the absence of appropriate controls and other information it would be regrettable if the communication by Dr. Jones Williams and his colleagues added to the confusion which already exists on this controversial subject.—We are, etc.

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- 1 Simpson, B. R., Strunin, L., and Walton, B., *British Medical Journal*, 1971, 4, 96.
- 2 Doniach, D., *New England Journal of Medicine*, 1970, 283, 315.
- 3 Paronetto, F., and Popper, N., *New England Journal of Medicine*, 1970, 283, 277.
- 4 Walton, B., et al., *British Journal of Anaesthesia*, 1972, 44, 904.
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- 6 Park, S. K., Brody, J. I., Wallace, H. A., and Blakemore, W. S., *Lancet*, 1971, 1, 53.
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Gastrin and Gastrointestinal Disease

SIR,—We were interested in your leading article on this topic (9 September, p. 604), but we think your statement that gastrin may affect intestinal motility needs qualification.

In doses producing near-maximal gastric-acid secretion both gastrin and pentagastrin were found to stimulate motility in the gastric antrum, but no effect on colonic motor activity could be detected.^{1,2} As you point out, serum gastrin levels are high in patients with pernicious anaemia but are likely to be low after total gastrectomy. Colonic pressure activity, however, especially after a protein-containing meal, is greater after total gastrectomy than in pernicious anaemia.³ It would therefore seem unlikely that gastrin is involved in the colonic motor response to meals.³—We are, etc.,

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- 1 Misiewicz, J. J., Holdstock, D. J., and Waller, Sheila L., *Gut*, 1967, 8, 463.
- 2 Misiewicz, J. J., Waller, Sheila L., and Holdstock, D. J., *Gut*, 1969, 10, 723.
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Psychiatrists in Training

SIR,—May I express concern at some current thinking in the training of psychiatrists? I feel that it is essential when applying for a consultant post to have as wide an experience as possible of different specialties, consultants, and types of unit. I also accept that rotation between units should be freely available, as desired by junior staff and advised by their senior colleagues. May I, however, express the view that if rotation to a reasonable extent has been achieved by the time the junior doctor has reached senior registrar level there are important advantages in spending the whole senior registrar period in one hospital and making up the deficiency by the process of secondment on a regular sessional basis to other units and by attending courses. This allows a senior registrar to learn skills that would be com-

pletely neglected by the senior registrar who had at the most spent one year in one place. It forces him to have continuing long-term exposure to the patient who will not get better. It allows him to become an important and powerful member of the Cog-wheel structure and to take part therein in the developments of a hospital and its policies. And it allows him to create long-term plans for the establishment of new units with the supervision of a consultant and to work through all their administrative and staff problems to full fruition. This view is at variance with the currently popular one, which seems in the main to hold that the best training is offered by wide rotation.—I am, etc.,

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Candidates for Coronaries

SIR,—It seems the ivory towers of the research workers are getting taller or we on the ground are being obscured by a deepening mist. Any general practitioner of reasonably long experience could join in the discussion of coronary personality types under consideration in your leading article, "Life Pattern for Coronary Arteries" (14 October, p. 63). They would generally be in agreement with the personality type of the Dunbar profile¹ and that not all people falling within this profile suffer from coronary artery occlusion. That is to say that coronary occlusion occurs in people who are conscientious, responsible, and lead stressful lives but that not all such people suffer coronary artery disease. There must be another consideration to be taken into account.

Time and time again patients who have suffered from their first or subsequent attack of myocardial infarction admit to have felt absolutely tired out for days, weeks, or months before the infarction episode. Often the more perceptive will say "I had felt so tired for weeks that I had come to accept this as a normal state of affairs." It is this acceptance of fatigue as being something to put up with, the trying to ignore it, and the trying to carry on normally despite its presence which I believe to be the common factor which has been missed in the coronary profile.

This accommodation to an abnormal strain may be useful in seeing a patient through a difficult time. If the attempt is unsuccessful the patient breaks down one way or another and serious physical harm is averted. It is in the stage of neither the strain being cleared nor the battle lost that the danger of coronary occlusion lies. Parallels may be drawn with the body's reaction of inflammation to infection or antigen/antibody abnormal reactions.

The significance may not lie so much in the prediction of an occurrence of myocardial infarction in an individual as in the education of a person recovering from such an episode in the prevention of further coronary occlusion. Unfortunately, I have no facts or figures to back the above but clinical impressions will do for me when research fails to produce an answer.—I am, etc.,

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- 1 Dunbar, F., *Psychosomatic Diagnosis*. New York, Paul B. Hoeber, 1943.

Predicting Coronary Artery Disease

SIR,—Your interesting leading article on the prediction of coronary artery disease (7 October, p. 3) perpetuates two false premises that I feel have made both the research into and discussion of this important subject more difficult. The first is the assumption that the aetiologies of atheroma and of overt myocardial infarction are the same. Atheroma develops chronically, is lipid-dependent, and occurs in many parts of the arterial tree. The events preceding an infarct of the myocardium probably involve the short-term disturbance of a complex thrombotic equilibrium, this disturbance being made more likely by the presence of atheroma in the coronary arteries. Why does a man suffer an infarct at a specific time when risk factors may have been present for years? What determines the sudden catastrophe? Do we wish to predict atheroma or the liability to myocardial infarction?

