Drugs for Angina Pectoris

SIR,—A casual reading of the article by Dr. Brian Livesley and others (17 February, p. 375) might leave one with the impression that their results demonstrate the superiority of verapamil and propranolol over isosorbide dinitrate on a number of criteria. Such an assertion is not made in the paper, nor is it supported by the statistical data provided.

Dr Livesley's table I gives comparative figures on trinitrin consumption, number of attacks, systolic and diastolic blood pressure, and work done for 16 subjects on each of five treatments—placebo, verapamil 120 mg thrice daily, verapamil 80 mg thrice daily, propranolol 100 mg thrice daily, and isosorbide 20 mg thrice daily.

We have carried out a reanalysis of these data. The first four treatments were compared with isosorbide by means of the Wilcoxon matched pairs signed rank test. Our reanalysis demonstrates a significant superiority of isosorbide over placebo on the criteria of trinitrin consumption ($P < 0.05$) and number of attacks ($P = 0.02$). The remaining differences are not statistically significant at the 5% level, and so the conclusion follows that the data do not indicate superiority of verapamil or propranolol over isosorbide.

There appears to be a logical discrepancy between the results of the original analysis and our reanalysis, but this is at least partially due to the effect of different sample sizes. In the original study 32 observations were available for the comparison of verapamil and propranolol with placebo, as against only 18 for the comparison of isosorbide and placebo. As is well known, larger sample sizes enable smaller effects to be detected by statistical analysis, and give higher significance for the same effects. Our reanalysis thus suggests that this effect is at least partially responsible for the fact that in the original analysis significant differences were found between verapamil and propranolol and placebo, but not between isosorbide and placebo.—We are, etc.,

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Hypocholesterolaemia in Hyperadrenal States

SIR,—Two years ago Tipton *et al.*¹ reported abnormally low serum cholesterol levels in a woman with an androgen-secreting adrenal tumour. The purpose of this letter is to report a very similar case to the one described by Tipton *et al.* and to comment briefly on this problem.

We have recently seen a woman with an androgen-producing adrenal tumour secreting large quantities of corticosteroids (urinary 17-oxosteroids ranging from 328 to 590 mg/24 hr). She had relatively low serum cholesterol levels (136–142 mg/100 ml in three preoperative samples) which promptly increased after removal of the tumour (164–175 mg/100 ml in three samples taken between the fifth and the ninth postoperative days).

Other authors have recently reported on the relationship between adrenal function and serum cholesterol levels. Dingman² reported the lowering of serum cholesterol by prolonged metyrapone administration. In

congenital adrenal hyperplasia Okuno and Nakayama³ found low cholesterol levels which increased after inhibition of the adrenal function by glucocorticoid administration. Nosedá and Schlumpf⁴ reported similar findings in idiopathic hirsutism.

Two different explanations of these phenomena have been suggested. Tipton *et al.* ascribed the low cholesterol levels seen in their patient to the high androsterone secretion by the tumour. This explanation was based on the finding that the intramuscular administration of androsterone is followed by a marked decrease in the serum cholesterol level.⁵ The other authors mentioned above interpreted their findings as being due to the excessive utilization of cholesterol for steroid biosynthesis. In our opinion the explanation suggested by Tipton *et al.* is more convincing. In fact, metyrapone administration, congenital adrenal hyperplasia, and androgen-secreting adrenal tumours are conditions in which androsterone secretion is likely to be increased and this may also be true in some cases of "idiopathic" hirsutism. However, the two hypotheses are not mutually exclusive and the possibility that the excessive utilization of cholesterol for steroid biosynthesis may play a part as a cause of hypocholesterolaemia in hyperadrenal states ought also to be considered.—We are, etc.,

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- 1 Tipton, R. H., Pennington, G. W., Lunt, R. L., and Clarke, R. G., *British Medical Journal*, 1971, 3, 744.
- 2 Dingman, J. F., *New England Journal of Medicine*, 1972, 286, 1214.
- 3 Okuno, A. and Nakayama, K., *New England Journal of Medicine*, 1972, 287, 467.
- 4 Nosedá, G. and Schlumpf, E., *New England Journal of Medicine*, 1973, 288, 106.
- 5 Hellman, L., Bradlow, H. L., Zumoff, B., Fukushima, D. K., and Gallagher, T. F., *Journal of Clinical Endocrinology and Metabolism*, 1959, 19, 936.

