic" limit. When vitamin A or carotene is given intravenously the excess is removed with great rapidity. 47 In this removal the cells of the reticuloendothelial system play a primary role, particularly the Kupffer cells of the liver. This

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has been shown by fluorescence microscopy \[48\] as well as by “blockade” experiments.\[49\] The increase in activity of these cells under the influence of overdosage with vitamin A may therefore be looked on as a factor in the defense against hypervitaminosis.

When excessive vitamin A is given to rats over a period of time, a rise in the level of serum lipid occurs, which, however, is temporary. This has been taken as evidence that one of the fundamental effects of vitamin A is on the metabolism of lipids, but that ordinarily the effect is adequately and promptly compensated for. When the vitamin is suddenly introduced in large amounts the compensatory process is temporarily overcome and a rise in blood lipid occurs. It has been suggested that this compensatory process involves increased activity of the thyroid gland.\[50\] Support for this idea comes from the demonstration of antagonism between vitamin A and thyroxin.\[51\] The continuance of the high content of lipid in the serum in the cases of carotenemia cited in this paper suggests that this compensatory factor may be more effective in the rat than in man.

**COMMENT ON THE CASE**

From this review of reports of experimental and clinical carotenemia and hypervitaminosis A, one obtains some insight into the significance of certain pathologic changes in the case which is reported. However, since final proof of the mechanisms involved is lacking, the interpretations which follow must be looked on as suggestions rather than as demonstrations of the manner in which excessive vitamin A acts.

**Abnormal Appetite.**—Whether or not it is justifiable to label as “abnormal” a liking for an article of food which most people would not eat by choice, there is no doubt that the child’s liking for halibut liver oil was a factor in the case which is reported. It is interesting that this desire for the oil was replaced by a desire for butter and carrots after the administration of the oil was discontinued, and that as the patient improved clinically he lost all such desires. Henschen’s patient with carotenemia had developed such an appetite for carrots that she was impelled to search garbage cans to satisfy her craving. Two of Hashimoto’s patients among Japanese peasants had an abnormal appetite for squash, the source of their carotene. Clausen and McCoord mentioned a case in which the patient had an abnormal craving for carrots; the serum carotene in this case was the highest in their series. These examples are cited to show that an abnormal appetite for carotene-containing foods may occur.

It is possible that the appetite existed first and was primarily responsible for the large intake, but it seems more probable that the increased intake was begun for economic or other reasons and that the abnormal appetite developed subsequently. Desire for some particular dietary constituent not infrequently results from the necessity of correcting a deficiency or some other condition, for example, the craving for salt in persons with adrenal insufficiency. It is conceivable that excessive vitamin A or carotene taken at first through economic necessity or zeal might give rise to changes that would create or increase the desire for the material that caused the changes. The change in desire from halibut liver oil to carrots and butter in our patient when use of the oil was stopped suggests that this was the case. It may be noted from table 1 that after the patient was discharged from the hospital the content of carotene in the serum rose for a short time to a definitely abnormal level, which confirms the history of increased intake of carotene.

**Hepatomegaly and Splenomegaly.**—The original impression of Gaucher’s disease was suggested by the presence of a large liver and spleen together with anemia of the hypoplastic type. The roentgenograms of the bones were not indicative of this condition except that the changes in the metacarpals and phalanges suggested the presence of a process replacing normal marrow with pathologic tissue. The increased storage of fat in animals subjected to intoxication with vitamin A suggests the possibility that such storage may have occurred in our patient; however, we have no direct evidence of this or of any reticuloendothelial proliferation, at least in the bone marrow, though such a proliferation may account for the enlargement of the liver and spleen. The improvement of the patient when ingestion of excessive vitamin A was stopped is evidence that vitamin A intoxication was primarily responsible for the clinical picture. It may be pointed out in confirmation that Henschen’s patient also had hepatomegaly and splenomegaly with a hypoplastic type of anemia, and that in the cases of carotenemia which I summarized the patients who had any symptoms tended to have leukopenia and a slight reduction in the number of red cells.

