sodium reabsorption has since been demonstrated more directly by Koch, Aynedjian, and Bank,⁶⁷ who studied the effect of acute hypertension on sodium reabsorption in the proximal tubule of the rat. Sodium reabsorption from the proximal tubule was measured by the split oil-droplet technique. They found that a rise in arterial pressure caused a decrease in reabsorptive half-time in the proximal tubule and therefore a diminution in sodium reabsorption.

It is not known how a change in peritubular venous capillary pressure can alter sodium reabsorption. Earley, Martino, and Friedler⁴³ were the first to propose that the change in sodium reabsorption which accompanies a change in peritubular capillary pressure may be due to a change in the interstitial volume between the cell and the peritubular capillary wall. Nutbourne,⁸⁸ who was the first to demonstrate that a hydrostatic pressure gradient can alter active sodium transport of a sodium-transporting membrane *in vitro*, suggested that this effect might be due to a distortion of the intercellular channels, for the change in sodium transport was far greater than could be accounted for by the pressure gradient. Nutbourne's experiments were performed on the frog skin. She designed an apparatus in which the pressures on each side of the frog skin could be controlled to within 0.5 mm. H₂O. She found that if the skin was made to bulge by a pressure gradient across the skin there was a marked effect on sodium transport, whereas if the same amount of bulging was produced by mechanical means there was no change in sodium transport. One of the most remarkable findings was that pressure gradients of less than 5 mm. H₂O had the greatest effect. And more recently the phenomenon has been confirmed with pressure gradients of only 0.5 mm. H₂O.^{88a} Nutbourne⁸⁸ concluded that increasing surface area did not influence sodium transport, whereas small hydrostatic gradients had a pronounced effect (Fig. 11).

The relevance of Nutbourne's findings to sodium reabsorption in the nephron are indirect, to say the least. On the other hand, they do provide the only *in-vitro* evidence that pressure *per se* can influence sodium transport across a sodium-transporting membrane. There are some similarities in the metabolic nature of the sodium pump in the proximal tubule and the frog skin. Anatomically also there are some fundamental similarities. The cells of the frog skin epidermis, like those in the proximal tubule, are each surrounded by intercellular spaces which open freely on the inner dermal side of the epidermis but are blocked at the outer layer of the epidermis.^{45 46 47 119} And a rise in pressure on the inside of the skin against the direction of net sodium transport corresponds to a rise in peritubular capillary pressure; and in both such a change in pressure causes a diminution in sodium transport.

The evidence suggests that the effect of hydrostatic pressures and plasma protein osmotic pressures may produce their effect on sodium reabsorption by a final common path which acts on the basal side of the cell. Perhaps both alter the volume of the interstitial space, and it is this which controls sodium reabsorption.⁴³ For instance, a rise in peritubular capillary pressure or a fall in plasma protein osmotic pressure may each increase the size of the interstitial space. Such an increase may dilate the basal infoldings or distort the intercellular channels in such a way that the efficiency of both the channels and the basal infoldings is diminished.

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[The conclusion of this lecture, with a list of references, will be published in our next issue.]

Control of Hyperlipidaemia in Juvenile Diabetes. Standard and Corn-oil Diets Compared Over a Period of 10 Years

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British Medical Journal, 1969, 3, 616–618

Summary: The results of the first 10 years of a prospective study of the effect of corn-oil and standard diets given to diabetic children since diagnosis suggest that the corn-oil diets currently available in Britain are not acceptable to most diabetic children and adolescents. Attempts to administer such diets may result in hyperpre-beta-lipoproteinaemia. In most diabetic children normal serum lipid levels can be maintained with adequate diabetic control and a standard diabetic diet.

Introduction

Hyperlipidaemia is common in diabetic children at the time of diagnosis (Chance *et al.*, 1969) and in diabetic adults during periods of inadequate control (Strisower *et al.*, 1958; Schrade *et al.*, 1963). It is now recognized that hyperlipidaemia is associated with atherosclerosis (Albrink *et al.*, 1961; Kannel *et al.*, 1964; Hatch *et al.*, 1966), and that in diabetic persons atheromatous lesions tend to appear at an earlier age and pro-

gress more rapidly (Kinsell, 1955). Thus prevention of hyperlipidaemia is probably an important consideration in the management of diabetes, particularly in children, since many of them are likely to develop vascular disease in early adult life (White, 1960).

