IDIOPATHIC HYPERLIPIDAEMIA

REPORT OF A CASE STUDIED WITH RADIOACTIVE IODINE-LABELLED FAT

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The diagnosis of hyperlipaemia is made when the total serum lipids exceed 1 g./100 ml. (Holt, 1954). Hyperlipaemia may be associated with disorders of carbohydrate metabolism as in diabetes mellitus and von Gierke’s disease; with liver damage due to hepatitis or poisoning with carbon tetrachloride, chloroform or phosphorus; with renal disease in ‘nephrosis’ and renal vein thrombosis; and with anoxia, anaemia, pancreatitis and hypothyroidism. A marked and persistent hyperlipaemia may be found unassociated with other conditions and is then known as idiopathic hyperlipaemia. Less than 50 cases of this type have been described in all age groups, but attention has been drawn to the condition by recent reports (Joyner, 1953; Gaskins, Scott and Kessler, 1953; Malmros, Swahn and Truedsson, 1954; British Medical Journal, 1954). A child with idiopathic hyperlipaemia is described below, together with studies with radioactive-iodine-labelled fat designed to try to find the cause of the abnormality.

Case Report

Alan, a 7-year-old boy, was admitted to the Children’s Hospital, Sheffield, at the end of 1954. When younger he had had rubella, whooping cough and scarlet fever. Seven months before admission he had infective hepatitis. The illness began with nausea and anorexia. He became jaundiced and his stools were pale and his urine was dark. After a month’s bed rest at home he apparently recovered completely.

During the previous two years he had had six attacks of vague central abdominal pain and fever. Each attack lasted about 24 hours and no cause had ever been found. He was admitted to hospital on this occasion with acute tonsillitis. Penicillin was given and the tonsillitis rapidly subsided.

Examination showed Alan to be a well-developed boy of average intelligence. The liver was easily felt two fingerbreadths below the costal margin and it was smooth and firm but it was not tender. The spleen was also firm and extended an equal distance below the left costal margin. The optic fundi showed the typical picture of lipaemia retinalis (Fig. 1). Xanthomata were not found.

When blood was drawn for liver function tests the serum was noted to be like cream. The total serum lipids were 4 g./100 ml. The excess lipids were neutral fat. The serum cholesterol was 237 mg./100 ml. Foam cells formed 1·6% of the bone marrow.

The full blood count and urine analysis were normal. The serum bilirubin was 0·5 mg./100 ml., the alkaline phosphatase 6·8 units (Jenner and Kay) and the serum proteins were albumin 3·2 g. and globulin 4·0 g./100 ml. Radiography did not show intra-abdominal calcification and the subcutaneous tissues were of normal thickness.

Alan was thought by his parents to be the weakling of the family. His parents and sisters did not show
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clinical evidence of hyperlipaemia and their serum lipids were:

Father . . . . . 360 mg./100 ml.
Mother . . . . . 540 mg./100 ml.
Sister (4 years) . . . . 730 mg./100 ml.
Sister (15 months) . . . . 670 mg./100 ml.

The hyperlipaemia persisted whilst Alan had a normal diet. The highest level of the serum lipids was 7·7 g. Within 48 hours of giving a diet containing less than 5 g. of fat a day the retinal vessels appeared normal and a day later the serum lipids had fallen to 1 g./100 ml. The size of the liver and spleen did not alter during a week on this very low fat diet nor did they change over the period of a year on a diet containing about 15 g. of fat per day.

Investigations with Radioactive Iodine

(I131)-labelled Fat

The basis of the investigations performed lies in the fact that during the metabolism of radioactive iodine-labelled fat the iodine is liberated and appears in the urine and the thyroid gland. If the thyroid gland is 'blocked' by the previous administration of potassium iodide then the radioactive iodine appearing in the urine indicates the quantity of fat that has been metabolized. This method has been used in the Department of Pharmacology of Birmingham University (Pover, Frazer and Sammons, 1955).

Olive oil was iodinated with the isotope I131. This iodinated oil was then incorporated into a quantity of butter fat as carrier. Two small portions of approximately 5 μc. of radioactive fat were weighed accurately on to rice paper. One portion was the test dose and was eaten on the rice paper. The other portion was dissolved in 50 ml. of a mixture of toluene, 3 parts, and chloroform, 1 part. A 1 in 100 dilution of this solution was made with the same solvent. The radioactivity of this standard solution was counted and from this the radioactivity of the dose given was calculated.

