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Early observations and their importance today. I diabetes in childhood, II theophylline in myasthenia gravis, III properties of cod liver oil

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I DIABETES IN CHILDHOOD

In a recent letter in the British Medical Journal Craig, Ford & McCuish (1977) reported on an increase in the number of newly diagnosed cases of diabetes in Glasgow among children under 13 years. At the Royal Hospital for Sick Children the occurrence has been assessed in 4-year periods. For the seven 4-year periods from 1933–1960 the mean value was 25 cases per period (range 17–41) with the low value of 17 occurring in the four war years from 1941–1944; for the three 4-year periods from 1961–72 the mean per period was 59 (48–66), but in the 4-year period from 1972–76 the number of cases rose some 100% to 113.

There was also some evidence of a similar rise at Stobhill Hospital and at the Glasgow Royal Infirmary. The authors pointed out that the mortality from diabetes is known to fall in wartime and they also said that the morbidity fell during the second war (1939–1945), not returning until the 1950's. As can be seen, the numbers increased in the 1960's and exploded in the middle 1970's. While there may be a number of reasons for this it is pertinent to ask if it might be that the childrens' diet had a predominance of carbohydrate and whether there would be benefit in increasing dietary fat as recommended for the treatment of human diabetes by Allen (1917), Newburgh & Marsh (1920) and Petren (1924). Haist, Campbell & Best (1940), from their studies of the insulin content of the pancreas, concluded that fasting, fat feeding and the injection of insulin are three factors which allow the pancreatic islets to rest. Marks & Young (1939) found that a diet of beef suet diminished both glycosuria and ketonuria in dogs made diabetic by injection of anterior lobe extracts, and this was confirmed by Dohan & Lukens (1939).

Shaw-Dunn & McLetchie (1943) showed that alloxan produced permanent glycosuria in rats and Burn, Lewis & Kelsey (1944)* demonstrated that this could be eliminated by diets of high fat content. They used 8 rats (~ 200 g) on a mixed diet and gave alloxan (160 mg kg^{-1}, s.c.) on two successive days. This produced glycosuria which in two rats disappeared after 4 days, but in six rats it persisted. These were further examined in pairs.

Fig. 1 shows the onset of glycosuria in one pair of rats kept in the same cage. On the second day after the second dose of alloxan, the glucose excretion rose to 5 g in 24 h, and on the 7th day to 7·7 g. The average glucose excretion over the first 13 days was 5·5 g over 24 h. On the 13th day the mixed diet was changed to one of 10% casein and 90% margarine. Fig. 1 further shows that the glycosuria dropped to 0·5 g on the first day and thereafter disappeared.

In the second pair of rats the glucose excretion on the normal diet rose during 9 days to 10·9 g in 24 h, with a mean of 7·0 g. On a high fat diet of 20% casein and 80% fat it fell at once to 0·3, 0·2 and 0·2 g

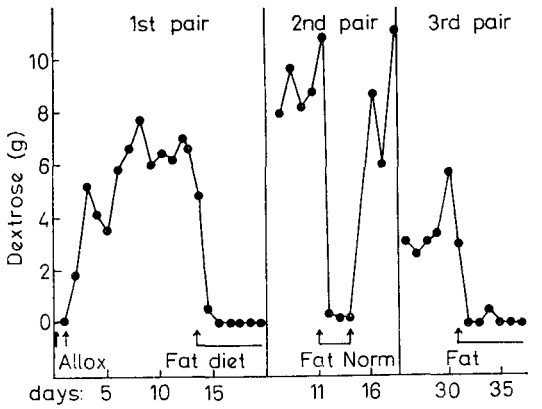

FIG. 1. Glycosuria in three pairs of rats made diabetic by the injection of alloxan. Effect of giving a high fat diet in abolishing the glycosuria. (Burn, Lewis & Kelsey, *Br. med. J.*, 1944, **2**, 752).

