CAROTINEMIA

REPORT OF A CASE IN AN ADULT

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Under the term carotinemia, Hess and Myers [1] described the occurrence of a peculiar yellow discoloration of the skin of the body with the presence of carotin, the characteristic pigment of carrots, in the blood of children fed on a diet containing carrots. We wish to report a similar occurrence in an adult, a case in which we were able to establish the casual relationship between diet and pigmentation, and to identify the offending pigment chemically, in a relatively large amount, in the blood.

The yellow pigment carotin is not confined to carrots. It is included with xanthophylls under the general term carotinoids. They are widely distributed in nature, often in close association, and can be separated from each other on the basis of solubility. The yellow color of milk fats, corpus luteum and egg yolk, is due to carotinoids which are sometimes called lipochromes and again, lutein. Among human vegetable food stuffs they are found especially in spinach, lettuce, oranges and carrots. Palmer [2] and his associates have done splendid work in clearing up the problems of carotinoid pigmentation. They have shown conclusively that the natural pigment of egg yolk, body fat and blood serum of the hen is physiologically identical with the carotin and xanthophylls of plants, with the latter present in far greater proportion. In the cow, the coloring of milk fat, body fat, skin secretions, corpus luteum and blood serum is similarly due to carotinoids, but in contrast to the hen, the carotin is in excess with only traces of xanthophylls. They were able to produce almost colorless milk fat or egg yolks by feeding a diet poor in the respective characteristic pigment. Fat is the storehouse of carotinoids and the absence of these pigments explains the colorless fat of swine, sheep and goats. There is, therefore, a wide variation among species in their behavior toward these pigments. Analysis of the fat of human milk showed tinting with both carotin and xanthophylls in nearly equal proportions. They concluded that the pigment of human fat is, no doubt, identical with the pigment of human milk fat.

With the exception of the article of Hess and Myers and an editorial [3] reference, we have found no description in the English litera-

1. Hess, A. F., and Myers, V. C.: Carotinemia: A New Clinical Picture, J. A. M. A. **73**:1743 (Dec. 6) 1919.

2. Palmer, L. S., and Eckles, C. H.: J. Biol. Chem. **17**:191, 211, 223, 237, 245 (March) 1914; Palmer, L. S.: Ibid. **23**:261 (Nov.) 1915; **27**:27 (Oct.) 1916.

3. J. A. M. A. **74**:32 (Jan. 3) 1920.

ture of a case presenting pigmentation resulting from a diet rich in carotin. A number of articles have appeared in the German literature, especially by pediatricians, during the period of the war when food shortage necessitated a change to a more vegetarian diet. Kaupe [4] observed, in a childrens home, a large number of otherwise healthy children, who showed a marked yellow pigmentation of the skin of the face. Carrots were present in the diet of all those affected but not all the children who ate carrots showed the discoloration. When carrots were withdrawn from the diet, the color disappeared and could be brought back by adding carrots to the diet again. The observations of Kaupe were confirmed by Stoelzner [5] who had seen many similar cases which he called pseudo-icterus. Klose [6] also reported cases of carrot pigmentation, and thought that well nourished children were more prone to the affection, probably dependent on the affinity of the fats for carotinoids. Many years ago, following the use of carrot soup, Moro [7] had seen a yellow discoloration of the skin develop. The actual presence of carotin in the blood was not established by chemical tests in any of the above reported cases.

The condition is not confined to the early years of life. Umber [8] used the term "Diabetische Xanthose" to describe cases of marked yellow skin pigmentation which he had seen in diabetics. He had seen fifteen cases in all and thought that the color varied with the intensity of the disease. The blood, however, contained an ochre gold color, not due to bile, but extractable with ether. The term "Xanthosis Diabetica" was originally used by von Noorden [9] to describe similar cases in diabetics of skin pigmentation varying from a canary yellow to a deep orange gold. In commenting on the reports by pediatricians of pseudo-icterus following the feeding of carrots, Saloman [10] states that it corresponds entirely to the description given by Von Noorden and himself of xanthosis. He had seen many cases, usually in diabetics, but several times in entirely normal people. Spectroscopic examination of the blood serum showed absorption bands identical with those of carotin. Schuessler [11] observed a marked golden

4. Kaupe, W.: Hautverfärbung bei Säuglingen und Kleinkindern infolge der Nahrung, München. med. Wchnschr. **66**:330 (March 21) 1919.