The idea that vitamin A and carotene are capable, under conditions that lead to accumulation in the blood, of causing a disturbance in the

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storage of lipids with certain features in common within the changes which occur in xanthomatosis, Gaucher’s disease or Niemann-Pick disease is an attractive one. However, the reported effect of vitamin A on reticuloendothelial proliferation in animals has not yet been thoroughly confirmed, nor has it been shown that the splenomegaly or hepatomegaly in clinical cases is actually due to

Increased "Vitamin A in Serum."—The vitamin A of the blood of our patient when first seen was at a level which has otherwise been encountered only at the height of the postabsorptive curve, four to six hours after a relatively large dose. Not only that, but it remained at a high level after all excess ingestion of vitamin A had been stopped and only slowly returned to normal over a period of six months. As stated previously, attempts to cause a rise in serum vitamin A in other patients to more than a limited extent or over more than a limited time have proved unsuccessful. While this paper was in preparation a child of 8 months was brought to the outpatient department after receiving 3 teaspoons of perco-

morph liver oil a day during a period of four months (corresponding to about 500,000 U. S. P.

units of vitamin A per day). The vitamin A of the serum was 110 U. S. P. units per hundred cubic centimeters and the total lipid 730 mg. per hundred cubic centimeters, both normal values. This case exemplifies the efficiency of the mechanism by which the constancy of the blood vitamin A is maintained and at the same time indicates that this mechanism in the patient whose case is reported here was seriously impaired.

In the discussion of the body’s protection against hypervitaminosis the role played by the reticuloendothelial cells in removing vitamin A and carotene from the blood was cited. If, as has been suggested, the cells of the reticuloendothelial system are made more active by an over-
dose of vitamin A the vitamin would be more, not less, effectively removed from the blood. The fact that in the case under discussion the vitamin was less effectively removed indicates either that the child had some defect in his reticuloendothelial response or else that intense, prolonged overdosage is capable of injuring this response. The only work that I could find bearing on this point is that of Ikegaki, who found that in early stages of overdosage with vitamin A liver function increased, whereas later it decreased; the functions dealing with removal of dye from the blood stream and with detoxification were particularly affected. In our patient, bromsulpha-

lein was removed normally but the serum bili-

rubin was consistently somewhat raised (1.6 mg. per hundred cubic centimeters). In Anderson and Soley’s cases of carotenemia, 5 of the 8 patients tested showed impairment of the ability of the liver to remove rose bengal from the blood.

A second possibility in this case is that the limit of the liver’s ability to store vitamin A was exceeded. While little is known of the capacity of the human liver, work on rats shows that when storage of vitamin A has been pushed to a high point the vitamin disappears with great rapidity when excessive intake is discontinued, supposed by oxidation or some other form of destruction. Whether or not prolonged administration of vitamin A could impair this mechanism for getting rid of amounts in excess of the storage capacity is not known. As I have pointed out, however, excessive storage has little influence on the level in the blood, so that it would be difficult to explain the continuance in this patient of a high level over a prolonged period after the intake of vitamin A was discontinued, especially since the total amount in circulation is only a minute fraction of the amount in storage.

Increased Level of Serum Lipids.—The increase in lipid in the blood in the patient under discussion was definite though not excessive. (The normal range is approximately 550 to 750 mg. per hundred cubic centimeters, though higher may be encountered in otherwise normal persons.) The gradual fall after excessive intake of vitamin A was stopped leaves no doubt regarding the causation. The level of carotene in the patient’s serum was not excessively high except on one occasion, as previously mentioned, just after his return home, when he had a craving for carrots and butter. It may be noted that on this occasion the content of lipids also increased slightly. A rise in blood lipids appears to be a significant part of the picture of hypervitaminosis A as well as of carotenemia. The cholesterol also takes part in the rise of lipids but in some cases, as in those reported by Anderson and Soley, the increase is not correspondingly great. The basal metabolic rate was not determined in the patient discussed with hypervitaminosis A, but it was decreased in most of my patients with caro-

tenemia. In fact, the picture of carotenemia resembles that of hypothyroidism to such an extent that a distinction may be difficult. Only the definite association of the condition with a vegetable diet and its disappearance as soon as the source of carotene was removed lead to a correct diagnosis of carotenemia. The explanation for the similarity between the two condi-
tions may lie in the vitamin A–thyroid antagonism to which reference was made previously, in which case the symptoms of hypothyroidism in carotenemia would be due to the presence of
an excess of thyroid antagonist and not to an actual diminution in the activity of the thyroid gland.

