claim, which will leave the diabetic with a heavy and unnecessary liability.—I am, etc.,

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Glucose and Insulin After Diet and Tolazamide Treatment

SIR,—Dr. J. R. Turtle's study of glucose and insulin secretory response patterns following diet and tolazamide therapy in diabetes (12 September, p. 606) confirms our own findings[1 2] in respect of the effects of long-term acetohexamide in non-obese, maturity-onset diabetes—namely, that after three months of treatment with acetohexamide (0·5g. b.d.) the effectiveness of endogenous insulin is enhanced.

Our patients differed from Dr. Turtle's in that their diabetes was more severe in terms of blood glucose levels. During treatment only 13 of our patients achieved a reduction in the area under the blood glucose curve of 16% or more of that at the initial test, before treatment, and the mean reduction after three months' treatment was by 40%. Also, in contrast to his patients, the mean area under the insulin curve at the time of our initial tests was significantly less than in our non-obese, non-diabetic controls. After two months' treatment the mean area under our glucose curves had fallen by 35%, but the mean area under the insulin curves had risen by 46%. After three months' treatment, however, although the mean area under the glucose curves was reduced further, by 40% of the initial value, the mean area under the insulin curves had declined, though it was still 31% above the initial value.

The differences between the results of our two studies appear to be due largely to differences in the severity of the diabetes. It is known that the insulin response to glucose in diabetics declines as blood glucose levels rise,[3] which may explain the differences in the initial insulin responses with respect to controls in our two series. During the first month or two of treatment in our patients insulin output increased as glucose tolerance improved, but by three months sustained or progressive improvement in glucose tolerance was accompanied by a decline in insulin output towards, or even below initial levels. Thus at this time, in both Dr. Turtle's and our patients, there appeared to be less antagonism to insulin. Dr. Turtle has also shown that with diet alone though relative insulin deficiency persisted insulin effectiveness increased.

It appears, therefore, that reduction in blood glucose levels, whether by diet, sulphonylureas, or indeed by exogenous insulin, is a common factor, possibly allowing initially for improved β-cell function. Prolonged hyperglycaemia may cause islet cell degeneration, and persistent diabetes in cats[4] and the insulin secretory mechanism in man becomes exhausted in the face of prolonged hyperglycaemia.[5] It is reasonable to suppose that recovery of islet cell function might take place when long-standing hyperglycaemia is reduced by any means. The subsequent reduction of insulin antagonism may possibly be a direct consequence of the initial rise in circulating insulin, as it is known that diminished insulin sensitivity in alloxan-diabetic animals may be counteracted by insulin.[6]—I am, etc.,

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Diabetic Ketoacidosis

SIR,—I welcome your leading article (10 October, p. 63) in which, in the last sentence, you stress that admission to hospital of children with diabetic ketoacidosis should be promptly sought. I have for some time been concerned at the delay over the admission to hospital of children with this condition. Having correctly diagnosed diabetes mellitus, the doctor has referred the child to the outpatient clinic, which results in a delay of a week or two.

Recently we lost a four-year-old child due to the sudden onset of cerebral oedema four hours after admission to hospital and the start of treatment. The danger of cerebral oedema, particularly in young patients, was pointed out again in a recent paper.[1] Though Clements[2] *et al.* have provided good evidence that this is due to a disturbance of the glucose-polyol metabolic pathway in the brain cells, the best method of treatment remains in doubt. Consequently, prevention of the advancement of the hyperglycaemia is essential. It may be that doctors are not differentiating clearly between the insulin-dependent diabetes of children and maturity onset diabetes, in which the rapid development of ketoacidosis is less likely.

It is important to appreciate that children and young adults are particularly at hazard from acute onset ketoacidosis and from cerebral oedema.—I am, etc.,

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SIR,—We think that Dr. P. Z. Zimmet and his colleagues (12 September, p. 610) do us less than justice when they cite only our paper[1] as an example of "over-correction" of diabetic acidosis with bicarbonate.

In fact, we commented there on the significance of the metabolic alkalosis encountered during treatment and then stated "from the experience gained in treating these patients, we now feel that if the blood pH is dangerously low (below 7·2) then a dose of 200 mEq bicarbonate should be given immediately intravenously and followed by insulin plus standard intravenous fluid replacement. If the pH fails to rise to 7·2, then further 100 mEq-aliquots of bicarbonate should be given until that level is obtained. With this regimen no significant metabolic alkalosis should develop."

This advice closely parallels that offered by Dr. Zimmet and colleagues as their "more rational approach."

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Folate and Vitamin B_{12} in Epilepsy

SIR,—May we comment on some of the issues raised by Dr. C. Neubauer's paper (27 June, p. 759), the accompanying leading article (p. 744), and subsequent correspondence.

Dr. Neubauer's uncontrolled observations are consistent with the hypothesis that drug-induced disturbance of folic acid and vitamin B_{12} metabolism is one of the factors that may contribute to the development of psychiatric complications in some epileptic patients.[1 2] This in no way undermines the importance of other well-recognized causes of mental illness in epileptic patients.

There is now evidence of a significant association between a variety of psychiatric diagnoses in epileptic patients and disturbed folate metabolism as measured in serum, red cells, and C.S.F.[3 4] Though, as commented by Dr. R. P. Snaith (18 July, p. 165), no specific diagnosis is incriminated there is a tendency for the lowest levels to be found in patients with intellectual deterioration. It is relevant to point out that recently three separate inborn errors of folate metabolism have been described, all associated with mental retardation.[5] Dr. N. S. Gordon (25 July, p. 226) refers to Jensen and Olesen's[6] report of "normal" whole blood folate levels despite the fact that 91% of their intellectually deteriorated epileptic patients had subnormal serum folate levels. In fact, no control values were included, and examination of their data reveals very low whole blood folate levels.[4]

Though there are conflicting reports of the effects of treatment with folic acid alone we would like to emphasize the importance of treatment with *both* vitamins.[2] Why the vitamin B_{12} is necessary is not clear, especially as serum vitamin B_{12} levels are usually normal, but it may be related to the fall in serum vitamin B_{12} levels that occurs in the majority of patients during treatment with folic acid.[1 2]

With regard to the effect of the vitamins on seizure control, although we would agree with Dr. Gordon that the evidence that folic acid aggravates seizures is not