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*Material from the *Br. med J.*, 1944, **2**, 752–756 with permission.

on 3 successive days. On restoration of the normal diet, it rose again to a mean of 7·6 g for the next 4 days. In the third pair of rats the normal diet was given for 30 days to observe whether any spontaneous arrest of glycosuria occurred. The mean glucose excretion was 3·5 g daily and showed no sign of declining. When the diet was changed to the 80% high fat diet, glycosuria disappeared in the first 24 h, and save for traces on 4 occasions, it remained absent for 6 weeks, when the rats were again placed on the normal diet, then it reappeared.

The sudden change to a high-fat diet produced ketonuria in varying degree, as shown in Table 1. In the rats given 90% fat ketonuria reached 132 mg on the 3rd day thereafter it declined. It was much less in the two pairs given the 80% fat diet.

Table 1. *Ketonuria on high-fat diet (mg acetone per day).*

Rats	Fat in diet %	Days of fat diet 1	2	3	4	5
1st pair	90	2	12	132	49	24
2nd pair	80	2	9	4	—	—
3rd pair	80	0	6	15	0	0

The rat is an animal which develops ketonuria less readily than man, and indeed, outside the spring months can eat a diet wholly fat for a week or more with little or no ketonuria (Burn & Ling, 1928). An attempt was therefore made to introduce fat in the diet gradually in order to avoid the occurrence of ketonuria for if ketonuria could not be avoided in the rat, it certainly could not be avoided in man.

The attempt to demonstrate the usefulness of fat had not been very successful because the mixture of casein, starch and margarine was disliked by the rats and they ate little. In another pair of rats fat was added gradually to the normal diet. The result is shown in Table 2. During the first period the rats were eating the unpalatable mixture (S); they were then given the normal diet (N) which although of approximately the same composition, caused the calorie intake to rise to about three times the previous value, the body weight to increase, and the glucose excretion to rise from 0·3 to 4·9 g per day. Margarine was then incorporated in increasing amounts in the normal diet, up to 70%. As the percentage of fat rose the mean daily excretion of glucose steadily fell. With 60% of added margarine the excretion was as little as 0·3 g per day, and with 70% the urine became glucose-free. While this occurred the calorie intake fell only a little. On the normal diet without added fat the calorie intake was 202 per day at a time when the glucose excretion was 4·9 g. When the diet contained 70% added fat, the calorie intake was 165 (that is to say about 80% of the previous intake) and since 5 g glucose, representing 20 cal, was no longer lost in the urine, the calorie usage was 90% of that on the normal diet. The maintenance of the calorie intake was reflected in the maintenance of the body weight, which remained near 490 g on the diets containing 30, 40, 50, 60 and 70% of added fat. After each change in the diet the urine was examined for acetone bodies on 3 or more successive days. Ketonuria occurred only on one day of the whole period of approximately 8 weeks. It amounted to 19 mg acetone, and occurred after the rats had been given 50% of added fat. Strangely enough there was no ketonuria when the added fat amounted to 60 or 70%. Thus in this experiment glycosuria was abolished by a high-fat diet which did not reduce the calorie intake sufficiently to affect the body weight.

Table 2. *Effect of gradual increase in dietary fat.*

Diet	No. of days	Mean daily calories	Mean daily glucose excretion g	Body weight at end g
S.20	6	68	0·3	378
N.	6	202	4·9	443
N.20	6	212	4·0	450
N.30	6	203	2·8	495
N.40	6	188	2·3	493
N.50	10	172	1·0	503
N.60	16	157	0·3	500
N.70	6	165	Nil	488

Conclusion

Application of these results to children is a long step and would obviously require an investigation to see whether the inclusion of more fat in the diet resulted in the development of ketonuria. Petren (1924) stated that a diet of butter diminished acidoses, whereas a protein diet increased it. Marks & Young (1939) said "The results of our investigations have shown that the ketonuria is at a maximum when a meat diet is given, and is lowest with the prolonged feeding of fat."

