mimetic in the treatment of asthma.—We are, etc.,

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HBsAg in Papular Acrodermatitis of Childhood

SIR,—Your leading article on Australia antigen in papular acrodermatitis of childhood (9 March, p. 407), criticizing Gianotti's¹ hypothesis that serum hepatitis and papular acrodermatitis of childhood (P.A.C.) are the same disease or are closely related, prompts us to report our own experience in the matter. We have recently seen three children with the characteristic picture of P.A.C. as described by Gianotti. Their serum bilirubin was normal and transaminases were at the upper end of the normal range. Using radioimmunoassay as described by Ling and Overby² we found that all three children were HBsAg positive. None were living in any institution. Their parents were HBsAg negative.

We agree that the presence of HBsAg in cases of P.A.C. needs further investigation, and the most sensitive method available for this is radioimmunoassay. If such studies confirm previous reports they will provide strong support for Gianotti's theory of a close relationship between serum hepatitis and P.A.C. P.A.C. would then be the only disease other than serum hepatitis to be consistently associated with HBsAg. Considering the prevalence of anicteric hepatitis in children P.A.C. might be a peculiar form of hepatitis in childhood due to a particular reactivity of the reticuloendothelial system to the viral infection.—We are, etc.,

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- 1 Gianotti, F., *Archives of Disease in Childhood*, 1973, **48**, 794.
- 2 Ling, C. M., and Overby, L. R., *Journal of Immunology*, 1972, **109**, 834.

Single-dose Tinidazole Therapy for Giardiasis

SIR,—Because of increased travel *Giardia lamblia* infestation has become more common. Giardiasis may cause no symptoms but it may also cause long-lasting diarrhoea and bowel troubles.¹ Tinidazole 300 mg daily for seven days has proved to be an excellent treatment regimen with a cure rate higher than 90%.²⁻⁴ Treatment with a single 2-g dose of tinidazole has given excellent results in cases of trichomoniasis, and this encouraged me to try the effect of single-dose tinidazole treatment in giardiasis.

Fifty-three adults (18 women and 35 men) aged from 18 to 47 years and nine children aged from 3 to 10 years were selected for study. All had contracted giardiasis when abroad, and in each case the diagnosis was

confirmed by finding *G. lamblia* cysts in two formalin-preserved stool specimens. Salmonella and shigella infections were excluded by negative culture. The adults were given 2 g and the children 1 g of tinidazole in a single dose. Two stool specimens from each patient were examined by the formalin-ether concentration method of Allen and Ridley⁵ at follow-up examinations one, four to six, and 12 to 16 weeks after the drug was given.

All 53 patients came to the first follow-up examination after one week. Cysts were found in the stools of two, both of whom complained of diarrhoea and periodic stomach pains. The second follow-up examination 4-6 weeks after treatment was attended by 49 of the 53 patients. Cysts were found in the stools of four, all of whom complained of bowel dysfunction. One had been to eastern Europe in the interval since the first follow-up, had had a relapse of symptoms, and had probably been reinfected. Thirty patients attended all three follow-up examinations and at the third were free from cysts and had no symptoms. Seven of the nine children attended for all three follow-up examinations. They were all symptom-free and had no cysts in their stools. Two of these seven had been given a second dose of tinidazole 1 g after an interval of three days. Stool examinations were negative at two follow-up examinations in two children but they were lost to further follow-up.

The overall cure rate was 90%. Generally, the bowel symptoms disappeared one to three days after treatment. In a few cases some bowel discomfort lasted for about a week. A second single-dose treatment was given to the six patients in whom the first treatment failed. Two of them were cured, one of them being the patient who had probably been reinfected. The other four were finally cured with mepacrine hydrochloride after metronidazole had failed.

The single dose of tinidazole was generally well tolerated. Only minor side effects, including slight nausea and worsened diarrhoea during the day of treatment, were noted in 15% of cases. The efficacy of the treatment seems to be equal to the conventional one-week regimen. A single dose is much easier for the patient. So far as can be concluded from the small numbers 1 g of the drug is adequate for children.—I am, etc.,

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- 1 *British Medical Journal*, 1974, **2**, 347.
- 2 Andersson, T., Forsell, J., and Sterner, G., *British Medical Journal*, 1972, **2**, 449.
- 3 Howes, H. L., jun., Lynch, J. E., and Kivlin, J. L., *Anti-microbial Agents and Chemotherapy*, p. 261. Proceedings of the 9th Conference, Bethesda, American Society of Microbiology, 1969.
- 4 Pettersson, T. (1973). In *8th International Congress of Chemotherapy*, Athens, Abstract A-453.
- 5 Allen, A. V. H., and Ridley, D. S., *Journal of Clinical Pathology*, 1970, **23**, 545.

Drugs for Rheumatoid Arthritis

SIR,—We are indeed perplexed by the comments about our paper (28 September, p. 763) made by Dr. P. J. Rooney and his colleagues (28 December, p. 771). Having tried to repeat the χ^2 on our table III severally and together on a number of occasions, we find that our computing

apparatus obstinately produces the answer which we originally published and refuses to disgorge theirs. We did in fact use Yates's correction, though they seem unable to believe this.

