most children emerges in the second or third year is acquired by conditioning or by any other method of teaching.

Joseph, although Lovibond and Coote,1 in a chapter published in 1970, unequivocally say that dryness follows the development of cortical control which involves both neural maturation and the development of supranuclear re-socketed reflexes" (p. 374), they also clearly imply (p. 375) that cortical control may happen from maturation alone, but they fail to notice the implications of this. There is indeed a fair amount of evidence that night-time bladder control is a behaviour pre

destined to appear once maturation has occurred.4 There is some analogy with walking, which will appear without teaching.5

If central nervous system maturation for bladder control at night has occurred in nearly all children by the age of 5, why have 10 or 20% not developed night-time dryness? It seems likely that the emergence of dryness at night can be prevented by negative factors acting at the time maturation occurs. Douglas6 and others7,8 have shown that children wetting themselves at 4 or 5 are commonly having a history of stressful episodes in the third year of life than do dry control children. The stresses reported on do not include what is very likely the commonest stress—having to train at toilet training. But since Brazilen92 has shown that with a child-oriented, low-anxiety system of toilet training, 98–5% were dry at the age of 5, it seems that if we gave our minds to it, we could be predicting nearly all cases of enuresis.—I am etc.,

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3 Braselton, T. B., Pediatrics, 1963, 29, 121.


10 Care, R., Lancet, 1958, ii, 1167.

11 Young, G. C., Medical Officer, 1965, 113, 19.

SIR,—In your leading article (14 April, p. 69) you say that "the electric buzzer is a highly effective method of treatment provided that it awaken the child . . .” but if it does not awaken the child, what then? It is not sufficiently widely known that the best drug to enable the child to wake to the buzzer is imipramine or another tricyclic antidepressant. This is so effective in most deep sleepers that it should be routine practice to check up within a week of starting treatment to see whether the child is waking promptly to the buzzer. If not he should be put at once on a small dose of imipramine—say, 25 mg.

This use of imipramine with the buzzer may perhaps provide a clue as to how these tricyclic preparations work in enuresis. Many heavy sleepers when roused are in a state of somnambulism—they cannot converse with their parents, they may walk in the wrong direction when instructed to go to the lavatory, and have no recollection of the event the following morning. After the first night or two of taking imipramine all this disappears—they wake promptly, can converse and co-operate freely with their parents and go off to sleep again without difficulty, while bladder control is rapidly acquired.

Treatment with tricyclic preparations and with the buzzer should no longer be regarded as in rivalry but as complementary. If the buzzer alone is insufficient, imipramine may turn the balance. Equally no one should be content with a mere reduction in the number of wet beds with imipramine, so unless good control is soon obtained the parents should be offered the opportunity of using the buzzer with or without the drug.—I am etc.,

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Immunological Destruction in Vitro of Cytomegalovirus Infected Cells

SIR,—The grossly abnormal morphology and behaviour of cytomegalovirus infected cells1 suggest that they are in some way antigenically distinct from normal cells and should therefore evoke an immune response in the naturally infected host. Laboratory observations made with ground squirrel (Citellus citellus) kidney cells infected with a ground squirrel strain of cytomegalovirus2 and exposed to antisera as viral cytopathic lesions became apparent seem pertinent with respect to mechanisms of immune reaction to the infected cells.

Mature ground squirrels were checked by the complement fixation test for antibody to cytomegalovirus, using an antigen prepared from the above-mentioned ground squirrel strain. Seropositive animals were often found to harbour in their salivary glands inclusion-bearing cells typical of cytomegalovirus infected cells.3

Immunofluorescence. Fresh sera retained from these specimens were pooled and incorporated at a 20% concentration into a tissue culture medium consisting of Hank's balanced salt solution and lactalbumen hydrolysate. For control purposes normal medium and media with added negative or heat-inactivated positive sera were used. Kidney cells were obtained, cultured, and inoculated as previously reported.4 The culture tubes were examined daily, and when cytopathic changes were seen antisera-containing medium was added and the ensuing morphological changes followed in situ and in colloidion film preparations stained with haematoxylin and eosin. Uninoculated control cultures were observed under the same conditions.