Consumption of a diet rich in polyunsaturated fat has been shown to reduce the levels of serum lipids in healthy volunteers, in diabetics, and in patients with hypercholesterolaemia (Shapiro *et al.*, 1957; Ahrens *et al.*, 1957; Malmros and Wigand, 1957; Kinsell *et al.*, 1959; Stone and Connor, 1963; Keys *et al.*, 1965; Dayton *et al.*, 1968). In 1958 Professor O. H. Wolff,¹ Dr. J. K. Lloyd,¹ and the late Mr. H. B. Salt began a prospective trial to examine the long-term effects of such a diet in a group of newly diagnosed diabetic children, a similar group who received the standard regulated carbohydrate regimen being used as "controls." The design of the trial, details of the diet, and results of serum lipid studies during the first five years have already been described (Salt *et al.*, 1960; Lloyd and Jukes, 1961; Lloyd *et al.*, 1962; Lloyd, 1966). During this period the initial objects of the trial—namely, to determine whether such a diet was practicable for children on

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a long-term basis and whether it was effective in reducing serum lipids—appeared to have been achieved. After five years, however, difficulties were encountered in obtaining adequate supplies of corn-oil-substituted foods, and some of the older children began to refuse the diet. In consequence, diabetic control was disturbed and the serum lipid levels were increased. This article reports the results of serum lipid investigations for the two groups until the end of 1968. The effects of a corn-oil diet on the management of the diabetic child are discussed. Clinical studies will be reported later.

Patients and Methods

The group of diabetic children consuming the corn-oil diet (hereinafter referred to as the corn-oil group) now numbers 18, four of the original 22 having withdrawn during the first two years owing to social or maternal psychological difficulties. Of the 20 children originally in the control group, 16 remain, four having moved to other districts. The original alternate allocation of children to the two groups on their admission to hospital resulted in a mean age difference at each review of two to three years, the corn-oil group being the younger.

Venous blood samples were taken at about yearly intervals, in the afternoon two to four hours after the children's usual meals. Serum total lipid was estimated by a modification of the turbidimetric method of De La Huerza *et al.* (1953) and total cholesterol by the method of Sackett (1925). Serum lipoproteins were separated by paper electrophoresis, stained with oil-red O, and an estimate of their lipid content was obtained by eluting the dye (essentially according to Salt and Wolff, 1957). By means of this method the "beta-lipoprotein" fraction included both beta-lipoprotein of Sf 3-9 and pre-beta-lipoprotein (Sf 15-100). The intensity of the pre-beta-lipoprotein band was assessed visually and graded as negative (not visible), + (trace), ++ (a distinct band), and +++ a very prominent band). Most strips were inspected on more than one occasion. The error of grading on randomized repeated sampling was 10%. This was mainly owing to differences in the grading of faint pre-beta bands.

Results

The mean values of serum total lipid, total cholesterol, and beta-lipoprotein for corn-oil and control groups are shown according to year of study in Fig. 1. (Means are not reported for the first 18 months of the study because of the small number of children in each group during this time.) Until 1964 the mean values for all serum lipids were consistently lower in the corn-oil group than in the control group, but after

FIG. 1.—Mean serum lipid values in corn-oil and control groups according to year of study. (○—○, control group; ×—×, corn-oil group).

1964 this trend was reversed. The difference between the means was not statistically significant owing to a wide scatter of results in the corn-oil group. In 1968 the mean serum total lipid in the control group was 50 mg./100 ml. lower than in 1960, while that of the corn-oil group was 175 mg./100 ml. higher.

The mean values of serum total lipid, cholesterol, and beta-lipoprotein for each group according to age are shown in Fig. 2. The younger children consuming corn oil had lower mean serum lipid levels than the control children of the same age. The differences were significant ($P < 0.05$) for serum cholesterol and beta-lipoprotein in the 8-10 years age group and for serum total lipid in the 8-9 years age group. During adolescence mean values for serum total lipid and beta-lipoprotein in the corn-oil group rose considerably, but the differences between the means for the two groups did not reach statistical significance. Cholesterol values were very similar in the two groups at age 14-16 years, which suggested that the much higher serum beta-lipoprotein levels in the corn-oil group were due to an increase in pre-beta-lipoprotein (and hence in serum triglyceride content). This increase in pre-beta-lipoprotein was confirmed by visual assessment of the paper electrophoretic strips. As the age of the children in the corn-oil group increased the percentage of children with no visible pre-beta-lipoprotein decreased, and the percentage with a very prominent pre-beta band increased. This trend was not seen in the control group (Table I).

FIG. 2.—Mean serum lipid values in corn-oil and control groups according to age. (○—○, control group; ×—×, corn-oil group.)

TABLE I.—Incidence and Degree of Pre-beta-lipoproteinaemia in Corn-oil and Control Groups at Different Ages

Age in Years	Pre-beta-lipoprotein Lipid									
	Corn-oil Group					Control Group				
	Total	—	+	++	+++	Total	—	+	++	+++
< 10	63	30 (48%)	23 (36%)	9 (14%)	1 (2%)	20	3 (15%)	13 (65%)	4 (20%)	0
10-13	44	14 (32%)	15 (34%)	13 (30%)	2 (4%)	36	12 (33%)	14 (39%)	10 (28%)	0
> 14	34	7 (21%)	10 (29%)	6 (18%)	11 (32%)	66	20 (30%)	33 (50%)	12 (18%)	1 (2%)

Recent dietary analysis (Table II) has shown that the mean substitution of corn oil for dietary fat has fallen in the group as a whole from 80% in 1959-60 to 18% in 1968. Three children are achieving a 50% substitution, and these have normal serum lipids. Most of the older children have now completely rejected the corn oil diet; some of these have normal lipids.