Perhaps we were open to criticism for other reasons. It might have been better to analyse table III as a 2×3 table and partition it after the manner of Kimball.¹ This approach in fact reinforces the significance of our findings, as does Fisher's exact test. Contrary to your correspondents' charitable suggestion, the expected frequencies in table III do not quite meet Cochran's revised criteria.² However, it is probably wiser to accept that any wrangle about significance levels where the numbers are rather small is fraught with risk. Our result lies just over the significance boundary; readers should draw their own conclusions about the biological significance of it from a study of the paper. In fact we believe that the weighting method which we described was sufficient to compensate for the inhomogeneity of the initial joint scores which was noted by your correspondents, and by ourselves. Differences between those given prednisone and others were in fact tested and found not to be significant.

The rest of the comments seem to boil down to the assertion that if one could foresee the outcome of a clinical trial one might stratify the propositi in a manner different from that selected when the trial was designed. This is undoubtedly true and we congratulate any of our readers who may have that prophetic insight which we admit we do not possess and thank them for their interesting discussions of a well-known problem in clinical trial design.—We are, etc.,

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¹ Kimball, A. W., *Biometrics*, 1954, **10**, 452.

² Maxwell, A. E., *Analysing Qualitative Data*, p. 38. London, Methuen, 1961.

Diagnosis of "Reflux Oesophagitis"

SIR,—The problem of orientation of endoscopic oesophageal biopsy specimens was mentioned in the paper by Dr. G. E. Sladen and others (11 January, p. 71). A recent paper from Japan offers some help to pathologists who have to cope with these small specimens. Conventional histological assessment of oesophagitis may not be possible with tangential cuts, but Kobayashi and Kasugai¹ have described an appearance of overlapping of capillaries on tangential sections due to the proliferation of vessels into the epithelial layer with the ingrowth of lamina propria. In 31 of 32 patients with such capillary overlapping the lamina propria extended more than half way across the epithelial layer on cross-section. This sign has been helpful in some of my own cases and it may not be widely known.

It is a pity that the acid barium swallow² was not mentioned. This test involves the swallowing of barium sulphate at a pH of 1-6. The normal oesophagus responds with normal peristalsis, while if oesophagitis is present a variety of abnormal contractions may be seen which can be recorded on videotape. In 1973 McCall *et al.*³ described

their experience of the acid barium swallow in 350 patients; the test was negative in only 9% of the patients who had heartburn or regurgitation. In the study reported by Dr. Sladen and his colleagues the acid perfusion test was negative in 5 out of 19 patients with typical symptoms of oesophagitis, and it may well be that the more cumbersome acid perfusion test has little or no advantage over a carefully conducted acid barium swallow, which takes only 10 minutes at the end of a barium-meal examination. A direct comparison between these two techniques would be valuable. The retrospective use of routine radiographs in this study was disappointing and the incidence of radiological reflux given is meaningless without more details. The prone or semiprone position quoted (but not necessarily used on all these patients) will demonstrate hiatus hernia readily, especially if a bolster is used, but since air and not barium lies against the cardia in this position it is not the most sensitive method of eliciting reflux. The use of radiology in endoscopic trials demands the active involvement of a radiologist from the start so that the x-ray examination may be tailored to answer the specific diagnostic questions relevant to the trial. Moreover, in one paper comparing endoscopy and radiology in the postoperative stomach using retrospective analysis of routine barium meals⁴ 10 out of 22 erroneous reports were corrected on review of the films by radiologists interested in gastrointestinal disease.

In the future, if the indications for radiology and endoscopy are to be accurately defined and both techniques used to maximum advantage it will be necessary to have much closer co-operation between endoscopists and radiologists in planning studies like the one reported.—I am, etc.,

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- 1 Kobayashi, S., and Kasugai, T., *American Journal of Digestive Diseases*, 1974, 19, 345.
- 2 Donner, M., et al., *Radiology*, 1966, 87, 220.
- 3 McCall, I., Davies, E. R., and Delahunty, J. E., *British Journal of Radiology*, 1973, 46, 578.
- 4 Cotton, P., et al., *British Journal of Surgery*, 1973, 60, 629.

Epipodophyllotoxin VP 16213 in Acute Non-lymphoblastic Leukaemia

SIR,—It has recently been reported that the bone marrow of people with acute non-lymphoblastic leukaemia may contain a meaningful number of monocytoid precursor cells.¹ We have documented a significant response to epipodophyllotoxin VP 16213 in 47% of our patients with extensive diffuse histiocytic lymphoma,² while it has been reported that four out of eight patients with acute monocytoid leukaemia experienced complete remission with administration of this agent.³

Earlier personal experience in treating individuals with acute non-lymphoblastic leukaemia using rubidomycin and cytosine arabinoside established that, when induction of remission was achieved, an average of four courses was required. In each course a single injection of rubidomycin (1.5 mg/kg body weight) and five daily intravenous injections of cytosine arabinoside (2.0 mg/kg) were administered. This was followed by a rest period of five days,

after which the course was repeated unless the patient had entered remission.⁴

Results in two patients with leukaemia suggested a possible role for epipodophyllotoxin in the induction regimen. These particular cases are of interest since both received the induction regimen described above and went on to develop peripheral pancytopenia accompanied by the persistence of marrow disease. Significantly, whereas typical myeloblasts had initially dominated the picture, the primitive cells were now more obviously monocytoid. The addition of epipodophyllotoxin at this time resulted in complete morphological clearing of the marrow and the return of the peripheral blood count to normal.

