on the service from all parts of Britain and many countries overseas, however, it is evident that its existence is well known, at least to the great majority of consultant microbiologists in the United Kingdom.

Since Dr Foley's letter and your leading article regrettably appear to give an entirely false impression of the available facilities I should like to make it clear that the service provided at Guy's remains fully active, is publicised through the proper channels, and is freely available to all who need to use it.

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Melatonin as a marker for pineal tumours

SIR,—In our short report (29 July, p 328) my colleagues and I recorded marked elevations of circulating melatonin levels showing a diurnal variation in a patient with a proved pineal tumour. It is difficult to explain these findings in the context of current ideas outlined in Dr E Tapp's letter (26 August, p 635) but we wholeheartedly agree that "the mechanisms controlling melatonin secretion . . . are . . . incompletely understood"—and merely offer tentative explanations. As far as we could judge and as stated in the report, normal pineal tissue could not be found at necropsy and, although it is possible that some may have been inadvertently included in the tissue enzyme assays, this seems improbable. Perhaps identification of the precise origin of the circulating melatonin will have to await the development of immunofluorescent antibody techniques for melatonin in tissue slices.

It is interesting that Dr Josephine Arendt (p 635) has also found a patient with a pineal tumour and high melatonin levels, though it is disappointing that no clinical details are available. Since the initial report we have published details of an additional five patients,¹ all of whom resembled the first in having mid-day serum melatonin levels at least five times normal. As we have suggested, further study of the effects of other diseases and of radiotherapy is necessary before the full value of our observations can be determined, but at the present time we believe our results to be consistent and promising.

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¹ Barber, S G, *et al*, *Lancet*, 1978, **2**, 372.

Whooping cough

SIR,—I am grateful for Professor G T Stewart's observations (9 September, p 768) on the Keyworth whooping-cough study (19 August, p 577) and I am pleased to answer his and Professor J A Davis's points.

The population studied is remarkably isolated, geographically and socially, for a semirural area. My partners and I can recall only one case of whooping cough in the years 1974-5 and I would suggest that the 1974 cohort was not exposed to whooping cough then. The 1977 cohort, which shows the lowest attack rate, had, I believe, the lowest rate of social interaction with affected individuals. My observation of the spread of the disease in the first two months of the

Nasopharyngeal swabs

Age (years)		0-1	1	2	3	4	5	6	7	8	9	10	11	12	Adult	Total	
<i>Bordetella pertussis</i> isolated	Immunised	0	0	0	0	0	5	2	0	1	1	0	0	0	0	9	23
	Non-immunised	1	5	3	3	0	0	1	0	0	0	0	0	0	1	14	
<i>Bordetella pertussis</i> not isolated	Immunised	0	0	1	4	3	4	2	3	1	1	2	2	1	0	24	34
	Non-immunised	1	3	3	3	0	0	0	0	0	0	0	0	0	0	10	

outbreak demonstrated acquisition of the disease only from recognised cases—between siblings, neighbouring children, relatives, etc—and a closer look at the affected members of the 1977 cohort shows a consistent picture. There were 10 families in the community with a child born during 1977 in which there was also an older child who developed whooping cough. Eight of these infants developed the disease, none of whom had had any pertussis immunisation. A further case was in an only child who was in contact with a child next door with whooping cough. Two of the 10 infants exposed did not develop the disease. One had had two doses of DPT and the other was given prophylactic erythromycin (this being the only instance of antibiotic prophylaxis in the study).

The attack rate in immunised siblings under 5 was 20%, in marked contrast with the non-immunised, in whom it ranged from 50% in those born in 1973 to 88% in those born in 1976. Positive swabs were obtained more frequently from the non-immunised than from the immunised (see table above).

The group of 20 serious cases, as defined by the presence of cyanotic attacks in children under 5 years old, breaks down as follows: seven aged 1 year, eight aged 3 years, and five aged 4 years. Three lived in three-bedroomed terraced council properties and 17 in owner-occupied detached or semidetached houses.

DOUGLAS JENKINSON

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Arenaviruses in perspective

SIR,—Your leading article (4 March, p 529) brings the arenaviruses into perspective and at the same time raises some interesting epidemiological and diagnostic features of the disease syndrome. As you state, all these viruses cause remarkably similar symptoms. In addition to the arenaviruses and Marburg and Ebola viruses mentioned by you, haemorrhagic fever (HF) syndrome may also be due to leptospirosis, bacterial septicemia, and viruses like yellow fever, dengue, chikungunya (mosquito-borne), Kyasanur forest disease, Omsk haemorrhagic fever, and CHF-Congo (tick-borne).¹ Because the disease is not characterised in the early phase a major problem is of differential diagnosis, particularly as the areas involved are far from free of other common pathogens.