The second false assumption brings me to the analogy of the horse and the stable door. Should we expect the lowering of a raised serum lipid level or a raised diastolic blood pressure to prevent the occurrence or extension of coronary artery disease? It may be too late. We may lower these levels but leave the primary cause of their rise unaffected. The primary rise above the accepted norms of these factors is more likely to be the important target for future prevention, and this prevention may be important far earlier in the patient's life than we have so far considered, perhaps in the second decade.

As you say, we know little of the prediction or prevention of this greatest single cause of death in Britain. We need to attack on two fronts. We need to prevent atheroma in those still young enough or lucky enough not to have developed it. We need to prevent those who now have atheroma and risk factors from developing clinical coronary artery disease. I do not believe that these two fronts are identical.—I am, etc.,

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Mechanisms of Rosette Formation

SIR,—Mr. M. Bewick and others (26 August, p. 491) do not distinguish between rosettes formed by the spontaneous adherence of human lymphocytes to sheep red cells and rosettes known to be formed by immune mechanisms. Recent studies have indicated that rosettes may occur through at least three different mechanisms: (a) specific antibody or antibody-like molecules at the surface of lymphoid cells;¹ (b) the affinity of non-specific lymphocytes to antigen-antibody complexes;^{2,3} and (c) non-immune mechanisms of the types required for the formation of tissues and organs of multicellular organisms.

Thymocytes and to a lesser extent non-thymic lymphocytes adhere through non-immune mechanisms to a variety of autologous and heterologous cell types. Thus guinea-pig thymocytes adhere to autologous macrophages,^{4,5} rabbit and rat thymocytes adhere to autologous red cells,⁶ and rat thymocytes adhere to autologous mast cells. Similar non-immune mechanisms may result in the adherence of guinea-pig thymocytes to rabbit red cells and mouse thymocytes to rat red cells.⁸ The main characteristics of

non-immune rosette formation are the facts that a relatively large proportion of lymphocytes of unimmunized animals participate in the reaction, and that thymocytes are more active than non-thymic lymphocytes.

The proportion of human lymphocytes which adhere to sheep red cells is often relatively large in non-immunized human subjects, and human fetal thymocytes are more active than peripheral lymphocytes.⁹ The adherence of non-immunized human lymphocytes to sheep red cells is therefore likely to occur through non-immune rather than immune mechanisms. The adherence probably occurs through fortuitous cross-reactivity of sheep red cells with human lymphocyte surface receptors concerned with an autologous non-immune adherence.—I am, etc.,

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- 1 Zaalberg, O. B., *Nature*, 1964, **202**, 1231.
- 2 Siegel, I., and Christy, N. P., *Federation Proceedings*, 1972, **31**, Abstract No. 2932.
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Major Accident Teams

SIR,—To my surprise the one member of the consultant staff not included in Mr. P. E. A. Savage's major accident action card (1 July, p. 42) is the ophthalmologist. Some 15 years ago an explosion in a coal mine resulted in about 20 patients being admitted to the Victoria Hospital, Burnley, where, thanks to the presence of the orthopaedic surgeon, a major accident procedure had been instituted. Every one of these patients had eye injuries.—I am, etc.,

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Activated Charcoal in Tricyclic Drug Overdoses

SIR,—The letter by Dr. J. L. Crammer and Dr. B. M. Davies (26 August, p. 527) calls for comment. It is stated, without reference, that tricyclic drugs undergo enterohepatic circulation and that "large amounts are secreted into the bile and delivered into the duodenum." The importance of being certain that "large amounts" of the active drug are excreted in the bile lies in the fact that if such secretion did occur then there would be a temptation to undertake biliary drainage as an emergency measure in the management of acute tricyclic poisoning.

At one time biliary drainage was considered an acceptable measure in severe acute glutethimide (Doriden) overdose¹ on the assumption, since discounted, that substantial enterohepatic circulation of the active drug occurred. Other heroic measures in tricyclic poisoning included gastrostomy undertaken by French toxicologists with no operative mortality but a death rate of 50% in 16 patients.² The procedure has understandably been discontinued.

Drs. Crammer and Davies also make an

inaccurate statement about the effect of activated charcoal on aspirin ingestion. They state "activated charcoal was shown to prevent the absorption of aspirin from the human gut." As your leading article in the same issue (p. 487) points out, activated charcoal does no more than reduce absorption of salicylate, the degree of reduction depending on a number of factors. It has never been claimed that prevention of absorption will be achieved.—I am, etc.,

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- 1 Maher, J. F., Schreiner, G. E., and Westervelt, F. B., *American Journal of Medicine*, 1962, **33**, 70.
- 2 Gaultier, M., Fournier, E., Gervais, F., Dalayun, J., and Frejaville, J. P., in *Deuxième Congrès Européen des Centres de Lutte Contre les Poisons*, 1966, p. 17. Paris, Masson et Cie, 1967.

