EFFECTS OF PROLONGED USE OF EXTREMELY LOW-FAT DIET ON AN ADULT HUMAN SUBJECT [1]

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That some animal species are unable to synthesize linoleic and other highly unsaturated fatty acids and that these particular substances are essential for the proper nutrition of rats are observations which have been firmly established by the work of several investigators (Burr and Burr, '29; McAmis, Anderson and Mendel, '29; Evans and Lepkovsky, '32). Young animals placed on a diet extremely low in fat soon manifest several characteristic abnormalities, namely, retardation or complete cessation of growth, severe dandruff, scaliness of the feet and tail, hematuria and premature death. They also exhibit abnormal respiratory quotients. Administration of very small quantities of the essential unsaturated fatty acids or their esters results in the resumption of growth and in the rapid disappearance of all signs of the fat-deficiency disease. No such beneficial effects follow the ingestion of saturated fatty acids even in large amounts.

Very little is known regarding the dietary requirements of the human subject for unsaturated fatty acids. Mention can be made of but two published reports pertaining to the use of nearly fat-free diets by human subjects. Van Gröer ('19) maintained two infants on a diet extremely low in fat over a period of several months. Although not ideal, the growth

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of these infants was fairly good. However, both developed rickets, due to the lack of the fat-soluble vitamin D in the special diet. One of them also developed a generalized eczematous eruption of the skin. The latter complication was regarded with surprise by the author, because it occurred in spite of a regimen which was considered at the time to be ideal for the treatment of eczema. When re-examined some months after resumption of a complete diet, both infants were found to be essentially normal. Of three infants maintained on extremely low-fat diets by Holt and his associates ('35) one developed marked eczema. This subject experienced a clinical remission when fat was added to the diet, but again became eczematous when the low-fat diet was resumed. More recently two somewhat older infants were kept under observation at the University of Minnesota Hospital for 10 weeks on a diet extremely low in fat, though complete in other respects. During this period they developed no evidence of rickets and no skin manifestations other than repeated mild attacks of impetigo. However, studies of their blood lipids showed a moderate decrease in the degree of unsaturation of the serum fatty acids, similar to that found by Hansen and Burr ('33) and by Hansen and Brown ('37) in rats suffering from the fat-deficiency syndrome and that reported by Hansen ('37), by Faber and Roberts ('35) and by Schornstein ('37) in infants with severe eczema.

So far as we are able to ascertain, there is no record of any normal human adult's having been restricted for an extended period of time to a diet extremely low in fat. The present investigation was undertaken, therefore, to determine the effect on a healthy man of a diet practically devoid of fat. One of us volunteered to serve as the experimental subject. Preliminary examinations proved him to be an essentially normal adult, except for a slight elevation of blood pressure and a partial loss of one extremity. There was no indication that these disabilities would interfere with the value of the study. Observations were repeatedly recorded over a period of 6 months regarding the following factors: subjective feelings, objective clinical changes, body weight, basal metabolic

rate, respiratory quotients, carbohydrate tolerance, serum lipids, blood count and urinary findings.

MATERIALS AND METHODS

Special 'fat-free' diet

The diet was limited to sucrose, potato starch, baking powder, sodium chloride, ferric citrate, viosterol, carotene (vitamin A), orange juice, citric acid, anise oil, liquid petrolatum and milk practically freed of its fat. The daily protein intake was derived from 3 quarts of the specially defatted milk, taken as such, and the cottage cheese made from an additional quart of the same milk. Sucrose provided the bulk of the carbohydrate allowance but was supplemented by a biscuit made from potato starch, skimmed milk, baking powder, salt and mineral oil. The mineral oil was added to serve as shortening and to prevent constipation. Daily supplements of 10 mg. of ferric citrate, 2.5 mg. of carotene, 0.02 cc. concentrated viosterol in oil (8000 U.S.P. units vitamin D) and the juice from one-half of a large orange were given to insure an adequate supply of iron and of vitamins. That the diet was of the extremely 'low-fat,' rather than the 'fat-free,' type was recognized when the experiment was planned, but experience with crude diets (Burr and Brown, unpublished data) in studies on the rat had shown this to be satisfactory for our purpose. The chief source of fat in the diet was the skimmed milk. Periodic analyses of this milk as specially prepared showed it to have an average fatty acid content of less than 0.08%. This type of fat (butterfat) has been found to be of such low protective or curative value for rats on a fat deficient regimen that the 2 gm. contained in the daily diet of our subject was not considered sufficient to affect seriously the experiment. As potato starch contains only minute traces of fat, the small amount fed was likewise considered unimportant. A uniform consumption of food, providing 2500 calories daily, was maintained throughout the experiment. The sugar was taken in the form of a syrup with citric acid or anise added for flavoring. Frequent small meals were