After exposure to fresh positive serum slowly progressing lysis of infected cells was observed (fig. 1), whereas the same serum did not cause lysis in the non-invaded areas of the test tubes or in uninoculated control cells (fig. 2). Moreover, the same serum did not cause lysis of infected cells either after inactivation for 30 minutes at 56°C.

Addition of guinea-pig complement to the inactivated serum restored its cytolitic properties. Fresh negative sera, inactivated negative sera supplemented with complement, or complement alone had no effect on the infected cells. Since no lysis occurred in the absence of complement or in the presence of complement heated at 56°C for 30 minutes the cytolytic substance was thought to be antibody, and we concluded that the phenomenon observed was that of immunological destruction in vitro of cytomegalovirus infected cells.

The immune surveillance against cytomegalovirus infected cells in vivo is highly efficient. The virus may sometimes be recovered from tissues lacking any characteristic morphological changes, but the inclusion-bearing cells are encountered only in the sheet lining the excretory salivary ducts, possibly because of the absence or inactivation of complement-fixing antibodies at these sites through digestion by proteolytic enzymes or interference with biological activity by changes in pH, temperature, or salt concentration. In immune depressed hosts, on the other hand, typical inclusion-bearing cells are often found scattered in different organs and tissues, suggesting that the virus-induced modifications in cellular surface antigens plays a major role in the pathogenesis of cytomegalovirus disease.—We are, etc.,

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Diabetes Mellitus and Refined Carbohydrate

Sir,—Those of us who have worked in Africa where diabetes appears to be uncommon must congratulate Dr. A. C. B. Wicks and Professor J. J. Jones (31 March, p. 733), who have extended the observations of other doctors1 in Salisbury, Rhodesia. They are beginning to elucidate the role of refined carbohydrates as a factor in the pathogenesis of diabetes mellitus.

If one wishes to state the degree of refinement of any starchy carbohydrate, it is desirable to record the crude fibre content; thus maize meal, such as that consumed by Africans in Rhodesia, might vary in crude fibre content from 0.7 g/100 g if of 60% extraction to 1.5 g/100 g if of 96% extraction. That of wheat homogenate extraction is 2.0 g/100 g, while white flour 70% extraction has only a trace,2 probably a crude fibre content of about 0.1 g/100 g. It would be helpful if investigators could state the degree of extraction of the maize meal consumed in Rhodesia. In South Africa a recent analysis reported that Bantu preferred maize meal 80% extraction (crude fibre 1.4 g/100 g), or 60% extraction (crude fibre 0.8 g/100 g).

Reports of the experimental production of diabetes mellitus in small rodents seldom mention the crude fibre content of the food offered, though tables3 can often supply these figures.

Interpretation has been that excessive calorie intakes encourage obesity and hyperglycaemia. This is correct, but a more comprehensive appraisal of the situation suggests that diets rich in undigested fibre have different satiety mechanisms because a larger proportion of the food remains undigested in the bowel; less is consumed. When an animal, on its traditional food, fed ad libitum, it seldom becomes obese or develops diabetes. Perhaps man has a similar response, for refined starchy carbohydrates have not been his traditional food in Africa or in the Western World.—I am, etc.

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Insulin and Glucose in Treatment of Cardiogenic Shock

Sir,—Dr. S. P. Allison and his colleagues (16 September 1972, p. 675) reported the value of daily infusions of insulin, glucose, and potassium in cases of severe congestive heart failure. Omitting the potassium, because hyperkalaemia was already present, we have been giving similar full effect to patients in cardiogenic shock after myocardial infarction.