SIR,—The communication of Dr. J. L. Crammer and Dr. B. M. Davies (26 August, p. 527), which was brought to our attention only in October, has prompted us to submit some preliminary results obtained by us.

Early this year we considered activated charcoal as a means of intercepting the enterohepatic circulation of imipramine and its active metabolite desipramine. We compared levels of imipramine plus desipramine in hearts, lungs, and livers of control rats and of rats pretreated with activated charcoal after parenteral infusion of imipramine (approximately 3 mg/kg intravenously and 10 mg/kg intraperitoneally). The parenteral route was chosen to prevent adsorption of imipramine to charcoal before intestinal absorption had occurred. Imipramine plus desipramine was determined by the method of Wallace and Biggs¹ using an improved extraction procedure according to Maes.²

We often found a lowering of the organ concentrations in the pretreated group, suggesting immobilization of part of the imipramine dose. The concentration ratios pretreated/control are shown in the Table. Owing to a large biological variation not all experiments yielded significant results. Equilibrium dialysis with charcoal showed a near quantitative binding at pH 7.4 in the concentration range 0.50 µg/ml under our conditions, 1 mg activated charcoal adsorbing 1.25 mg imipramine at 50 µg/ml. We are now changing the design of our animal experiments to obtain more clear-cut results.

	Intravenous Infusion			Intraperitoneal Infusion		
	A	B	C	D	E	F
Heart ..	0.54*	0.90	0.70	0.47*	1.00	0.92
Liver ..	0.60*	0.94	0.85	0.76	1.10	1.10
Lungs	0.72*	0.70*	0.75	0.74	0.84	0.66*

*Significant at the 0.05 level.

Even if binding is not quantitative and irreversible the resulting levelling off of the imipramine load on the target organs may improve the prospects of patients with imipramine poisoning. On the basis of these preliminary results the National Poison Control Centre in the Netherlands now stresses the use of activated charcoal even in cases where absorption of the tricyclic anti-

depressant dose may well be complete before therapy is started.—We are, etc.,

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- 1 Wallace, J. E., and Biggs, J. D., *Journal of Forensic Sciences*, 1969, **14**, 528.
- 2 Maes, R., 1972, personal communication.

Hormones in the Treatment of Psychoses

SIR,—I believe the neurophysiological matrix of tension and depression is a central functional organizational scheme related to stress and increased drives, while the neurophysiological matrix of schizophrenia is a central functional organizational scheme related to reduced stress and drives. It seems that the hippocampus and the pineal gland are related to the second functional scheme, and the biochemistry of the pineal is related to that of schizophrenia. I believe, further, there are some hormones which affect these functional schemes of adaptive behaviour. In recent years in my outpatient practice I have found that Choriogonin (chorionic gonadotrophin) is effective in the treatment of affective disorders and tension with depression. I used this hormone in doses of 1,500 I.U. to 3,000 I.U. daily, using four or more injections for a course.

Oxytocin had a favourable effect in the treatment of acute schizophrenia and, in a less degree, in the treatment of chronic schizophrenia. I used 10 I.U. to 15 I.U. of oxytocin intravenously (with 10 ml to 15 ml of glucose) or 20 I.U. to 25 I.U. of oxytocin intramuscularly (one daily injection); the course is six to ten injections. I observed some rapid therapeutic effects and, then, some hospitalizations were prevented. It seems that prolactin has also some antipsychotic effect (25 I.U. daily).—I am, etc.,

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Spirolactone and Ammonium and Potassium Chloride

SIR,—In a programme of intensive drug monitoring we have found a possible interaction between spironolactone, ammonium chloride, and potassium chloride.

The patient, a 58-year-old woman with paralysis due to a compression fracture of the D 8 and 9 vertebrae and extradural compression of the cord, required an indwelling catheter and urinary antiseptics. Treatment with digoxin and frusemide for mild congestive heart failure was continued after admission, and potassium supplements were given as potassium chloride (about 50 mEq/day). The plasma potassium fell slowly to reach 2.9 mEq/l. 14 days after admission. Frusemide was discontinued and spironolactone, 25 mg four times a day, substituted. The potassium chloride was continued, and a week later ammonium chloride 4 g/day together with methenamine mandelate was started.

At the beginning of spironolactone treatment plasma sodium was 140 mEq/l., plasma potassium 4.1 mEq/l., plasma CO₂ content 28 mEq/l., and blood urea 28 mg/100 ml. Twenty days after beginning ammonium chloride the patient's condition deteriorated and she appeared acidotic. All drugs were stopped. On this day the plasma sodium was 120 mEq/l., plasma potassium 5.7 mEq/l., plasma CO₂ content 13 mEq/l., blood urea 24 mg/100 ml, plasma