found to be most satisfactory. The syrup was taken at hourly intervals from the time of rising until the time of the evening meal. The orange juice was taken at bed time. Cottage cheese with the biscuit and milk comprised the evening meal. It was calculated that a rat, consuming this diet in proportion to its caloric requirements, would receive less than 4 mg. of fat daily. This amount would be equivalent to approximately 1 drop of oil per week. In order to check the diet as to its effect on experimental animals, a group of twelve rats was placed on a mixture of potato starch and sucrose, supplemented by the specially skimmed milk given ad libitum. They

TABLE 1

Average growth of test rats maintained on the experimental diet as compared with that of control rats on normal stock diet

AGE	RATS ON LOW-FAT DIET	RATS ON NORMAL DIET
days	*Weight in grams*	*Weight in grams*
28	52	49
56	106	124
84	140	164
112	155	190
140	159	195
168	166	200
196	167	210
224	167	215
252	160	218

developed all of the characteristic symptoms of the fat deficiency syndrome in approximately the same time and with the same degree of severity as recorded for rats on Burr's diet 550B. The retardation in their growth is shown in table 1 in which their average weights at different ages are compared with those of control animals on a regular stock diet.

Methods used

The serum lipids were determined on fasting blood specimens by the oxidative methods of Bloor ('28). The iodine absorption capacity of the serum was determined by the pyridine sulphate dibromide method (Yasuda, '31). The linoleic

and arachidonic acids were determined by the technic described by Brown and Hansen ('37). One set of determinations of the serum lipids was made by the method of Wilson and Hansen ('36) 2 months after the normal diet was resumed. Standard methods were used for counting the erythrocytes and leucocytes of the blood and for examining the urine and stools. The same scale and mercury manometer were used throughout for determining the body weight and the blood pressure. The basal metabolism was determined by the ordinary indirect technic, and the respiratory quotients by the closed chamber method. Routine urinary and physical examinations were made at weekly intervals.

RESULTS

The results of the study are presented below.

Clinical data

The subject remained clinically well throughout the entire period of observation, not having even a common cold. There was never any itching of the skin nor pain. At no time did any of the food ingredients [2] become distasteful. One of the most noticeable subjective effects of the diet was the marked absence of fatigue. The somewhat tired feeling usually experienced after a day's work in the laboratory disappeared within a few days from institution of the diet. From childhood the subject had suffered from frequent attacks of migraine. These had been occurring at intervals of 7 or 8 days immediately before the present experiment was begun. After being 6 weeks on the diet, he observed that these periodic attacks of headache had subsided completely. Strangely enough, they have never recurred.

The complete physical examinations, made 1 week apart just before the experiment was begun, revealed no definite abnormality other then a mild degree of arterial hypertension.

[2] The authors wish to express their gratitude to Margaret Day Hansen for her invaluable assistance in preparing the fat-free diet.

It was particularly observed that the skin and mucous membranes were clear and soft. The only demonstrable physical changes resulting from the diet, as determined by regular weekly examinations were a moderate loss of body weight and a decrease in blood pressure. Blood pressure readings, taken when the subject was on a normal diet, varied between 140 to 150 mm. of mercury systolic and 95 to 100 diastolic, values which were regarded as being definitely higher than normal. There was a distinct decrease in the blood pressure after institution of the fat-free diet, the minimum values being obtained 4 to 5 months after the diet was started. Readings at that time remained quite consistently around 130 mm. of mercury systolic and 85 to 88 diastolic. Several months after the low-fat diet had been discontinued, the blood pressure had again risen to its former level.