5. Stoelzner, W.: Ueber Pseudoikterus Nach Mohrrübengenuss, München. med. Wchnschr. **66**:419 (April 11) 1919.

6. Klose, E.: Hautverfärbung bei Säuglingen und Kleinkindern infolge der Nahrung, München. med. Wchnschr. **66**:419 (April 11) 1919.

7. Moro, E.: München. med. Wchnschr., 1908, p. 1562; ibid. **66**:674 (June 13) 1919.

8. Umber: Diabetische Xanthose, Berl. klin. Wchnschr. **53**:879 (July 24) 1916.

9. Von Noorden: Internat. Dermatologenkongress, 1904.

10. Salomon, H.: Von Noorden's Handbuch der Pathologie des Stoffwechsels, Ed. 2 **2**:290; München. med. Wchnschr., May 23, 1919, p. 564.

11. Schüssler: Ueber Hautverfärbung durch Mohrrübengenuss, München. med. Wchnschr. **66**:596 (May 30) 1919.

brown (orange) pigmentation of the entire body, without involvement of the sclerae, in three men past middle life who had eaten heavily of carrots as a substitute for potatoes, which were scarce. He made no chemical analyses, and his only explanation for the phenomenon was the excessive ingestion of carrots.

In studies of the pigments found in human blood serum, Hymans van den Bergh and Snapper [12] found serums showing a high lipochrome content. In some of these cases, usually diabetics, a peculiar orange yellow color of the skin, without scleral involvement, was present. Buerger and Reinhart [13] studied a number of cases of xanthosis. They found that there was an increased quantity of lipochrome in the blood serum, that the xanthosis and the parallel increase of lipochrome in the blood came from the food and could be influenced by diet, and that the lipochrome corresponded in chemical and spectroscopic tests to the carotinoid group of pigments which are closely associated with chlorophyll in green plants. Hymans van den Bergh and Mueller [14] confirmed the observation of the dependence of blood lipochrome on the lipochrome content of food. They were able to increase the normally small and somewhat variable quantity of lipochrome in human serum by feeding a diet rich in green leafy vegetables and eggs, and they found increased values in the summer months when vegetables of this type are eaten more freely. The diet peculiar to diabetics leads to an increase of pigment in the blood, and, therefore, to the development of xanthosis. Carotin was found in excess of xanthophylls. They also estimated the lipochrome content of various organs in many diseased states and found a surprisingly high percentage in the suprarenals with lesser quantities in the liver, spleen, fat and blood in the order given. The lipochrome content of the organs seemed independent of the amount in the blood or of any particular disease.

The condition is apparently harmless as no symptoms are ascribed to it. Furthermore, Wells and Hedenburg [15] found no toxic effects in guinea-pigs from intraperitoneal injection and none of consequence on intradermal injection of carotin extracted from carrots, dissolved in olive oil, and used in relatively enormous doses. It is probable, that the carotinoids perform no useful physiologic function in the body.

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12. Hymans van den Bergh and Snapper: Die Farbstoff des Blutserums, Deutsch. Arch. f. klin. Med. **110**:540, 1913.

13. Bürger, M., and Reinhart, A.: Ueber die Genese der Xanthose diabetica, Deutsch. med. Wchnschr. **45**:430 (April 17) 1919; Ztschr. f. d. ges. exper. M. **7**: H 3.

14. Hymans van den Bergh and Müller, P.: Das lipochrome Pigment in Blutserum und Organen, Xanthosis, Hyperlipochromämie, Biochem. Ztschr. **108**:279 (May) 1920.