TABLE II.—Percentage of Dietary Fat Consumed as Corn Oil

	Range	Mean
1959-60	71-85%	80%
1966	0-80%	42%
1968	0-51%	18%

Discussion

In the early years of this trial the corn-oil diet appeared to be of potential benefit to diabetic children, since the mean serum lipid levels were consistently lower in the corn-oil group than in the control group. Latterly, however, serum lipids increased in the corn-oil group, particularly during the years 1964 and 1965 (Fig. 1) and in those aged 14–16 years (Fig. 2). A slight increase in the mean serum total lipid was also found in 1968, when most of the children in the corn-oil group reached puberty (mean age 14 years; Fig. 1). There are several possible reasons for these increases.

During 1964 production of corn-oil "milk" ceased and a low-fat powdered milk was substituted in the diet. Unfortunately this change coincided with an increasing reluctance on the part of the older children to accept the necessity for eating mainly white meat and fish and using only corn-oil-substituted margarine and cheese. Dietary and adipose tissue fatty acid analyses during 1966 showed that while a few children were consuming adequate quantities of corn oil overall consumption was reduced and some children were consuming none at all (Albutt and Chance, 1969). Some parents continued to restrict their child's intake of animal fat. This resulted in diets which were inadequate in protein but high in carbohydrate. Lees and Fredrickson (1965) showed that high carbohydrate intakes cause increases in pre-beta-lipoprotein in adults, and we feel that these abnormal diets were partially responsible for the raised serum lipid values in the corn-oil group.

Until 1965 the children were maintained on insulin zinc suspension, but this earlier insulin regimen has been changed and most children are now given separate insulins to mix at home in proportions adjusted to their individual requirements (Chance, 1969). In many instances, particularly in pubertal children, the improvement in diabetic control has been accompanied by a fall in serum lipid values and disappearance of pre-beta-lipid from electrophoretic strips. Some adolescent members of the corn-oil group, however, have resisted repeated suggestions for altered insulin regimens. Their diabetic control has not been optimal during puberty, and hyperpre-beta-lipoproteinaemia has persisted.

Hyperpre-beta-lipoproteinaemia is common in young adults with occlusive vascular disease (Carlson, 1960; Albrink *et al.*, 1961; Hatch *et al.*, 1966; Blankenhorn, 1968) but is very rare in healthy children. Its presence in juvenile diabetics who are prone to early atheromatous disease may therefore be significant. Likewise the fact that it decreases with improved diabetic control may be important as regards the ultimate prognosis.

Though the hypolipidaemic effects of diets rich in polyunsaturated fats have been recognized for some years, the role of these diets in the prevention of atherosclerosis is not yet established. There is little evidence of benefit in established symptomatic disease, and results of studies of primary prevention, though encouraging, indicate the need for more extensive and prolonged investigations (Christakis *et al.*, 1966; Turpeinen *et al.*, 1968). Dayton *et al.* (1968) suggested that the diets themselves may not be without risk. Thus, though they found a lower incidence of atherosclerotic complications in men aged 54–65 years living in institutions who were given carefully supervised polyunsaturated fat diets for eight years, some excess of non-atherosclerotic mortality was evident. The authors tentatively suggest that this could be due to toxic effects of the experimental diet.

It is disappointing that only 11 of the children are still consuming corn oil, and that, even with full co-operation of their families, they will accept only up to half of their dietary fat as corn oil. Sterky *et al.* (1966) reported a similar experience; of 27 young diabetics nine failed to adhere to a diet in which only 22% of the dietary fat was polyunsaturated.

The Committee of Food and Drugs of the American Diabetes Association has recommended the routine use of polyunsaturated fat diets in diabetes. Our recent experience suggests that before such a recommendation is widely adopted great care should be taken to ascertain that the diet is both palatable and socially acceptable, otherwise the diabetic patient whose diet is already restricted may be adversely affected.

This study has provided serial records of serum lipid values in a group of 34 diabetic children since diagnosis. These records may eventually provide important information on the relevance of serum lipid and lipoprotein changes to the development of secondary complications of diabetes. We therefore plan to continue the yearly reviews of these children's serum lipid values into adult life.

We are grateful to the consultant staff of the Children's Hospital, Birmingham, for referring their patients to the Diabetic Clinic, to Professor D. V. Hubble for his encouragement, and to Professor O. H. Wolff and Dr. June K. Lloyd for their continued interest and permission to use information acquired in the earlier years of the study. We are particularly indebted to Sister H. R. Jukes, S.R.N., who has given valuable assistance throughout. The investigation has been supported by grants from the British Diabetic Association and the Endowment Research Fund of the United Birmingham Hospitals. Finally we wish to acknowledge the continued help of Alfons Foods Ltd. and the Midland Counties Dairy Co. Ltd.

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