There was a gradual decrease in weight during the first 3 months from 152 pounds (69.1 kg.) to 138 pounds (62.7 kg.). The weight thereafter remained about the same for nearly 3 months, that is, until the special diet was discontinued. This decrease in body weight in spite of a supposedly adequate caloric intake is of special interest. Unfortunately, however, the exact composition of the weight loss could not be determined.

Energy metabolism

The basal metabolic rate before and several months after the experimental period varied between —9 and —12% on four occasions, whereas it was found to be —2% just before the low-fat diet was discontinued. The respiratory quotients showed a distinct alteration. One of the most striking effects of low-fat diet on the rat is the rise in respiratory quotient after a meal. A similar tendency was found in the case of our human subject. During the sixth month of the experimental diet the following respiratory quotients were obtained: 1.03, 1.11 and 1.14. To attain these quotients it was necessary to starve the subject overnight and then give him a liberal supply (over 2000 calories) of the sugar-milk diet within the

course of 2 hours. Two hours later the maximum quotient was reached. Using the same technic the highest quotients reached before and after the low-fat experimental period were 0.99 and 0.97. It would seem, therefore, that in this respect the human subject reacts to a low-fat diet in the same way that the rat does.

Blood constituents

The data on the serum lipids are presented in table 2. It is apparent that the iodine number of the total fatty acids was definitely lowered as a result of the fat-poor diet. The total drop in iodine number from an average of several preliminary determinations was approximately 30. There was

TABLE 2

Serum lipids of experimental subject on normal diet and on low-fat diet

DATE	IODINE ABSORPTION	CHOLESTEROL	T.F.A.	TOTAL LIPIDS	I.N. OF T.F.A.
		Normal control diet			
	mg. per 100 cc.	*mg. %*	*mg. %*	*mg. %*	
11–23–33	664	252	402	654	124
12– 1–33	775	252	504	756	121
		Low-fat diet			
1–26–34	753	298	607	899	92
2–10–34	799	228	705	933	92
5–20–34	643	206	538	746	94

no essential change in the serum cholesterol as a result of the change in diet. However, the total fatty acid values increased somewhat, especially in the early part of the special dietary period. A determination of the serum lipids by the microgravimetric technic of Wilson and Hansen ('36) 2 months after resumption of a normal diet gave essentially normal values as follows: unsaponifiable fraction, 305.0 mg. per cent; total fatty acids (saponifiable fraction), 449.0 mg. per cent; average molecular weight of total fatty acids, 293; iodine number, 97, with 1.23 double bonds per molecule of fatty acid. This value for the iodine number of the total fatty acids is within the normal range as determined by this method.

The finding of a fall in the degree of unsaturation of the serum lipids on a low-fat regimen tends to confirm for the human subject the observations of several investigators regarding various other species of animals. Hansen and Burr ('33), Williams and Maynard ('34), and Hansen, Wilson and Williams ('36) found the iodine numbers of the serum lipids to be definitely decreased by low-fat diets in rats, goats and dogs, respectively. Hansen and Brown ('37) observed that small quantities of unsaturated fatty acids caused a regression of the fat deficiency symptoms well in advance of an appreciable change in the iodine number of the serum fatty acids.

