METHIONINE MALABSORPTION IN A MENTALLY DEFECTIVE CHILD

A GIRL, aged 2 years and 3 months, was observed in our clinic because of mental deficiency, convulsions, attacks of hyperpnœa, and periodic diarrhœa. She had white hair, blue eyes, and a characteristic sweet smell. Her height and weight were respectively 83·5 cm. and 11·7 kg.

On a normal diet, α-hydroxybutyric acid was present in the urine as well as in the fæces. In addition we found large quantities of methionine and branched-chain aminoacids in the fæces. The aminoacid excretion in the urine was normal. A methionine-loading test caused much diarrhœa, with a significant increase of α-hydroxybutyric acid and methionine in the fæces. Control patients, including one with phenylketonuria, one with gastroenteritis, two with a cœliac syndrome, and one with tyrosinosis, did not show α-hydroxybutyric acid either before or after a methionine-loading test, nor did the methionine induce diarrhœa.

When the child was fed with a low-methionine diet, α-hydroxybutyric acid disappeared from the urine and the fæces, and the large quantities of branched-chain aminoacids also disappeared from the fæces. Clinically she showed improvement as regards the convulsions and diarrhœa, and the smell disappeared too.

The electroencephalogram, which had previously been pathological, became normal. The ' Phenistix ' reaction was persistently negative.

We have not been able to do any biochemical investigations on other members of the family. Some of them also had white hair, but they were not mentally retarded.

DISCUSSION

Experimentally α-hydroxybutyric acid was found in the fæces of a dog after introduction of methionine through a colostomy, but not after the administration of methionine by mouth. A bacterial cause for the formation of α-hydroxybutyric acid from methionine was considered likely because this acid could be prepared in vitro in a culture medium of non-pathogenic coliform bacilli after the addition of methionine, and its smell was like that of the untreated child. We therefore think that our patient suffered from a primary methionine malabsorption defect with secondary formation of α-hydroxybutyric acid by bacterial action in the gut. The malabsorption of branched-chain aminoacids could also be a secondary product.

Our case resembles partially the condition described by Smith and Strang in 1958,[1] and known as " oasthouse disease ". So far this is the only case reported in which α-hydroxybutyric acid has been found in the urine. They did not detect this hydroxy acid in the fæces.

Clinically, as far as the mental deficiency, convulsions, characteristic smell, attacks of hyperpnœa, and white hair are concerned, the two cases are identical. Our patient has blue eyes, which was not mentioned in the previous case. Clinically Smith and Strang's patient differed from ours in the early onset, the presence of œdema, and the rapidly fatal progress. They also found a positive phenistix reaction and other abnormalities of phenylalanine metabolism unlike our case.

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1. Smith, A. J., Strang, L. B. *Arch. Dis. Childh.* 1958, **33**, 109.

NEW INTERPRETATION OF ORAL GLUCOSE TOLERANCE

INCREASE in the blood-glucose level has long been considered to be the primary stimulus for the secretion of insulin by the pancreas. Whether or not the islet cells are physiologically stimulated by substances other than glucose is disputed.[1]

Recently doubt has arisen about the efficacy of hyperglycæmia alone as a β-cell stimulator. Colwell [2] failed to produce systemic hypoglycæmia by infusion of glucose into the arteries supplying the pancreas of normal dogs. Yalow and Berson [3] performed oral glucose-tolerance tests with normal people and found that large increases in plasma-insulin often accompanied relatively small increases in the blood-sugar level. This would be unexpected if the sole stimulus to the islets were hyperglycæmia.

Arnould et al.[4] gave glucose by gastric tube to unanæsthetised dogs. They found rises in insulin-like activity (fat-pad assay) which were higher than expected for the blood-glucose levels obtained. They concluded that some factor other than blood-glucose level must be important in stimulating insulin-like activity.

Scow and Cornfield [5] concluded from the results of experiments in rats that the removal-rate for oral glucose is considerably higher than that for glucose administered intravenously. They felt that the most likely explanation was a greater uptake by the liver in the case of glucose given by mouth. It has been shown that glucose administered by a tube placed in the jejunum is absorbed very rapidly.[6] We have therefore compared the results of administering glucose, at the same rate, by both intravenous and jejunal routes, in order to elucidate the mechanisms of the superior glucose tolerance accompanying oral administration.