Considering the overall epidemiological, clinical, and immunopathological features of dengue haemorrhagic fever (DHF) in South-east Asia I proposed a dual aetiology—interaction of virus and parasite infecting a human host around the same time.² It would not be too far-fetched to suggest a similar phenomenon for the serious manifestations resulting from arenaviruses and other viruses causing HF. This would explain the differences noted in clinical features—for example, gastrointestinal haemorrhages in one region, a

renal syndrome in another—as being due to the prevalence of not only a certain type of virus but also a particular type of parasite in a given region. Within a particular region the wide spectrum of clinical manifestations caused by infection with a virus may be dependent upon whether there are simultaneous infections, as also on the type and the stages of these infections.

According to this concept the ultimate outcome would be dependent on the host's immune response to such infections. For the pathogenesis two types of hypersensitive reaction are envisaged: (1) deposition of antigen-antibody complexes (both viral and parasitic) leading to complement activation and local inflammation; and (2) reagin- or IgE-mediated release of histamine from the sensitised cells leading to increased vascular permeability and vascular collapse.

Heavy parasitisation being common in the involved regions the IgE levels would be expected to be high to begin with. However, we could demonstrate significantly higher values for IgE in the sera of DHF patients from Bangkok as compared with controls.³ These were observed from the early phase of the illness, around the third day. It is suggested that an early test for IgE may help in predicting a grave prognosis among those patients who show significantly higher levels of IgE than the levels normally encountered in a particular region.

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¹ WHO Weekly Epidemiological Record, 1976, **51**, 325.

² Pavri, M, *Indian Journal of Medical Research*, 1976, **64**, 713.

³ Pavri, K M, *et al*, *Indian Journal of Medical Research*, 1977, **66**, 537.

Underdiagnosis of childhood asthma

SIR,—How often, in general practice, do we wait for our hospital colleagues to highlight a theme which is really our concern? Dr A N P Speight's revelations (29 July, p 331) about the underdiagnosis of childhood asthma have spurred us to report the current status of this condition in our own practice, which now operates a comprehensive morbidity register. We hope to publish a fuller report at a later date, but in the meanwhile your readers will be interested to know that asthma is the "market leader" in our chronic morbidity list (No 2 is hypertension). In fact 2.4% of the practice list of 7451 patients are registered as asthmatics and 36% of these asthmatics are children in the 0 to 14 age range. Moreover, random sampling suggests that 90% of these children were diagnosed as such before the age of 6 years.

Dr Speight correctly highlights some of the negative factors blocking the diagnosis. We would like to emphasise some positive factors which we believe have led us to make the diagnosis perhaps more often than other

doctors. Skin-testing facilities and pulmonary function equipment available on the premises assist in more accurate diagnosis, although the history is still the most important factor. A reluctance to prescribe antibiotics unnecessarily and the realisation that cough linctuses are of doubtful value has meant that we have to look more carefully at the fundamental reasons for a child's cough, and a number of these children have been found to have asthma. Acute episodes of childhood asthma in the practice number three per month and many of these are new cases which are confirmed as asthmatics on investigation.

Perhaps the most revolutionary factor in diagnosing asthma in recent years is the knowledge that we now have effective prophylactic treatment with sodium cromoglycate and that this can be used even in very young children. The realisation that we can assist children to lead a normal life has removed any fear of the word "asthma." The results in individual cases have been remarkable: children who have coughed or been breathless for several years have become symptom free and will, we hope, develop into normal adults.

We suspect that many of our adult chronic bronchitics are really asthmatics of long standing and as a result of detecting asthma in children we are taking a second look at their wheezy grandparents. Are the chronic bronchitics diagnosed 30 years ago the grandparents of the child asthmatics of today?

No doubt a special interest in and knowledge of allergic disorders has played its part in diagnosis, but we would like to emphasise that different general practitioners can be found with different interests covering the whole range of medicine and as a body we have the responsibility of providing the actual details of prevalence, incidence, and early signs of disease processes, many of which are treated for years (or for ever) without ever going near a hospital outpatient department.

ANTHONY D CLIFT
B J DAY

Manchester

HDL cholesterol and coronary artery occlusion

SIR,—The recent interesting article by Dr P J Jenkins and others (5 August, p 388) on an inverse relationship between the plasma high-density lipoprotein (HDL) cholesterol concentration and the extent of coronary artery occlusion in 41 patients provides additional support for the observed epidemiological association between the clinical expression of coronary heart disease and this particular blood lipid class. While our own findings with a larger group of patients¹ agree with the observations of Dr Jenkin's group, several others of the reported correlations were not seen in our patients or in other patient groups. For instance, Castelli *et al*² found little or no correlation between the HDL cholesterol levels and the age of several thousand patients participating in a co-operative lipoprotein phenotyping study. Indeed, this relative "constancy" of the HDL cholesterol levels during the adult years provides additional advantage over the total blood cholesterol level, which usually increases with the age and may not correlate with the presence of coronary

artery disease. It has been our own experience³ and that of other investigators⁴ that the relationship between the total plasma cholesterol level and the extent of coronary artery occlusion holds mainly for younger patients. Since coronary artery disease increases with progressing age³ without a corresponding change in the HDL level² the "protective" effect of a given HDL level seems to be less for the older patients than for the younger ones.

