Indeed, in his 1961 Report the Minister states²: "Returns for the previous years were scrutinized during the year and in selected cases, where 'acceptance rates' for vaccination in infancy were apparently deteriorating, inquiries were made. A factor influencing this fall appeared to be postponement of smallpox vaccination until 1 year of age or later."

I am in favour of vaccination in the second 6 months of the child's life, but if this policy is to be abandoned I would rather accept Professor Dick's plea for epidemiological control than rely on an indifferent acceptance rate in the second year of life, with but very shaky evidence that the post-vaccinal mortality rate would be any lower.—I am, etc.,

County Hall,
Truro, Cornwall.

E. R. HARGREAVES.

REFERENCES

- ¹ Ministry of Health, *Memorandum on Vaccination Against Smallpox* (memo 312/Med 1946—revised 1956 and 1962). H.M.S.O., London.
- ² *Report of the Ministry of Health for the Year 1961. Part II: On the State of the Public Health, 1962*, p. 56, Cmd. 1856. H.M.S.O., London.

Insulin Ineffectiveness

SIR,—On reading your report (November 10, p. 1250) of the Cambridge meeting of the Medical and Scientific Section of the British Diabetic Association (September 28–29) I recalled some work which may bear upon the views of Dr. C. N. Hales given at that meeting.

In the *Biochemical Journal* of 1924 or 1925 I published some simple observations on normal human subjects who had been kept without any food or drink for some 36–40 hours, at which time it had been found that a considerable ketosis was established, and, I suggest now, almost certainly a high blood non-esterified fatty acid level was present. In these conditions the blood sugar was usually a low normal, the respiratory quotient (uncorrected for urinary nitrogen) was normal, and the urine contained all the usual acetone bodies with the ratio of β -hydroxybutyric acid to aceto-acetic acid about 1.5 to 2.5 or so. On administering 50 g. of glucose in these conditions it was easy to show (control data having been obtained in normal conditions) (a) an abnormal blood-sugar curve with glycosuria; (b) much diminished rise in R.Q. (normal rise to 1.0 after 12 or so hours' starvation); (c) disappearance of ketone bodies in about an hour.

In those days it seemed reasonable to speak of some lag in insulin secretion and, certainly, delay in the anti-ketogenic action of the sugar and respiratory metabolic response. But it may be more reasonable to suppose now that the ketone body production and excretion were rather the expression of anti-insulin action.

In later work it could be shown that these effects could all be accentuated by ingestion of 100 g. molten butter in similar conditions. Further, the disappearance of the ketone bodies from the urine was accompanied by a fall of blood sugar well below the initial value, which seemed to be attributable to an abnormally high stimulation of the islet cells.

In other experiments (with Dr. (now Professor) R. W. B. Ellis) at a later date in similar conditions of starvation it was possible to negate the apparent inactivity of endogenous insulin by the ingestion of 300 ml. of 5% ethanol, hypoglycaemic levels of blood sugar being rapidly reached as well as fall of R.Q. to the theoretical level for ethanol, and a large rise in blood lactic acid (all experiments at complete rest). This

latter was almost certainly due to the secretion of adrenaline secondary to the hypoglycaemia.

It may be of some interest to repeat these experiments with the more erudite methods now available, and especially the apparent anti-glucagon effect of alcohol.—I am, etc.,

Istituti Clinici di Perfezionamento, M. W. GOLDBLATT.
University of Milan.

REFERENCE

- ¹ Goldblatt, M. W., *Biochem. J.*, 1925, 19, 948.

Aetiology of Schizophrenia

SIR,—Dr. Clifford Allen (December 1, p. 1475) rather overlooks the point of my letter (November 10, p. 1259), which is that we must look beyond individual glands and their hormones to the gland responsible for hormonal balance. All that he says of the adrenal is true, but the balance between it and other glands of internal secretion is the function of the pineal. The neurological aspects associated with metabolic disorders clamour for co-ordination, and this means co-ordination with disorders in other systems.