Alan had been receiving a consistent diet for at least five days before each test. The radioactivity of his urine was measured to ensure that there was no residual activity from previous tests. Four 0·1 g. doses of potassium iodide were given at equal intervals during the 24 hours before the test. At the start of each test a specimen of venous blood was drawn for the estimation of the serum lipids, the patient emptied his bladder, and then the test dose of fat was given on an empty stomach. Thereafter all the urine voided was collected for four days. The urine was preserved with toluene. The radioactivity of each 24-hour specimen of urine was counted, and the results, after correction for decay, were expressed as a percentage of the activity of the test dose.

Three tests were performed. In the first test the patient was on the normal ward diet, with a fat content of approximately 45 g. per day. The second test was with a diet containing not more than 5 g. of fat per day. In the third test the fat content of the diet was approximately 15 g. per day. Table 1 shows the weight and radioactivity of the test doses and standards, the fat content of the diets and the serum lipid levels at the start of each test.

Results

The results obtained are shown in Table 2. The results obtained by Sammons and Pover in a normal child using the same method are included for comparison. In the three tests upon the patient there is a similar pattern of excretion of radioactive iodine in the urine. Between 22% and 46% of the total dose was present in the urine within 24 hours and between 47% and 69% within 48 hours. Up to 10% of the total dose appeared in the third 24-hour period, but thereafter much smaller amounts were present. In tests 1 and 3 more than 75% of the test dose had appeared in the urine after 96 hours. In test 2 57% of the test dose had been detected after 96 hours. In the normal child 12% of the test dose was detected after 24 hours, 58% after 48 hours and 70% after 96 hours.

Discussion

The cases of idiopathic hyperlipaemia in children that have been reported present a characteristic
clinical picture. Joyner (1953) has pointed out that the features are not as evident in the adult cases. There are often attacks of abdominal pain and fever. The liver and spleen are enlarged. The serum is milky and when the serum lipids exceed about 3.0 g./100 ml. the retinal vessels appear white (Davies, 1955). The patient reported showed all these features. In addition his parents looked upon him as the weakling of the family. This frailty may be part of the clinical picture in children, for it is mentioned in half the case reports (Opitz, 1935; Franklin and Avery, 1937; Holt, Aylward and Timbus, 1939; Bernstein, Williams, Hummel, Shepherd and Erickson, 1939; Goodman, Shuman and Goodman, 1940; and Harsslof, 1948).

The illness seven months before the patient was admitted to hospital was probably hepatitis. This probably did not cause the hyperlipaemia as such tests of liver function as the serum bilirubin, the alkaline phosphatase and the plasma proteins were normal. The flocculation tests of liver function were found to be unreliable in the presence of hyperlipaemia.

In the case reported there was no family history of hyperlipaemia, but it has been reported in other cases (Holt et al., 1939; Levy, 1946; Bruton and Kanter, 1951; Movitt, Gerstl, Sherwood and Epstein, 1951; Gaskins et al., 1953; Malmros et al., 1954).

Aetiology

Holt et al. (1939) suggested that the attacks of abdominal pain and fever were due to the rapid accumulation of fat in the liver and spleen. In their patient the attacks occurred when the serum lipids exceeded 8 g./100 ml., and they were associated with further enlargement of the liver and spleen. This variation in the size of the liver and spleen was not seen in the present case but the lipids did not reach quite such high levels.

The liver biopsy studies of Koszalka and Levin (1950), Movitt et al. (1951), and Bruton and Kanter (1951), and the necropsy reports of Chapman and Kinney (1941) and Thannhauser (1950) showed that there may be a considerable accumulation of fat in the liver. The appearances suggested passive accumulation of fat rather than defective metabolism of fat by the liver.

One case of idiopathic hyperlipaemia has been reported by Goodman et al. (1940) in which there was an absence of lipase in the serum. This was not found in the cases reported by Bloomfield and Shenson (1947), Thannhauser (1950), Bruton and Kanter (1951) and Joyner (1953). The serum lipase was not estimated in the present case.