It is also not clear whether Dr Jenkins and his colleagues gave proper weight to the occlusion of the more proximal branches of the coronary tree when constructing their coronary artery score. An occlusion of the left main coronary artery may be more significant and lead to more serious clinical symptoms of coronary artery disease than an occlusion of the more distal second marginal branch of the circumflex coronary artery. Some explanation would also be desirable for the observed relatively low proportion of moderate to heavy smokers (57%) among their male patients. Our data⁵ and those of others⁶ have shown a higher prevalence of smoking among patients with coronary artery disease.

In spite of some of the differences in observed correlations, the reported inverse relationship between the HDL cholesterol levels and coronary artery occlusion is an important finding which should serve as an encouragement for a wider use of plasma HDL cholesterol determinations as well as for a more expanded research into factors which modify the HDL cholesterol levels.

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¹ Barboriak, J J, *et al*, *Federation Proceedings*, 1978, **37**, 801.

² Castelli, W P, *et al*, *Journal of Chronic Diseases*, 1977, **30**, 147.

³ Barboriak, J J, *et al*, *American Heart Journal*, 1974, **87**, 1974.

⁴ Murray, R G, *et al*, *British Heart Journal*, 1975, **37**, 1205.

⁵ Barboriak, J J, *et al*, *Vascular Surgery*, 1975, **10**, 81.

⁶ Herbert, N H, *Chest*, 1975, **27**, 49.

Adverse reactions to intravenous induction agents

SIR,—In your recent leading article on this subject (2 September, p 648) it was disappointing to note that there was no mention of a factor common to Althesin and propofol; I refer to the solubiliser, polyethoxylated castor oil (Cremophor EL). Some years ago I reported to the Committee on Safety of Drugs (as it was then styled) a case of apparent anaphylactic reaction to propofol. The patient concerned had been uneventfully anaesthetised by me with the same agent 14 days previously. I received a very helpful letter from the senior medical officer of the committee supplying me with the histories of five other reported cases similar to my own, in two of which the patient had suffered cardiac arrest and were successfully resuscitated, while in another the patient had died. In the published report of my own case¹ I made no mention of the possibility that the solubiliser might be a contributory or sole cause of the anaphylactic reaction since this was purely speculative, prompted by a discussion of my case with a biochemist in my hospital.

Now that similar reactions have occurred with Althesin it would seem appropriate to

take a further look at the role of Cremophor in such cases if this has not been done already. In comparing the overall safety of intravenous induction agents due account must be taken of the length of time that they have been in general use (and thus the comparative number of administrations) and the number of recorded adverse reactions. Thiopentone, as you point out, has been in dominant use for 44 years and, with 44 recorded cases of anaphylactic reactions, in this respect compares very favourably with its more recent competitors, even allowing that some cases of thiopentone anaphylaxis might have been misinterpreted or unrecorded in the past.

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¹ Thornton, H L, *Anaesthesia*, 1971, **26**, 490.

Lord Mayor Treloar Hospital, Alton

SIR,—Concerning the proposed closure of the Lord Mayor Treloar Hospital may I add one more point to those so well expressed by others? It is that the country orthopaedic hospital was primarily established for the treatment of skeletal tuberculosis. Girdlestone¹ in the first edition of his *Tuberculosis of Bone and Joint* described in vivid language the remarkable improvement in patients suffering from skeletal tuberculosis after transfer from a city hospital to a country orthopaedic hospital and Somerville and I² in a later edition added our witness. Chronic sinuses would heal rapidly; after a preliminary period major operative surgery could be undertaken without fear of sepsis or post-operative pulmonary embolism.

Such effects have not been seen by the modern generation of surgeons so they are more difficult to realise. But there is scope for the application of this principle to other diseases and it is very sad that such a magnificently built hospital as "Treloar's" should be closed. I have been told that the Swiss have been successful in adapting their previous tuberculosis accommodation to modern needs.

M C WILKINSON

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¹ Girdlestone, G R, *Tuberculosis of Bone and Joint*, 1st edn, p 15, London, Oxford University Press, 1940.

² Girdlestone, G R, *Tuberculosis of Bone and Joint*, 3rd edn, revised by E W Somerville and M C Wilkinson, p 21, London, Oxford University Press, 1965.

Negotiating rights for junior hospital doctors

SIR,—Mr Richard Rawlins's comments (19 August, p 572) on my letter (22 July, p 282) make depressing reading and augur ill for attempts to improve co-operation between organisations representing juniors in their negotiations with the Health Departments. Some can be dismissed as the politician's inveterate effort to score propaganda points—for example, his side-swipe (albeit inaccurate) at the constitution of the Hospital Junior Staffs Committee. Others are irrelevant, such as his "suggestion" that there is greater need for unity in a post-Review Body situation, this being no new thought but already widely appreciated by juniors and voiced in my letter. A few remain which cannot be disposed of so easily.