15. Wells, H. G., and Hedenburg, O. F.: The Toxicity of Carotin, J. Biol. Chem. **27**:213 (Oct.) 1916.

An abnormal pigmentation of the skin, therefore, has been seen to arise from a diet containing unusual amounts of carotinoids. The color is described as varying from a lemon yellow to a rich orange in well developed cases, and can easily be differentiated from jaundice by the difference in color and the fact that the sclerae are not affected. Some portions of the body may be more heavily tinted than others; the palms of the hands, the soles of the feet, the forearms, sternum, the nasolabial folds, cheeks and forehead are especially mentioned in some reports. There is apparently some variation in individuals with respect to the ease with which the pigmentation may develop; possibly being more likely to occur in well nourished persons. When the excess of carotin bearing food is removed from the diet, the skin resumes its normal color more or less slowly. It is reasonably certain that the xanthosis diabetica of the older writers is carotinemia without a correct interpretation having been made. Several observers had previously suspected, from spectroscopic study, the true nature of the serum pigments, but the demonstration of an increase of the carotinoid group of pigments in the blood serum, dependent solely on the same pigments in the food supply in these cases of pigmentation, is a very recent achievement. The condition produces no harmful effects.

REPORT OF CASE

History.—J. B., male, aged 35, bank clerk. Family and previous history unimportant. He was first seen in January, 1919, presenting the classical symptoms of diabetes mellitus which had been present in severe form for about two weeks. He was then on a restricted carbohydrate diet prescribed by his local physician. Physical examination showed nothing of importance aside from moderate emaciation. The urine contained a moderate amount of sugar and acetone bodies. Hemoglobin, 78 per cent. Starvation for twenty-four hours cleared up the glycosuria following which a fairly liberal diet was gradually established without its reappearance. He was taught how to test his urine for sugar and was sent home with instructions to report at intervals for examination.

The next visit was in April, 1919, at which time he called attention to a light yellow tinging of the skin which he and others had noticed. A correct explanation could not be given but a true jaundice was ruled out on the absence of symptoms, bile in the urine and discoloration of the sclerae. Examination of the eye grounds by Dr. Campbell of Minneapolis, showed no fundus changes, and the visual disturbance of which the patient complained was explained as astigmatism. In August, 1919, he was still sugar-free; the Wassermann was negative, and the blood showed a moderate secondary anemia. In November, 1919, he returned feeling well, with a fairly high carbohydrate tolerance and a blood sugar reading of 0.148 per cent. In February, 1920, sugar appeared in the urine with the blood sugar 0.18 per cent., after a fairly large carbohydrate intake.

He had not been seen for about a year when he reported for examination in January of this year. During the entire period since he first presented himself many urinalyses by himself (almost daily) and our laboratory, showed no sugar, except when determining tolerance. Acetone bodies had been consistently absent. He had held his weight and strength and his general condition was excellent. In his correspondence he referred from time to time to the yellow color which he had already called attention to in one of his early visits.

Examination.—His appearance was certainly very striking. There was a high grade, diffuse, generalized, bright orange yellow pigmentation of the skin of the entire body, varying somewhat in its intensity of distribution, being especially vivid in the palms of the hands. The sclerae were normal. There were some dirty brown chloasma-like patches on the skin of the upper abdomen. He stated that the yellow color would last only a few days, sometimes three; his wife might also notice the heightened color and then it would suddenly disappear. This seems to us to be faulty observation as it had been present for many months and did not behave in this manner while under direct observation. He had no abdominal pain and no discomfort whatever but worried constantly about his unusual appearance as he was fearful that it meant some serious derangement. The blood sugar was 0.167 per cent. The urine was free from sugar, acetone, diacetic acid and bile pigments. Blood examination showed hemoglobin, 73 per cent.; erythrocytes, 4,475,000; leukocytes, 5,250. Differential count: polymorphonuclears, 57.5 per cent.; lymphocytes, 33 per cent.; large mononuclears, 5 per cent.; transitionals, 2 per cent.; eosinophils, 2 per cent.; basophils, 0.5 per cent. Inquiry showed that he had eaten heavily of cabbage and carrots and scarcely ever ate any other vegetables.