It was pointed out previously that the rise in lipids which occurs in animals subjected to continued excessive doses of vitamin A or carotene was a temporary phenomenon and that the return to normal levels was evidence of the development of a compensatory process. Wendt suggested that the compensation might involve an increase in thyroid activity.\textsuperscript{100} I have suggested that the diminution of the high levels of lipids in the patient reported on here might also indicate that the "compensatory" process is less effective in man than in rats. The fact that the dose required to elicit the lipid response in man is relatively far smaller than that for rats\textsuperscript{13} points in the same direction. If, as suggested, increased activity of the thyroid supplies the "compensatory" process, its relative failure in man might explain both the persistence of the high levels of serum lipid and the symptoms of hypothyroidism.

**Skeletal Abnormalities.**—The skeletal changes which occurred are difficult to evaluate, and the biopsy was of no aid. The speed of decalcification was in line with the observation that in animals decalcification of bones is one of the most constant effects of hypervitaminosis. The most outstanding features in the roentgenograms of the patient were the evidences of a more rapid epiphyseal development, the irregularities, the apparent stippled effect of the epiphyseal centers, the increased distance between epiphysis and diaphysis and the advanced development of carpal centers of ossification. Even two and a half years after the removal of excessive vitamin A the carpal centers were in advance of the patient's chronologic age. The child, however, has not grown unduly and at present is no more than at the upper limit of normal stature for his age. It may be mentioned that Wolbach and Bessey\textsuperscript{4} in a recent review stated the opinion that vitamin A acts to increase the rate of development of bone; however, they gave none of the evidence on which the opinion was based.

**Associated Abnormalities.**—Four other abnormal conditions present in this case are worth noting. (a) The rise in serum phosphatase depends on the activity of processes which also give rise to changes in the bones, and it is to be considered in relation to these. Phosphatase is also increased in diseases of the liver, and, as has been pointed out, there is evidence of hepatic damage in this case. (b) The low level of serum protein, especially of the globulin fraction, is probably of considerable significance, but it cannot be evaluated in the present state of knowledge. (c) Sparse, coarse hair was a prominent characteristic of the clinical picture. Loss of hair by rats subjected to vitamin A intoxication has been a prominent feature of some descriptions. In the patient, the return of hair of normal texture and distribution was almost the first sign of improvement. (d) Clubbing of the fingers was a striking feature of the clinical picture when the child was first seen. It was still present though less prominent after two and a half years. Its significance is not known, but it may possibly indicate damage to the liver, since clubbing of the fingers and toes is not infrequently observed in cirrhosis in children.

The question of complete recovery of the patient in the case reported is still open. Clinically the child is well and has remained so during the past two years. The only causes for anxiety are the continued presence of splenomegaly and to a less degree of hepatomegaly and the persistent advance in skeletal development. In Henschen's case splenomegaly was slow to disappear and leukopenia persisted for at least a year. In view of the magnitude and the duration (three years) of the intake of vitamin A it would be surprising if some permanent change had not resulted. My fear is not so much that there may be a progressive process still active as that there may have been some scarring of the liver that will later give rise to trouble.

**SUMMARY**

Severe hypervitaminosis A occurred in a boy of 3 years who had received about 240,000 U. S. P. units of vitamin A daily since he was about 3 months of age. The condition was characterized by hepatomegaly, splenomegaly, hypoplastic anemia, leukopenia, increased serum vitamin A, increased serum lipids, advanced skeletal development, clubbing of the fingers and sparse, coarse hair; it was accompanied with an abnormal appetite for halibut liver oil, the source of the vitamin. Most of the symptoms cleared promptly when the excess vitamin A was removed from the diet.

Experimental and clinical observations indicate the existence of a mechanism for the maintenance of a constant level of vitamin A in the blood, possibly related to the activities of the reticuloendothelial cells. No such mechanism seems to exist for carotene. The occurrence of hypervitaminosis A in this child indicates either that some defect existed in the system responsible for the protective reaction or else that intense, prolonged overdosage is capable of injuring the regulatory mechanism.

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