When Sir Macfarlane Burnet speaks of the dependence of immunity on the thymus (September 29, p. 807) he also points to something deeper: "the development of the immunological competence of the body is part of the process of morphological and functional differentiation in the embryo."

Richter¹ says that "the brain develops first because it is required early as a controlling centre for the neuro-endocrine functions of the body. The medulla and hypothalamus are the first regions to mature in the embryo." This is hardly exact enough for our purpose—what part of the medulla and hypothalamus appear first? This is likely to be the channel through which genetically stored information is translated into specific protein structure.

No one suggests that either the adrenal or the thymus controls hormonal balance, but this function is claimed for the pineal.²

Are we sure that the pulsating point which appears in the chick within 24 hours of fertilization is the origin of the vascular system only or does it represent nerve as well?—I am, etc.,

London W.14.

GRIFFITH EVANS.

REFERENCES

- ¹ Richter, D., *Schizophrenia*, 1957. Pergamon Press, London.
- ² Hubble, D., *Brit. med. J.*, 1961, 1, 523.

Anticoagulant Treatment

SIR,—Dr. L. Poller's answer (November 24, p. 1402) to Professor J. McMichael's comment (October 13, p. 992) would appear to contain contradictory statements, some of which I think need serious consideration.

Prothrombin Time.—Dr. Poller criticizes the omission of the number of days patients were below the 10% in Hilden's trial.¹ Yet he admits he keeps his patients "a little higher" than 10%. How much above 10% and how regularly this is attained he does not mention. We are all only too familiar with the sudden changes in the prothrombin times in patients receiving coumarin drugs, hence the necessity for frequent laboratory control.

Haemostasis and Thrombosis.—Dr. Poller states: "The aim, in fact, is to give adequate protection against further thrombosis without interfering with the normal process of haemostasis." This simple sentence has wide implications. Surely thrombosis is not caused by abnormal coagulability only. Factors other than blood

coagulation contribute to this condition. The factors responsible for haemostasis are complex, comprising blood coagulation, vascular wall, chemical reagents, etc. Therefore we cannot say that because surgery is possible in a patient receiving coumarin therapy there is no interference with this complex process. We may, however, say that there is laboratory but no clinical evidence to this effect. Other physiological or anatomical processes (known or unknown) may compensate *in vivo* for a reasonable reduction in certain blood-clotting factors.

Dilution Curve.—As mentioned by Dr. Poller, when plasma is diluted with saline, all coagulation factors are reduced irrespective of whether they are affected by anticoagulant treatment or not. Whether or not Dr. Poller wants us to believe that dilution in saline gives a better assessment of the effect of coumarin drugs, I would like to point out that dilution curves of any kind are apt to give a false impression of the clotting mechanism as affected by coumarin drugs.² While each of the factors involved (Factors II, VII, IX, and X) is affected differently by coumarin drugs, dilution reduces equally these factors. Dilution may also introduce or lower the level of other unknown substances.

Bleeding During Coumarin Administration.—None of the methods available for estimating prothrombin time is an absolute assurance against haemorrhage.³ I have seen bleeding in patients with Quick's prothrombin times of 18 and 19 seconds. Nor can the prothrombin time be taken as a measure of intravascular coagulability.⁴ Bearing in mind these points, one would rather consider the high incidence of bleeding in Hilden's trial as being a more valuable indication to adequate dosage. Accordingly, in his statement, "Anticoagulant treatment should be so controlled that there is ample safety from haemorrhage," Dr. Poller would appear to be a little too ambitious and inconsistent, having subscribed to a different view in a previous paper⁵ wherein he stated, "Among the forty-three patients there were three non-fatal haemorrhages, and in each of these the Quick test results were within the therapeutic range," and "No one-stage method is entirely safe in controlling anticoagulant treatment."

To condemn the Danish trial on the fact that they used a different laboratory test (October 13, p. 992) is really unjustifiable. I regret to say that this habit of ignoring the work of others seems to be spreading. May I therefore end this letter by saying—let us give credit (however small) where credit is due?—I am, etc.,

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Bristol.