Before the special diet was given to our subject, the values for both arachidonic acid and linoleic acid of the serum were similar to those found in other normal subjects by Brown and

TABLE 3

Arachidonic and linoleic acid content of serum of experimental subject on normal diet and on low-fat diet

DIET	ARACHIDONIC ACID	LINOLEIC ACID
	per cent of T.F.A.	*per cent of T.F.A.*
Normal (11–30–33)	3.2	5.7
Low-fat (for 6 months)	1.87	3.2

Hansen ('37). Tängl ('30) reported normal ox blood to contain arachidonic acid to the extent of 5 to 10% of the total fatty acids. We have been unable to find any other work dealing with this phase of the blood lipid picture. The finding, as shown in table 3, of a marked drop in the content of both arachidonic and linoleic acids in the case of our subject confirms the previously mentioned observation of a drop in the iodine number of the total fatty acids of the serum as a result of the low-fat regimen. No other information is available concerning the effect of diet on these individual highly unsaturated fatty acids of the blood. It may be mentioned that Brown and Hansen ('37) found the content of both arachidonic acid and linoleic acid to be significantly decreased in active infantile eczema, as determined on pooled lipid extracts from many samples of blood taken from patients with

this disorder. The values found for the eczematous infants were of approximately the same magnitude as those found in the case of this subject after he had remained for some months on the low-fat diet. The change in the serum lipids in eczema, however, has not been related to use of a low-fat diet in the subjects studied.

Other blood constituents showed no significant change. The fasting blood glucose remained normal and the sugar tolerance curve was found to be normal on two occasions toward the end of the study. The increase in blood sugar following the oral administration of glucose was accompanied by the normal phenomenon of a decrease in the level of the inorganic phosphorus of the plasma. Fasting values of the inorganic phosphorus on two occasions during the experimental period were 3.43 mg. and 2.64 mg. phosphorus per 100 cc. of plasma, respectively. Six months after the resumption of the normal diet, the fasting inorganic phosphorus of the plasma was 4.2 mg. per cent. The serum calcium level was uninfluenced by the special diet, remaining throughout the entire period around 10.0 mg. per cent. The total proteins of the serum were found to be 6.98 gm. per cent while on the normal diet and 8.06 gm. per cent on the low-fat diet. Corresponding values for the non-protein nitrogen of the serum were 29.4 and 32.1 mg. per cent on these occasions.

No definite morphological change occurred in the blood, other than a tendency to leucopenia. The hemoglobin remained between 90 and 95% during the low-fat dietary period with an average red cell count of 4.6 million per cubic millimeter. The leucocyte count was usually 4000 to 5000 per cubic millimeter on the low-fat regimen, while at other times it was 5000 to 6000. On one occasion during the experimental period, it fell to 2000 cells per cubic millimeter. The differential count always remained essentially normal as regards the distribution of the various cell types. The hematologist was unable to detect any abnormality in the morphology of the cells during the experimental period.

Urine examinations

Since the occurrence of hematuria is a distinct characteristic of the fat-deficiency syndrome in rats and is a serious prognostic omen, the urinary sediment was examined very closely, especially for blood. Frequent routine examinations of the urine failed to show any abnormality as to the presence of protein, sugar, abnormal sediment, diacetic acid or acetone.

DISCUSSION

That an adult human being can subsist on a diet containing a total of less than 2 gm. of fat per day (0.03 gm. per kilogram of body weight) for at least 6 months without demonstrable harm is somewhat remarkable. There is no assurance, however, that this subject or any other could be maintained indefinitely in a state of good health on such a regimen. The young rats, that developed typical signs of fat-deficiency diseases on this diet, lived a very much larger percentage of their life span on the regimen before showing abnormalities than that represented by 6 months in the span of a human life. Age or maturity is undoubtedly an important factor influencing the susceptibility to this as to other types of dietary deficiency also, the mature subject usually being much more resistant than the rapidly growing subject.

The mere fact that our subject at the end of the 6-month period showed changes in the serum lipids (decrease in the unsaturated fatty acids) and respiratory quotients, which were the same as those shown by rats suffering from unsaturated fatty acid deficiency, indicates that the response is qualitatively the same in the two species. While the human subject, like the rat can synthesize some fats, he apparently cannot fabricate the highly unsaturated fatty acids in sufficient amounts to maintain their concentration in the serum at levels found to exist when they are available in the diet. In all probability, therefore, the human subject, as well as the rat, would ultimately show clinical evidence of this deficiency, if the restricted diet were continued over a much longer period of time.

