Sex Difference in Normal Neutrophil Count

SIR,—I wish to draw attention to a minor inaccuracy in the valuable study on normal haematological values by Drs. Barbara J. Bain and J. M. England (8 February, p. 306). The significantly lower neutrophil counts in women than in men found by Allen and Alexander¹ were confined to the postmenopausal age groups and were not a feature of the whole age range 18–65. In fact, in a larger series of blood donors (408 male, 789 female) Cruickshank² and Cruickshank and Alexander³ found higher mean neutrophil counts in premenopausal women (age groups 18–23 to 36–41) than in men, though the differences failed to reach statistical significance. The influence of the menopause on the neutrophil count of women has to be borne in mind when interpreting individual values.—I am, etc.,

M. K. ALEXANDER

Group Pathology Laboratory,
Warwick

¹ Allen, R. N., and Alexander, M. K., *Journal of Clinical Pathology*, 1968, 21, 691.

² Cruickshank, J. M., D.Phil. Thesis, Oxford, 1970.

³ Cruickshank, J. M., and Alexander, M. K., *British Journal of Haematology*, 1970, 18, 541.

Osteosarcoma—New Hope

SIR,—In my opinion the restrained optimistic note of your leading article "Osteosarcoma—New Hope?" (15 February, p. 355) is justified. Nevertheless, the title may obscure the broader fundamental principle contained in assessing the benefits of "prophylactic" adjuvant chemotherapy for osteosarcoma. The basic hypothesis now to be tested is whether the occult micro-metastases of any sarcoma—not necessarily osteosarcoma—can be restrained or destroyed by prolonged chemotherapy administered to an apparently well patient. In this context it is obviously necessary to investigate a whole spectrum of malignancies. Even if this were proved it is still imperative to emphasize that any successful initial treatment must completely control the primary tumour. For many osteosarcomas this cannot be effected by radiotherapy alone. Thus early adjuvant chemotherapy is also on trial in order to ascertain whether in combination with radiotherapy it can effectively destroy the primary. This we shall learn in time from the response of tumours in inoperable sites. Early last year the Bristol Bone Tumour Registry set up a local clinical trial to compare the results in patients given adjuvant "prophylactic" chemotherapy with the past records of those treated by radiotherapy and surgery alone. This study employs a fairly simple protocol (methotrexate with folinic acid rescue and doxorubicin). So far the early results appear to follow those to which you refer.^{1,2}

There are two useful early criteria obtainable from clinical records for assessing the value of this new therapy: (1) the time in months from starting treatment when half of the patients are free from disease, and (2) the proportion of patients free from disease after one and two years. Nevertheless, all treated patients must be closely observed for at least five years for late metastases which may appear, though seldom in children. Moreover, delayed side effects of cytotoxic drugs may present

clinical problems. Nor is it to be expected that the chemotherapeutic arsenal will remain static for long. Inevitably, clinicians will be asked: "Is this new and sometimes unpleasant treatment effective now?" One can only emphasize that with osteosarcoma any disease-free survival over six months may be a step towards an improved prognosis, and that freedom from disease after 24 months (30 months in a child) forecasts the likelihood of ultimate recovery. Recent American reports that prophylactic chemotherapy retards the appearance of metastases must be regarded only as the first significant advance towards effective anti-metastatic treatment.—I am, etc.,

C. H. G. PRICE

Bristol Bone Tumour Registry,
Bristol Royal Infirmary,
Bristol

¹ Jaffe, N., et al., *New England Journal of Medicine*, 1974, 291, 994.

² Cortes, E. P., et al., *New England Journal of Medicine*, 1974, 291, 998.

Factors Related to Relapse in Multiple Sclerosis

SIR,—The death of Dr. C. E. Lumsden in 1974 struck a harsh blow at the process of correlating current evidence as to the causes of multiple sclerosis (M.S.). In fact a solution may now be in sight. It seems that an autoimmune reaction causes the M.S. plaque, and those who develop M.S. have anti-brain autoantibodies circulating in the blood—a peculiarity which may have been acquired during an illness in infancy. The destructive autolysis in the M.S. plaque is activated by another factor, perhaps viral or environmental, and the latter is most favoured.