Holt et al. (1939) suggested that fat metabolism in their patient was normal because she had a normal respiratory quotient and when starved she developed ketosis promptly and normally. Thannhauser and Stanley (1949) carried out original experiments with radioactive iodine-labelled fat and maintained that idiopathic hyperlipaemia was due to a decreased utilization of fat by the tissues. Twelve adults were studied. Ten were normal and two had idiopathic hyperlipaemia. These patients were given olive oil tagged with radioactive iodine $^{131}I$ and the radioactivity of the serum, urine and thyroid gland was measured. The total activity in the urine and thyroid gland was thought to represent the fat that had been metabolized. In all the patients the peak of activity in the serum was reached between three and six hours but in those with hyperlipaemia the peak level was two to five times higher than in the normal patients. The disappearance of activity from the serum was prolonged in the patients with hyperlipaemia as compared with the normal patients. The rate of metabolism of the labelled fat as measured by the $^{131}I$ in the urine and thyroid gland was lower in those with hyperlipaemia than in the normal adults during the early hours of the test, which is the period covered by the graphs of the results. This result may have occurred because during this period the radioactive iodine was accumulating in the serum.

Hahn (1943) showed that alimentary lipaemia could be reduced or abridged by the injection of heparin. The agent in the serum following an injection of heparin which is responsible for this phenomenon has become known as the clearing factor. Engelberg (1955) has reviewed the knowledge of this factor. Absence of the clearing factor would give rise to hyperlipaemia, but Lever, Herbst and Lyons (1955) concluded that so far there was insufficient evidence to warrant the conclusion that this was the cause of idiopathic hyperlipaemia.

Present Investigation

Thannhauser and Stanley (1949) studied adults and employed larger doses of radioactive material and a technique different from the present investigation. It is not feasible, therefore, to compare their results with those obtained in this study. The results reported here suggest that delayed metabolism of fat was not the cause of the hyperlipaemia. As judged by these few results the general pattern of metabolism was similar in the patient and in the normal child. In tests 1 and 3 the proportion of the total dose of radioactivity appearing in the urine in the first 24 hours was considerably greater in the normal child. There are too few observations to justify the conclusion that in these tests the meta-
bolism of fat was more rapid than in the normal child, but it would seem unlikely that there was a delayed fat metabolism.

In test 2 less of the total dose of activity appeared in the urine than in either tests 1 and 3 or in the normal child. This test was done when the patient was taking an almost fat-free diet, and the serum lipids were relatively low. The result observed may have been due to an increased retention of fat in the serum in this instance.

These observations do not support the theory of Thannhauser (1950), but would be in accord with an absence of the clearing factor. Grossman (1954) has described how the clearing factor can be estimated in human plasma and it is hoped that it will soon be possible to study this factor in the patient reported.

TREATMENT

Both in this patient and in most of the other reported cases there was a prompt and appreciable fall of the serum lipids following a low-fat diet. Bruton and Kanter (1951) showed by liver biopsy studies on their patient that after a few days on a low-fat diet most of the fat accumulated in the liver had disappeared. It would seem to be reasonable, therefore, to prescribe a low-fat diet for these cases. This seems to relieve the attacks of abdominal pain. Ahrens (1954) has reported recent studies on the patient originally described by Holt et al. (1936). She had reached 29 years of age and enjoyed reasonably good health. The liver and spleen were not now enlarged and occasional attacks of abdominal pain were thought to be due to lapses in the low-fat diet. Malmros et al. (1954) and Lever, Herbst and Hurley (1955), however, have stated that atherosclerosis may be a serious long-term problem and they recommend the use of very strict diets. The patient reported here was able to tolerate a low-fat diet which kept him free from attacks of abdominal pain, but when the fat content was reduced further in an attempt to obtain normal serum lipid levels, he refused to keep to the diet. Lever, Herbst and Hurley (1955) have suggested that heparin should be used in conjunction with a low-fat diet to keep the serum lipid level as low as possible. An injection of heparin may be justified to hasten the lowering of the serum lipid level during an attack of abdominal pain. The routine use of this drug would probably not be tolerated, and, as heparin is a drug which is not free from hazards, such a course is probably not justified.

Holt et al. (1939) studied the action of lecithin, choline, thyroxin, insulin, lipocine, anterior pituitary factor and liver extract but failed to observe any response. Gaskins et al. (1953) used cortisone and A.C.T.H. but the results were variable.

A moderately low-fat diet within the limits tolerated by the patient would seem a reasonable recommendation for these cases at the present time.

Summary

The case of a 7-year-old boy with idiopathic hyperlipaemia is recorded.

Studies with radioactive-iodine-labelled fat upon the patient are compared with similar studies on a normal child. There was no evidence of a delay in the metabolism of the labelled fat in the patient.

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