The small but definite decrease in the subject's blood pressure was probably due to loss in body weight, rather than to a specific effect of the low-fat diet. Disappearance of long experienced, periodic attacks of headache cannot be explained on any known basis, unless it be assumed that this symptom complex had been independent in part upon the moderate degree of arterial hypertension that existed before the special diet was used. That blood pressure was not the sole factor in the causation of the headache, however, is suggested by the fact that the symptom had failed to recur many months after resumption of a normal diet and return of the blood pressure to its previous degree of elevation.

The most interesting subjective effect of the 'fat-free' regimen was the definite disappearance of a feeling of fatigue at the end of the day's work. This experience was diametrically opposite that reported by Murlin and co-workers ('33) from the use of diets extremely high in fat and low in carbohydrate. It is impossible to say, whether this difference in feeling is simply a subjective representation of a difference in energy availability from the two diets, or, whether the sedative or slightly toxic effect of the ketone bodies accumulating in the tissues as a result of the latter type of diet is responsible for this effect.

That the subject of this experiment showed no increase in susceptibility to acute infections as a result of his extremely low fat intake is worthy of special note in light of recent observations regarding the relationship of fat metabolism to infection. For instance it has been pointed out repeatedly that a high-fat, low-carbohydrate dietary appears to reduce susceptibility to acute respiratory disorders (Spiesman and Arnold, '37; Hoelzel, '37). In fairly severe acute infections all of the blood lipids are greatly reduced and the iodine number of the serum fatty acids is decreased (Achard, Grigant, Leblanc and David, '28; McQuarrie and Stoesser, '35; Stoesser, '35). A possible explanation for our subject's apparent failure to manifest an increased susceptibility to infections may be found in the fact that his total serum lipids

were maintained at normal levels. Obviously the point does not deserve to be stressed because the factor of exposure to outside sources of infection was not adequately controlled.

SUMMARY AND CONCLUSIONS

1. An adult human subject was maintained for a period of 6 months on a nearly fat-free diet (less than 0.03 gm. of fat per kilogram of body weight per day) without demonstrable harm.

2. Young rats placed on the same diet developed the typical fat deficiency syndrome.

3. The only objective clinical effects of the diet on the adult human subject were a) a gradual loss of body weight during the first 3 months from 69 to 62 kg. and b) a coincident reduction to normal of a slightly elevated arterial blood pressure.

4. Subjectively the most striking effects were, a) disappearance of a previously experienced feeling of fatigue at the end of the day's work and b) disappearance of recurrent attacks of migraine-like headache from which the subject had suffered for some years prior to the time of the present experiment.

5. The respiratory quotient following a large meal of the experimental diet rose to 1.04, 1.11 and finally to 1.14 on different occasions during the sixth month of the low-fat dietary period; whereas under identical conditions before and after the period, it never rose above 0.97 and 0.99 respectively. In this respect the effect of the diet on the human subject is the same as that in the rat.

6. Repeated determinations of the basal metabolic rate before and after the experimental period gave values varying between — 9 and — 12%, whereas during the sixth month of the low-fat dietary period it was — 2.

7. The iodine number of the total fatty acids of the serum from fasting blood specimens was decreased from an average of 123 before the special dietary period to an average of 93 during the period. At the same time the linoleic acid of the serum was found to have fallen from 5.7 to 3.2% of the total fatty acids and arachidonic acid from 3.2 to 1.8%. These

changes in the serum fatty acids are similar to those found in rats suffering from the use of diets deficient in unsaturated fatty acids (Hansen and Burr, '33) and in human infants suffering from eczema (Hansen, '33, '37; Brown and Hansen, '37).

8. Decrease in the unsaturated fatty acids as a result of the low-fat regimen indicates the probability that even the normal adult human subject, like the rat, is unable to fabricate the highly unsaturated fatty acids, which should, therefore, be provided in the diet.

9. In the light of this latter observation, it cannot be assumed that the human subject could subsist indefinitely on a diet completely devoid of the unsaturated fatty acids.

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