Remembering that Haist and his colleagues (1940) found that fat feeding was one of the factors that allowed the pancreatic islets to rest, it would seem worth investigating whether the inclusion of more fat (preferably of a selected polyunsaturated variety) in the diet of a diabetic child might improve the control of diabetics.

II TREATMENT OF MYASTHENIA GRAVIS

The following is a brief account of observations which may have an application to the treatment of myasthenia.

Viets & Schwab (1939) observed that patients with myasthenia gravis responded better to a combination of ephedrine and neostigmine than to neostigmine alone. Bülbring & Burn (1942) subsequently studied the interaction between adrenaline and neostigmine on neuromuscular transmission in cats. Fig. 2 illustrates the kind of results they obtained. The cats were anaesthetized with chloralose, the sciatic nerve

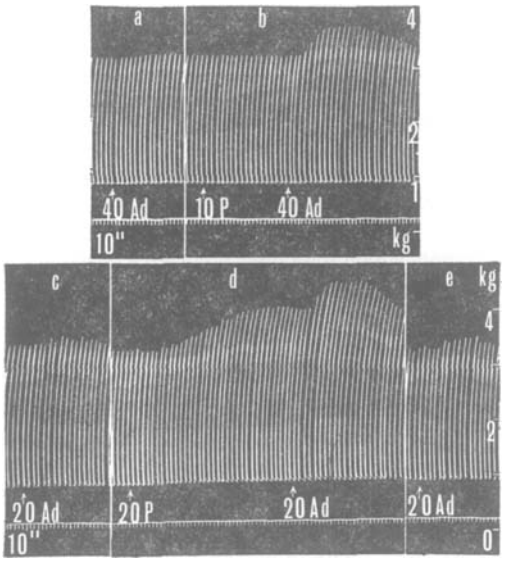

FIG. 2. The interaction between adrenaline (Ad) and neostigmine (Prostigmine) on neuromuscular transmission in the cat (Bülbring & Burn, *J. Physiol., Lond.*, 1942, **101**, 224, with permission).

of one side was exposed for stimulation, and the gastrocnemius muscle of that side was attached to a tension lever. The contractions in (a) of Fig. 2 were about 3·5 kg in tension. The intravenous injection of 40 μg adrenaline did not affect the contractions. After 10 min, an intravenous injection of 10 μg neostigmine was given and this also was without detectable effect. This injection was followed about 5 min later by an injection of 40 μg adrenaline, which this time produced an increase in tension of about 0·5 kg in the response of the gastrocnemius to stimulation of the sciatic nerve. In section (c) adrenaline was injected again but in half the dose. In (d) neostigmine was injected again but also in half the dose. After about 10 min more adrenaline was injected as in section (c); again the adrenaline increased the neostigmine effect.

When I was in St. Louis and making experiments of this sort with Dr Matschinsky, Bruce Breckenridge (now the professor of pharmacology in Rutgers University, U.S.A.) suggested that we should try the effect of theophylline in addition to the combination of neostigmine and adrenaline, because theophylline prevents the destruction of cyclic (c) AMP, and it was thought possible that adrenaline too owes its action to an increase in the cAMP content of the nerve endings but mediated by stimulation of adenylate cyclase. We tried this and got results like those in Fig. 3. This Figure shows a great increase in the response to the combination of neostigmine and adrenaline which was produced by the inclusion of theophylline as well. This result was obtained in a series of 10 experiments.

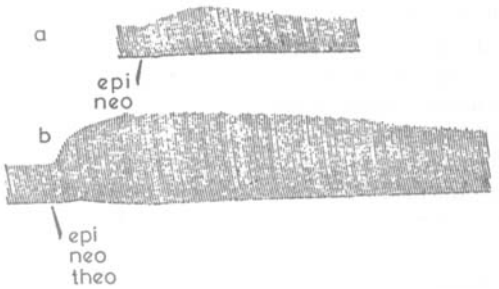

FIG. 3. (a) Showing the effect of 30 μg neostigmine (neo) and of 30 μg adrenaline (epi) on the response of cat gastroenemius to stimuli applied to sciatic nerve. (b) Showing the much greater response of the same preparation when 100 μg theophylline (theo) was given in addition to the above doses of neostigmine and adrenaline.