In a pilot study 16 patients have been treated with a continuous infusion of cytosine arabinoside in a dosage of 2.0 mg/kg body weight every 24 hours and have received simultaneously a daily intravenous injection of 60 mg/m² epipodophyllotoxin and 40 mg/m² adriamycin on day 6. Of these patients, eight (50%) failed to respond, and as seven of this group died within two weeks they are difficult to evaluate. The remaining eight (50%) achieved complete remission—two within three courses, a further two within two courses, and the remaining four following only a single course. It is this reduction in the time needed to obtain remission that is of interest.

Though these results are entirely preliminary and based on a very small number of observations with only short follow-up, they are reported in order to draw attention to the possible value of adding epipodophyllotoxin to the induction regimens of patients with acute non-lymphoblastic leukaemia. A controlled prospective trial is now in progress to try to confirm these early data and to define statistically the incidence and duration of complete remission that may attend the use of this regimen. We would be interested to hear of other experiences with similar programmes.—We are, etc.,

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We thank Sandoz Ltd., for supplying the epipodophyllotoxin VP 16213.

- 1 Glick, A. D., and Horn, R. G., *British Journal of Haematology*, 1974, 26, 395.
- 2 Jacobs, P., King, H. S., and Sealy, R., *South African Journal of Medicine*. In press.
- 3 European Organization for Research in the Treatment of Cancer, *British Medical Journal*, 1973, 3, 199.
- 4 Crowther, D., et al., *British Medical Journal*, 1973, 1, 131.

Economies in the N.H.S.

SIR,—There is much interest in the costs of providing a health service and in how economies can be made without reducing standards. Dr. H. P. Hughes (5 October, p. 41) and Dr. M. C. Connell (2 November, p. 291) raised the question of unnecessary x-ray examinations in casualty departments, and Dr. J. L. Taylor (16 November, p. 406) emphasized the need for an adequate history in deciding whether to request an x-ray.

During five weeks in June and July 1966, while working as a casualty officer in a general hospital in an industrial town, I sent 401 patients for radiography to exclude fractures or dislocations. Sixteen of them had more than one injury, so a total of 421 injured parts were x-rayed. I made a note of whether I thought on clinical grounds that there was a bone injury. My diagnosis was later related to the radiological diagnosis. The 421 injuries fell into three groups: clinically negative, 181 (43%); clinically doubtful, 191 (45%); and clinically positive, 49 (12%).

Each of these groups was subdivided according to the x-ray results, assessed by the casualty officer's interpretation at the time and the radiologist's report afterwards. The casualty officer's and the radiologist's independent initial interpretations differed in 31 cases (7%). Of the 181 injuries in the clinically negative group 152 (85%) were radiologically negative, 11 (6%) were radiologically doubtful, and 18 (10%) were radiologically positive. Of the 191 injuries in the clinically doubtful group 111 (58%) were radiologically negative, 15 (8%) were radiologically doubtful, and 65 (34%) were radiologically positive. Of the 49 injuries in the clinically positive group 4 (8%) were radiologically negative, five (10%) were radiologically doubtful, and 40 (82%) were radiologically positive. Of the 421 injuries x-rayed 101 were in children under 14 years old. These gave very similar results when analysed separately.

The cases of special interest are those which were clinically negative but x-ray showed some bone injury. These numbered 18, which is 10% of the clinically negative group and 4% of the total. Of these 18 seven were in children. None of the injuries was such as would have caused danger or serious disability if undetected.

The x-ray results were also analysed according to whether the patient had come directly to the casualty department (197), had been referred by a nurse or doctor (99), or had been referred by a nurse or doctor with specific mention or strong implication in the referral letter of a need for x-ray examination (125). On analysis by x-ray results these three groups gave remarkably similar results, and the lack of any difference between the direct attenders and those referred with a specific suggestion of x-ray examination was unexpected and interesting.

These figures from nine years ago suggest that x-ray examinations were being done unnecessarily. The recent correspondence in your columns suggests that this may still be the case.—I am, etc.,

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Visual Evoked Potentials and Transient Ischaemic Attacks

SIR,—The letter from Dr. L. Bergström and others (11 January, p. 93) is of considerable interest to us. We have just completed a series of recordings of both somatosensory and visual evoked potentials from 200 consecutive patients admitted to the neurological or neurosurgical unit for investigation of a suspected intracranial lesion and from 50 "normal" subjects. Though the analysis of the results is not complete, we