F. NOUR-ELDIN.

REFERENCES

- ¹ Hilden, T., Iverson, K., Raaschou, F., and Schwartz, M., *Lancet*, 1961, 2, 327.
- ² Nour-Eldin, F., 69th Meeting of Clinical Pathologists, London, 1962.
- ³ ——— *Brit med J.*, 1962, 2, 118.
- ⁴ ——— *New Istanbul Contr. clin. Sci.* (in the press).
- ⁵ Lempert, H., and Poller, L., *Lancet*, 1960, 2, 1115.

Anaesthesia for Burns

SIR,—The interesting and important article by Dr. G. H. Bush and his colleagues (October 27, p. 1081) calls for some comment. Their conclusion that "vagal overactivity" is the most likely explanation of these cases of cardiac arrest is by no means fully supported by the evidence.

In their first episode the carotid pulse is described as "weak and rapid," and they draw analogy with the

case of recurrent cardiac arrest reported by Finer and Nylén.¹ These observers very carefully recorded the heart rate during the second induction and noted "rapidly increasing pulse rate until uncountable." This is not the picture of "vagal overactivity." Indeed it is just the opposite and suggests sympathetic overactivity.

To me these seem like apprehensive patients, insufficiently sedated and surgically stimulated (by the anaesthetist) while not deeply enough unconscious to obtund sympathetic response. They appear to have something in common with those deaths which used to occur from time to time during induction with chloroform, which were usually considered to be due to ventricular fibrillation. Fleming's case² (quoted by Dr. Bush) on both occasions had the chest opened and ventricular fibrillation was found.

Pre-operative apprehension was noted in most of the cases quoted by Dr. Bush. For example:

Bush *et al.*, Case 1, first episode: "Extremely apprehensive." Second episode: "Even more apprehensive than on the previous occasion." It is to be noted that sedation was reduced to 50 mg. promethazine while induction was with the tiny dose of 125 mg. thiopentone.

Bush *et al.*, Case 2: "Patient was acutely anxious." Again it is to be noted that the only preoperative drug was atropine, and that the induction was with 200 mg. thiopentone.

Finer and Nylén, first episode: "He . . . was in a state of extreme anxiety, in spite of premedication with morphine, 10 mg., and scopolamine, 0.3 mg. . . he was moaning, restless, and terrified of the repeated attempts at venepuncture." Eventual induction was with "narkotal" 300 mg. Second episode: "Because of his state of anxiety. . . ." Fleming's report of two episodes of cardiac arrest in the same patient did not contain any reference to the child's psychological condition, but one notes that induction on the first occasion was with 120 mg. thiopentone and on the second occasion with nitrous oxide and oxygen only. Each time after the injection of suxamethonium the lungs were inflated with oxygen. Can one doubt that the child must have been near the level of consciousness when intubation was performed?

It is possible that some of these episodes of cardiac arrest were due to "vagal overactivity," but it is certain that others were due to a very different cause.

Am I terribly old-fashioned in my belief that we should give adequate pre-operative sedation and ensure unconsciousness during so-called "general anaesthesia"?—I am, etc.,

Chesterfield Royal Hospital,
Chesterfield, Derbyshire.

H. E. POOLER.

REFERENCES

- ¹ Finer, B. L., and Nylén, B. O., *Brit. med. J.*, 1959, 1, 624.
- ² Fleming, W. B., Hueston, J. T., Stubbé, J. L., and Villiers, J. D., *ibid.*, 1960, 1, 157.

Triamterene

SIR.—We were interested in the paper by Drs. W. R. Cattell and C. W. H. Havard on the diuretic action of triamterene in man (November 24, p. 1362).

We have now used triamterene with success in the treatment of fluid retention in more than 60 patients. There have been few side-effects, but a rise in blood urea has been noted in many patients by ourselves¹ and by other workers in this country.^{2,3}

The suggestion that triamterene has a uricosuric action is of interest. We have studied the serum uric