More recent work has cast doubt on the original premise underlying the inclusion of theophylline. This supposed that both adrenaline and theophylline acted through a cAMP mechanism, the former increasing the production of the nucleotide and the latter preventing its destruction. However, adrenaline (and noradrenaline) facilitate neuromuscular transmission by acting directly on the release mechanism to increase the probability of transmitter release from the nerve endings (Kuba & Tomita, 1971). In contrast, cAMP or theophylline appear to be without a direct stimulant effect on the release mechanism, but they probably stimulate the metabolic activity associated with the synthesis, storage and mobilization of the transmitter (Quastel & Hackett, 1971; Miyamoto & Breckenridge, 1974; Wilson, 1974). Thus theophylline and adrenaline (or ephedrine) appear to act together to increase the amount of acetylcholine released in response to nerve impulses, and neostigmine acts to prolong its duration of

action, so that all three drugs synergise to facilitate neuromuscular transmission. Hokkanen & others (1972) have demonstrated a beneficial effect of papaverine (also a phosphodiesterase inhibitor) in myasthenia gravis, and have recommended that either papaverine or theophylline be used in this condition. However, the combined synergistic use of all three drugs with different mechanisms of action (ephedrine, neostigmine and theophylline) does not appear to have been previously suggested. Such use may have the advantage that the reduction in individual dosage permitted by the combined therapy may minimise the side-effects of each drug.

III BRONCHITIS AND COD-LIVER OIL

Bronchitis is a serious disease, the death rate from which, perhaps surprisingly, is greater in England and Wales than in any other country in the world.

At the beginning of this century cod-liver oil was commonly given to children with coughs and colds. However by 1930 the presence in cod-liver oil of vitamins A and D became commonly known, and now the British Pharmacopoeia lays down that "cod-liver oil must contain in 1 g not less than 600 units of vitamin A activity and not less than 85 units of antirachitic activity (vitamin D)". This requirement has led many to believe that the therapeutic value of cod-liver oil is mainly due to these vitamins. Certainly cod-liver oil is of value for treating rickets because of the vitamin D it contains, but there is little or no evidence that the vitamin A content of cod-liver oil is efficacious in controlling respiratory ailments. Indeed, preparations containing large amounts of vitamin A, put forward because they lack the taste of cod-liver oil, are valueless for treating bronchitis.

My experience with cod-liver oil began when a member of my family, aged 60, had to give up his work because of chronic bronchitis. A regular course of cod-liver oil relieved the condition and he lived until he was 74. In the last few years I have had experience of the value of cod-liver oil among 9 persons of my acquaintance to whom I have recommended it for bronchitis. I ask each to begin with 1 teaspoonful after breakfast and to increase the dose to one tablespoonful which they should continue to take until all cough has gone. Of those concerned 6 were men and 3 were women. The results have been extremely good, and have led to the conclusion that the regular prescription of the oil for bronchitis would lead to a fall in the number of deaths. There is as yet no evidence what the curative factor in the oil may be. The cod comes out of the sea in which it feeds on a diet that includes plankton and other ingredients which may have a curative effect; the oil contains iodine and unsaturated fats.

There is more precise evidence that cod-liver oil also has an effect on plasma cholesterol, which is described by Kingsbury, Morgan, Aylon and Emmerson in a paper published in the Lancet, 1961, vol. 1, p. 739. They used young, healthy students 19 to 25 years old. They found that 25–30 g cod-liver oil when taken daily reduced plasma cholesterol by 20 to 25%. The higher the iodine value of the oil, the lower was the minimum effective dose. They also say that 15 g (1 tablespoon) produced falls of 17 mg/100 ml cholesterol.

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