If this is so, those who develop M.S. must be vulnerable to a factor which affects vast numbers of people without obvious harm to any save the M.S. few. If this factor can be identified and countered, then M.S. activity should cease entirely and this is the only realistic type of "cure." The plaques appear around venules in the white matter where the blood-brain barrier is most vulnerable and in those regions where the circulation is normally most tenuous and terminal—once again we are forced to consider possible stresses to the circulation in communities where M.S. is well known. The normal circulation in the white matter (unlike the grey) increases in volume during the first 12 years of life and then slowly withers during the next decade—this second decade corresponds to the first appearance of cases of M.S.

M.S. rarely if ever develops in athletes in training or in heavy manual workers, and this is in striking contrast to the vulnerability to a virus disease such as poliomyelitis. Many people with M.S. discover for themselves a pattern of living which enables the disease to become more or less stationary, often by adopting a planned balance of rest and exercise for their daily routine. The purpose of this letter is to urge family doctors and relatives to supervise the patient's pattern of living and to study carefully the circumstances related to any relapse that occurs. All must realize that arrest of the process is the only possible cure; old scars cannot be removed and the so-called remission merely represents the

12–18 months often required for the spinal cord to readjust to a previous injury. As a fully retired clinician I am not available to give advice, but am glad to collect carefully prepared records or life-stories of patients from those who are prepared to study environmental influences in relation to M.S. activity.—I am, etc.,

W. RITCHIE RUSSELL

31 Belsyre Court,
Woodstock Road,
Oxford**Unity and Diversity in Schizophrenia**

SIR,—For an idea to be lost in the swirl of controversy would be a pity, particularly if it deals with an important issue and is also testable. Your leading article (21 December, p. 673) was concerned with our thesis of two types of schizophrenia.¹ This is based on two sets of findings.

First, hebephrenic probands have more familial schizophrenic illness than paranoid probands. This would support a polygenic hypothesis in schizophrenia, hebephrenia being more clinically severe than paranoid schizophrenia. In fact, the data do show that paranoid schizophrenia is less likely to lead to social incapacity.² An alternative hypothesis would be that of two types of schizophrenia each transmitted differently. We cited a number of studies showing an increased schizophrenia risk in the relatives of the hebephrenics. Our own data as originally published contained a slight error (our own fault). The correct morbid risk for schizophrenia in relatives of hebephrenic probands is 2.4% and for paranoid probands 9.8%, a threefold difference. Controlling for age, the proportion of 112 hebephrenics under 40 with schizophrenia in the family was 13.4%; that for 62 paranoids under 40 was 6.1%. These are not significant differences; they are in the direction of other and larger studies. The low yield of familial schizophrenia is simply the result of the fact that the data come from records rather than personal examination. Record studies from other centres also show small amounts of familial schizophrenia as this method taps only those family members with clear deteriorating illnesses. If one examines family members personally the risks increase.

Second, our hypothesis proposed that if a polygenic hypothesis were responsible for all schizophrenias schizophrenic primary relatives of hebephrenic probands should be of the paranoid subtype in 50% or more of the cases. Thus the subtype should not breed true particularly. Here we have a difference of opinion in that, unlike your article, we believe there is a large body of data which supports breeding true to type. Slater,³ analysing Kallmann's 1938 material, showed a highly significant ($P < 0.001$) relationship between probands and family members in regard to subtypes. From the Kallmann material one may note that hebephrenics had 70 schizophrenic relatives, 70% hebephrenic and 30% paranoid. Paranoids had 18 schizophrenic relatives, 28% hebephrenic, 72% paranoid ($P < 0.005$). Slater also evaluated material from Zehnder and found that of 18 pairs of sibs with at least one hebephrenic, 11 (61%) were hebephrenic-hebephrenic pairs. Böök⁴ in a North Swedish investigation showed a striking subtype similarity between probands and their schizophrenic relatives. In this study most of the schizophrenics were considered catatonic or hebephrenic-catatonic. Some of our own data indicate that it may be quite difficult to differentiate chronic catatonia and hebephrenia.¹

In your leading article it was noted that we had not taken into account studies which came from our own department.^{5,6} The simple reason for this is that our paper was written and submitted several months before these subsequent studies. Of importance, however, is the fact that the newer studies also indicate an increase in the amount of schizophrenic illness in the family members of hebephrenics when they are compared with paranoids. However, these data show no subtype similarity between probands and relatives. The relatives were diagnosed by physicians who were blind to the subtype of