Polyvinyl T-tubes in Biliary Surgery

SIR,—Polyvinyl chloride loses much of its flexibility after prolonged contact with bile. Despite a printed warning on Portex packets against the use of these T-tubes for prolonged biliary intubation, this is not common knowledge among general surgeons. The purpose of this letter is to publicize this warning.

A 34-year-old woman underwent cholecystectomy for cholelithiasis elsewhere on 26 October 1971. At operation the gall bladder was found adherent to the common hepatic duct, which was damaged during dissection. Two catgut stitches were inserted to close the hole in the duct. She developed a biliary fistula, was transferred to this hospital on 30 October, and was re-explored on 5 November 1971. A stricture was found at the junction of the common hepatic duct and common bile duct. Cholangiography demonstrated a complete blockage. The stricture was excised and, after mobilization of the duodenum, end-to-end anastomosis was performed over a Portex T-tube. The tube was brought out below the one-layer anastomosis made with 4/0 silk.¹ An initial biliary leak ceased spontaneously and she was discharged on 4 December. It was intended to leave the T-tube in situ as a splint for six months at least.² Advice on further management was sought from Mr. Rodney Smith. He drew attention to the loss of flexibility of the Portex T-tube after prolonged contact with bile and advised its immediate removal. The tube was visualized radiologically, using 3 ml of 45% Hypaque (sodium diatrizoate), and removal moni-

tored under the image intensifier. Marked rigidity was noted and considerable force was needed to remove the tube. This force could have caused further damage to her biliary duct system. So far she is quite well, and 15 months after operation she is afebrile, has normal liver function tests, and an intravenous cholangiogram shows no evidence of stricture.

Damage to the biliary duct system should usually be avoidable if adequate exposure, good illumination, and careful dissection are ensured.^{3,4} If the ducts are damaged, the best results follow immediate excision of the damaged area with end-to-end anastomosis. Where possible, patients with established bile duct injuries should be sent to special centres.⁵ Financial and geographical considerations made this impossible for this patient. While opinions vary nowadays whether drainage of the bile ducts is necessary after simple exploration, most specialized centres agree on the need for prolonged splintage of the anastomosis after excision of a stricture.³ If T-tube splints made of polyvinyl chloride are used, they will so lose their flexibility during prolonged contact with bile that their removal is likely to cause further damage to an already injured duct, with increased risk of further stricture. In this patient, even after 12 weeks, great rigidity had developed. That she is still well is fortuitous. A stricture is still possible.

Portex Ltd. print a warning on the wrappers of their T-tubes stating they are unfit for prolonged intubation. Nevertheless, when this patient was demonstrated at the East Mediterranean Medical Congress in Cyprus in 1972 many British surgeons were unaware of this problem with polyvinyl chloride T-tubes. This supports the suggestion that such patients should be sent to special centres when possible. Obvious loss of flexibility is evident in these T-tubes after only 10 days and it is probably preferable to use latex or rubber every time.

I am indebted to Mr. Rodney Smith for his helpful written advice on this patient, also to the Director General of Medical Services (R.A.F.) for permission to publish this letter.

—I am, etc.,

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- 1 Catell, R. B., and Braasch, J. W., *Surgery, Gynecology and Obstetrics*, 1957, 109, 531.
- 2 Warren, K. W., *et al.*, *Surgical Clinics of North America*, 1971, 51, 711.
- 3 Warren, K. W., and Hardy, K. J., *Surgical Clinics of North America*, 1967, 47, 1077.
- 4 Maingot, R., *Annals of the Royal College of Surgeons of England*, 1963, 32, 42.
- 5 Cooke, R. V., *Annals of the Royal College of Surgeons of England*, 1971, 48, 323.

Lymphocyte-depletion Hodgkin's Disease

SIR,—The clinical and pathological picture of the cases of "lymphocyte-depletion Hodgkin's disease" described by Neiman *et al.*¹ and referred to in your leading article (16 June, p. 625) is very similar to the two cases described as reticular Hodgkin's disease in 1957 in my M.D. thesis.² Both patients were relatively young males (31 and 44 years old) and presented with fever, progressive weight loss, some involvement of hilar lymph nodes and massive enlargement of abdominal lymph nodes, enlargement of liver and spleen, severe anaemia, and leucopenia. The time of survival from the beginning of their illness was 6½ and 7 months respectively. The

histological picture was characterized by a massive, almost syncytial growth of reticulum cells with many Reed-Sternberg cells, severe lymphocyte depletion, and absence of eosinophils, plasma cells, or fibrinoid necrosis. This picture was completely different from the entity described as Hodgkin's sarcoma.