METHODS

Two normal ambulant subjects, each weighing approximately 95 kg., were maintained on a liberal carbohydrate intake before and during the tests. Each was infused on two occasions with 5% glucose solution delivered at a rate of 15 ml. per minute by means of a constant-infusion pump. On one occasion the glucose was administered intravenously, and on the other the solution was infused into the upper jejunum through a polyethylene tube. The position of the tube was confirmed radiographically. An interval of 3 days separated the infusions, and both were performed after an overnight fast.

An 18-gauge Riley needle was placed in a brachial artery and used for all sampling. Three fasting blood specimens were taken, and sampling was continued at 15-minute intervals over the next 2 hours.

Blood-glucose was measured by a specific glucose-oxidase method,[7] using a kit obtained from C. F. Boehringer & Sons.

Plasma-insulin was measured immunologically, using a modification [8] of the original method of Yalow and Berson.

RESULTS

The results are presented graphically in figs. 1 and 2. During jejunal infusion of glucose, the blood-levels of glucose were lower than those found during intravenous infusion. But the initial rate of rise with jejunal administration shown in fig. 2 is good evidence for the rapidity with which glucose can be absorbed from the intestine.

Despite the lower blood-glucose levels, there was a much

1. Field, J. B. *Metabolism*, 1964, **13**, 407.
2. Colwell, A. R. *Diabetes*, 1963, **12**, 437.
3. Yalow, R. S., Berson, S. A. *J. clin. Invest.* 1960, **39**, 1157.
4. Arnould, Y., Bellens, R., Franckson, J. R. M., Conard, V. *Metabolism*, 1963, **12**, 1122.
5. Scow, R. D., Cornfield, J. *Amer. J. Physiol.* 1954, **179**, 435.
6. Holdsworth, C. D., Dawson, A. M. *Clin. Sci.* (in the press).
7. Huggett, A. St.G., Nixon, D. A. *Lancet*, 1957, ii, 368.
8. Samols, E., Bilkus, D. *Proc. Soc. exp. Biol., N.Y.* 1964, **115**, 79.

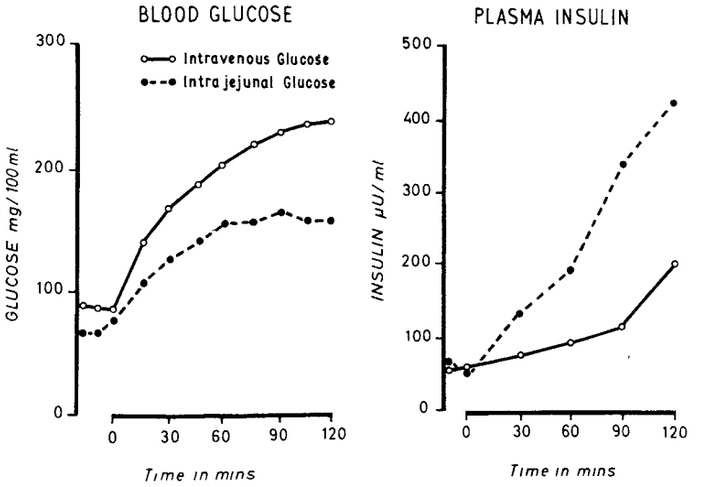

Fig. 1.

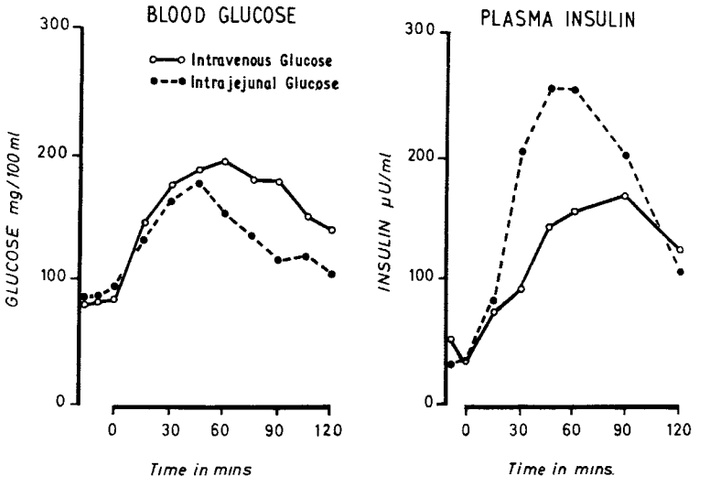

Fig. 2.

higher plasma-insulin response to glucose given jejunally than to glucose given by intravenous infusion.