A diagnosis of carotinema was made and carrots were eliminated from his diet immediately. He was kept under observation for a period of six days during which a perceptible fading of the color occurred. About 20 c.c. of blood were drawn by venipuncture. A small amount of the blood was allowed to coagulate in a test tube, and the supernatant serum showed a bright golden yellow color (Fig. 1) which contrasted strongly with the straw color of normal serum (Fig. 2).

The remainder of the blood was oxalated and sent to Leroy S. Palmer, associate professor of agricultural biochemistry of the University of Minnesota, whose brilliant researches with carotin have been mentioned previously. His report reads:

> I have examined the sample of blood from the case of suspected carotinemia and beg to report as follows: There is no question regarding the presence of carotin in relatively large amounts in this blood, the serum color being due almost exclusively to this pigment. It is likely that traces of xanthophylls, the other class of carotinoids, are present also. This being the first sample of human blood I have had an opportunity to examine for carotinoid pigments, I took occasion to obtain an approximate estimation of the amount of pigment present. So far as I am aware, no measurement of carotinoids in human blood has heretofore been made, although a procedure for the determination of these pigments in other materials has been worked out. The result of the quantitative determination showed approximately 0.00057 gm. carotin per 100 c.c. of blood. This is, of course, a very small amount. However, carotin is a very intense pigment. Just how intense it is may be judged from the fact that butterfat from cows on fresh pasture grass contains on the average 0.025 gm. carotin per kilogram of fat. Assuming 5 per cent. blood in the human body, an individual weighing 75 kg. with 0.00057 gm. carotin per 100 c.c. of blood would have sufficient carotin in the entire blood to color about 1 kg. of "June" butterfat. I thought these figures might interest you.
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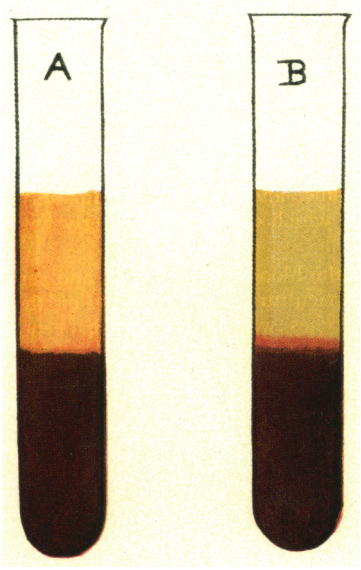
> Permit me to say a word regarding the application of this examination to the case in question. It is only fair to point out that the finding of carotin in this blood is not necessairly a sure criterion of the carotinemia suspected. Carotin is unquestionably a normal constituent of human blood, the amount depending on the character of the diet. Carotinoids have already been reported in human blood from individuals presumably not suffering from carotinemia. I have found the pigments to be normal, although of varying constituence, in human milk fat. Human adipose tissue is notoriously yellow, as you know, due to the same pigments. The only sure index of the carotinemia suspected will be the disappearance of the pigment from the skin, at least so it seems to me, now that the source of the pigment has been removed. This will be slow, judging from my experience with animals and the cases reported by Hess with children. It might be of interest to examine the blood again.

After being on the carrot-free diet for one month the patient wrote: "The yellow is very nearly gone, the face and the rest of the body is clear. The palms of the hands show a trace of it yet. I am getting along fine." After two months he wrote: "The yellow color is very nearly gone but there is a trace of it left yet on the inside of my fingers."



A, orange yellow color of serum of patient, J. B. B, straw color of normal serum for comparison.

SUMMARY

We report a case of marked orange yellow skin pigmentation, most intense in the palms of the hands, without involvement of the sclerae, in an adult with moderately severe diabetes. Carrots had formed a heavy component of the previous diet. The blood serum showed a bright golden yellow color which was chemically demonstrated to be due to carotin. The urine showed no bile pigments, and withdrawal of the carrots from the diet caused a disappearance of the pigmentation.