Deelman⁸ and I concluded that this disease could be described, both on clinical and on pathological grounds, as a separate entity. I had the opportunity to discuss these cases personally in 1955 with both Dr. F. Parker and Dr. R. J. Lukes, who were at that time rather sceptical about my proposal to mark off this disease from classic Hodgkin's disease as a separate subgroup. However, it should be borne in mind that in 1955 discussions about the immunological nature of Hodgkin's disease were still unheard of. A good account of identical cases had already been given in 1953 by Miss A. M. Hippchen.⁴—I am, etc.,

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¹ Neiman, R. S., Rosen, P. J., and Lukes, R. J., *New England Journal of Medicine*, 1973, **288**, 751.

² Offerhaus, L., *Borderline Cases of Hodgkin's Disease*. Assen, Van Gorcum and Cie., 1957.

³ Deelman, H. T., *Leerboek der Pathologische Anatomie*, vol. III. Haarlem, De Erven, F. Bohn N.V., 1962.

⁴ Hippchen, A. M., M.D. Thesis, Frankfurt, 1953.

SIR,—Immunity may vary widely in individuals and particularly during different stages of a disease. Patients with lymphocyte-depleted Hodgkin's disease die rapidly, presumably because the illness is advanced by then and the immunity is almost spent. Untreated cases showing thrombocytopenia were also found in one series at Hammer-smith Hospital (unpublished) to have died unusually promptly. The immune changes in this disease may originate some time before the symptoms and signs appear. Until the natural history of the illness is completed, however, the significance of the clinical and histological findings must remain doubtful. The pathological mechanism has to be traced to its source before it can become meaningful.

Both Hodgkin's disease and sarcoidosis sometimes show a familial incidence and blood eosinophilia, and occasionally they are combined.^{1,2} Moreover, sarcoidosis is more likely to develop into Hodgkin's disease after the infiltration has healed, considering the time factor. Patients with Hodgkin's disease may have the same immune patterns as late-stage sarcoidosis, but they do not exhibit the early complications, such as sarcoid hyperthyroidism. During the course of sarcoidosis the immunity may often alter considerably, but usually the aggression is directed only defensively. The humoral response may lead rarely to early and inappropriate endocrine stimulation, and sometimes later to gland failure.³ Cell-mediated responses are both active and prolonged in this disorder,⁴ and when they are overactive one result perhaps may be Hodgkin's disease. The four types of Hodgkin's disease⁵ probably arise because the degree of immunity is eventually different in each form. The scars of the immune contest are obvious, but the reason for them is still obscure. Sometimes the sarcoid agent⁶ is

possibly responsible for all types of Hodgkin's disease.—I am, etc.,

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Chilworth, Surrey

¹ MacGregor, G. A., *Lancet*, 1973, **1**, 322.

² MacGregor, G. A., *Lancet*, 1973, **1**, 997.

³ Karlsh, A. J., and MacGregor, G. A., *Lancet*, 1970, **2**, 330.

⁴ Caspary, E. A., and Field, E. J., *British Medical Journal*, 1971, **2**, 143.

⁵ *British Medical Journal*, 1973, **2**, 625.

⁶ Mitchell, D. N., and Rees, R. J. W., *Lancet*, 1969, **2**, 81.

American Medicine

SIR,—We enjoyed Dr. I. L. Gregory's visit to this hospital as a locum consultant surgeon in 1970 but did not realize how unobservant he was. He states (7 July, p. 50) that in none of the five provincial hospitals where he worked did he find an intermittent positive-pressure breathing machine. May I assure him that at that time we had in the operating theatres of this hospital four such machines and in the intensive care unit four ventilating machines for adults and two for babies and children. For 10 years we have had a 24-hour blood gas analysis service. I cannot, of course, make observations on his other comments about British or American medicine.—I am, etc.,

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Serum Immunoglobulins in Ankylosing Spondylitis