DISCUSSION

These results suggest strongly that the superiority of oral-glucose tolerance over intravenous-glucose tolerance is due, at least partly, to greater release of immunologically active insulin from the pancreas. We believe that the most likely explanation is that a humoral substance is released from the jejunal wall during glucose absorption, and that it acts, along with a rise in blood-glucose, by stimulating the release of insulin by the pancreatic islet-cells. In 1928 Zunz and LaBarre [9] described a hypoglycæmic effect following injection of impure " secretin " extracted from duodenojejunal mucosa. They also showed by cross-circulation experiments that its effect was mediated through the pancreas.

Further experiments are in progress, to establish the mechanism of the findings described here.

One of us (N. M.) holds a Medical Research Council junior research fellowship. C. D. H. is in receipt of a grant from the Medical Research Council.

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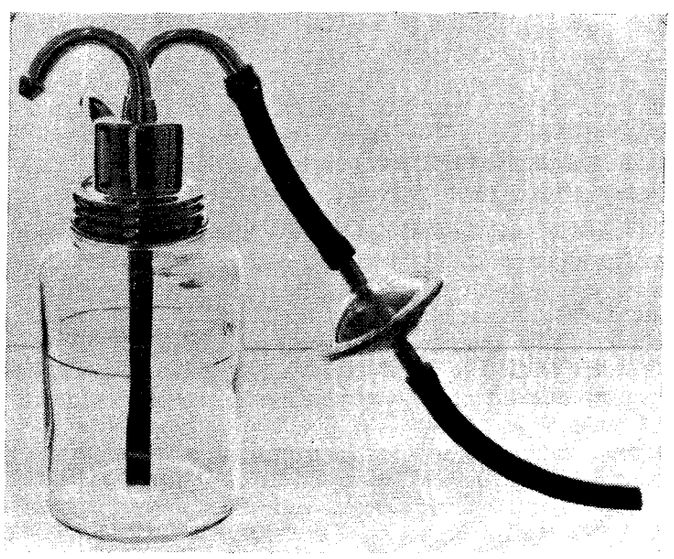
9. Zunz, E., LaBarre, J. *C.R. Soc. Biol., Paris*, 1928, **98**, 1435.

New Inventions

BACTERIAL FILTER FOR SUCTION APPARATUS

THE exhaust of a suction apparatus contains an aerosol of any liquid sucked into the collecting bottle. When this liquid contains bacteria, the exhaust is also contaminated. When the apparatus is used for aspirating purulent secretions, this source may be a significant factor in the contamination of hospital dust and in the production of cross-infection.

The problem can be solved in three ways: (1) the exhaust can be led outside the clean area; (2) a piped vacuum system can be used; or (3) a bacterial filter can be interposed between the collecting bottle and the vacuum source.



Filter connected to standard $^1/_4$ in. pressure-tubing on the vacuum side of a collecting bottle.

A suitable filter for this purpose is the ' Mackley 10 litre per minute Line Filter '. In this the filtering medium consists of two layers of 100% glass-fibre paper held between discs of perforated aluminium, which in turn are sealed into a spun-aluminium housing. The sodium-chloride penetration of this filter when passing 10 litres per minute is less than 0·001%—i.e., the filter has an efficiency greater than 99·999% when tested with particles down to 0·01 μ in size. The $^3/_8$ in. inlet and outlet tubes fit standard $^1/_4$ in. pressure-tubing. The filter has a resistance of 1 in. Hg at an air-flow of 10 litres per minute and of 3 in. Hg at a flow of 26 litres per minute. These resistances are not significant when compared with those of long lengths of tubing and fine catheters. The filter has been incorporated in an electric pump apparatus, an oxygen injector apparatus, and a vacuum line system. In no case did it noticeably alter performance. One filter has been on an apparatus which has been in daily use for four months, and its resistance has not altered in this time. This indicates that these filters would only need changing because of blocking at long intervals.

Though this filter prevents the passage of dusts and aerosols it becomes ineffective when soaked or flooded. If flooding of the filter is likely, a glass tube containing cotton-wool can be placed in the line before the filter; and inspection of this will show whether any liquid has been drawn over from the collecting bottle. If flooding occurs or is suspected the filter can be removed, autoclaved, and reused.

There is little point in fitting a filter to an apparatus that is already contaminated.

My thanks are due to Dr. J. H. Hale and Dr. J. B. Selkon, of the Public Health Laboratory, Newcastle upon Tyne, for help in selecting and testing the filter, and to E. N. Mackley Ltd. for their cooperation and the provision of filters for testing. The filter may be obtained from E. N. Mackley, Ltd., Hawkes Road, Gateshead, Co. Durham.

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