The table shows typical findings in a case of cardiogenic shock before and during the course of one hour after the infusion of glucose 20 g and insulin 20 U over a period of five minutes. Apart from these results, we have seen diuresis begin after 30 minutes in some cases. Our experience prompts us to recommend glucose and insulin infusions in cases of this kind when immediate lowering of serum potassium concentration and an improvement in cardiac efficiency is required.—We are, etc.,

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Prolonged Action of Pindolol

Sir,—Dr. P. D. Nigam and A. S. Malhotra (24 March, p. 742) reported that in a comparative clinical trial of pindolol and propranolol in angina pectoris they observed a prolonged action of pindolol (Visken, LB 46) for about one week after cessation of treatment. However, they pointed out that a sudden withdrawal of beta-adrenoceptor blocking drugs might precipitate myocardial infarction in patients with angina pectoris. A prolonged action of pindolol could therefore offer some advantages.

Our studies in human volunteers4 showed, in agreement with experiments in anaesthetized dogs,5 a significantly longer duration of action for pindolol than for propranolol: 5 mg of pindolol and 100 mg of propranolol were equipotent in reducing the increase in heart rate in response to exercise on the cycle ergometer two hours after oral administration. After eight hours pindolol still elicited 84% of its full effect and propranolol 67%. After 24 hours the figures were 36% and 16% respectively.

While the duration of action of pindolol is clearly longer than that of propranolol it is, however, no pharmacokinetic evidence that pindolol accumulates with prolonged administration. At the end of a 52-week toxicity study in monkeys given oral daily doses of 2.5 mg/kg and 25 mg/kg blood levels and urinary excretion data were comparable to those found after a single oral dose of the drug.6 Similar results were found in a pharmacokinetic study in man with an oral dose of 5 mg pindolol three times daily for eight days. Blood levels varied within the same range throughout the treatment period and they declined on the last day with the same half-life as after a single dose.7 There were therefore no measurable amounts of pindolol released from the tissues when treatment was stopped.—We are, etc.,

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1 Stone, R., Lancet, 1973, i, 156.

Acute Water Intoxication from Compulsive Drinking

Sir,—Dr. E. R. Alexander and others (13 January, p. 89) reported an interesting case of water intoxication in relation to acute psychogenic disorder. We have seen a very similar case of acute water intoxication from compulsive water drinking,1 and we investigated the patient's water metabolism a week after his admission to hospital, when the intoxication had disappeared. An oral water loading test (15 ml/kg) was followed by a constant negative concentration of water (as with inappropriate antidiuretic hormone secretion), and this was hardly compatible with the profuse diuresis of low specific gravity observed after his admission to hospital.

To find the reason for this we tried to reproduce the water intoxication by infusing isotonic (5%) sorbitol at a rate of 1.000 ml/hr, and every half hour we checked the water concentration. The infusion produced a noticeable lowering of serum osmolality (260 mOsm/kg water). Initially the water concentration was negative, and it became positive only when the serum osmolality reached a value below 260 mOsm/kg water. A similar impairment of the water excreting mechanism was found by Hobson and English.

Water intoxication therefore occurs only when there is impairment of water excretion as well as excessive water intake. Our findings, which differed from those in neurogenic hypernatraemia,5 made us think that the water intoxication in our case was due to excessive thirst and a lowered threshold for vasopressin release.—We are, etc.,

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1 Linquett, M., Fossati, P., Lefebvre, J., Cappoen, J. P., and Chapel, H., unpublished results to be published.

Artificial Infection by Donor

Sir,—May I, as a practitioner of A.I.D., be permitted to comment upon the conclusions of the panel on human artificial infection dealing with Sir John Peal (Supplement, 7 April, p. 3)?

Selection of Donors.—Medical students, as a group, are not the best donors. The best donor is a man who has fathered two or three healthy children, which is the only

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2 Dioso, P., Babuscac, L., and David, C. Archiv für die gesamte Virusforstuch, 1967, 14, 383.

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