SIR,—We were interested to read that Dr. D. N. Golding (16 June, p. 663) found that one or more of the serum immunoglobulins was abnormal in five of his 10 patients with ankylosing spondylitis. We are currently studying this subject and would like to report our preliminary findings in view of the current interest in the aetiology of ankylosing spondylitis with its high incidence of HL-A W27¹ and the familial and clinical links with other seronegative arthropathies.²

Blood samples have been obtained from 25 patients with definite ankylosing spondylitis. Abnormally high results were found for IgG in 10 (40%) and for IgA in 12 (48%), while none had raised IgM or IgD values. Kriegel *et al.*³ also found high levels of IgA and slight but insignificantly raised IgG levels in patients with progressive forms of the disease. Even more striking were the markedly raised immunoglobulin levels which we have found in the synovial fluid of patients with peripheral joint involvement.⁴ These observations do not prove anything but suggest that immunological mechanisms may be playing a part in the aetiology of ankylosing spondylitis and are a stimulus for further research in this field.—We are, etc.,

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¹ Brewerton, D. A., *et al.*, *Lancet*, 1973, **1**, 904.

² Wright, V., and Moll, J. M. H., *British Journal of Hospital Medicine*, 1973, **9**, 331.

³ Kriegel, W., Burger, R., Kapp, W., and Alexopoulos, J., *Verhandlungen der deutschen Gesellschaft für Rheumatologie*, 1969, **1**, 206.

⁴ Kendall, M. J., Farr, M., Meynell, M. J., and Hawkins, C. F., *Annals of the Rheumatic Diseases*. In press.

Hepatitis-associated Antigen in V.D. Clinic Patients

SIR,—The data of Dr. D. J. Jeffries and others (26 May, p. 455) raise some interesting points in relation to the changing views on the mode of transmission of hepatitis B.¹⁻⁴

The increased hepatitis B antigen carrier rate in European homosexuals supports the proposed possibility of venereal transmission of the disease in homosexuals.⁵ Skin and mucous membrane lesions usually present in homosexuals may indeed play some role in transmission. Since such lesions are also present in female prostitutes we should expect that they would also have an increased hepatitis B antigen carrier rate. However, the data presented by Dr. Jeffries and his colleagues argue against venereal spread in the heterosexual sense.

The results of a study to be published soon are in agreement with these findings. Thus hepatitis B antigen was found in nine (3.6%) out of 247 prostitutes who are regularly referred to us for check-up. A similar frequency (3.4%) was found in a sample of 379 pregnant women of similar age and of relatively low socioeconomic level. In view of the above results it would seem appropriate to look for additional reasons for the increased carrier rate among homosexuals.—I am, etc.,

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¹ Krugman, S., and Giles, J. P., *Journal of the American Medical Association*, 1970, **212**, 1019.

² Cossart, Y. E., and Vahrman, J., *British Medical Journal*, 1970, **1**, 403.

³ Papaevangelou, G. J., Kourea, T., and Tsoukas, S., *Pathologia et Microbiologia*, 1971, **37**, 361.

⁴ Hersh, T., Melnick, J. L., Goyal, R. K., and Hollinger, F. B., *New England Journal of Medicine*, 1971, **285**, 1363.

⁵ Vahrman, J., *Lancet*, 1970, **2**, 774.

Hepatitis B Antigen in Ascitic Fluid in Cirrhosis

SIR,—Hepatitis B antigen (HBAG) is considered to be either the aetiological agent of type B hepatitis or at least closely related to it.¹⁻⁴ This antigen has been demonstrated in the serum of subjects with persistent hepatitis, chronic aggressive hepatitis, and cirrhosis.⁵⁻⁷

We have investigated the possible presence of HBAG in ascitic fluid from patients with cirrhosis whose serum was positive for the antigen. Samples of serum and heparinized ascitic fluid were tested for the presence of HBAG by an immunoreoelectrophoretic method,^{8,9} using kits supplied by Farmitalia Laboratories. The specimens were collected simultaneously from subjects who had not previously undergone paracentesis and care was taken to ensure that the ascitic fluid did not contain blood. This study was performed on 12 patients with hepatic cirrhosis in the ascitic phase, eight of whom were HBAG-positive and four negative. The diagnosis of liver cirrhosis was always confirmed by laparoscopy and liver biopsy carried out after collection of the ascitic fluid.

HBAG was found in the ascitic fluid of all eight HBAG-positive subjects at a titre similar to that in the blood. The antigen was not detected in the ascitic fluid of the four HBAG-negative subjects, indicating that the