working party² make it clear what sort of people it is intended to detain in these places or what objectives will be attained by doing so.

The proposed units are not to be used for long-stay care (Butler Report, para. 17; D.H.S.S. Report, para. 44). But a major problem with discharge from special hospitals now is the reluctance of staff in ordinary hospitals to take these patients (Butler Report, para. 5). No reasons are given why discharge from a regional security unit should be any easier. Faith is placed in the possibilities for "therapy" in the proposed units (Butler Report, para. 9; D.H.S.S. Report, paras. 23, 28, 29(3), and 50) but its nature is not discussed. The Butler Committee is justifiably concerned about overcrowding in special hospitals, but if this is due to the number of people there who have "dangerous, violent, or criminal propensities" (para. 4) it is not made clear how overcrowding is going to be relieved by the provision of units which are not to house people who would be an immediate danger to the public (para. 12). This can be achieved only if we succeed in convincing many people that many of those now in special hospitals are less dangerous than they have hitherto thought them to be. Otherwise the security at regional units cannot be less strict (D.H.S.S. Report, para. 8) than at special hospitals.

The working party states (paras. 28 and 29) that "the meaning of security is no longer well understood," but neither report clarifies the important issues involved. They mention the difficulties experienced by staff in ordinary psychiatric hospitals when dealing with clients whose behaviour presents problems of management on the ward (Butler Report, para. 9; D.H.S.S. Report, paras. 7, 19, 20, and 22). Admissions to regional security units will clearly be from among patients whose behaviour is disruptive. However, no indication is given of any help likely to be provided to staff in existing psychiatric hospitals to develop rich and sophisticated rehabilitation programmes which could decrease the frequency of disruptive behaviour and avoid the need for restraint. Without such help it seems likely that transfers from ordinary hospital to security units could soon fill the new places created and merely regionalize the problems now faced in the State security units. We are concerned that alternative ways of providing resources for training patients referred to security units should be developed before new units are created.

We have every sympathy with the points made by Dr. D. Tidmarsh (2 November, p. 286) but we cannot see how, in the absence of a clearly stated admission policy and goals of treatment, the proposed regional units can be prevented from becoming as badly blocked as the existing special hospitals.—We are, etc.,

ALBERT KUSHLOCK
GERALDINE CANSICK
JOHN W. PALMER

Health Care Evaluation Research Team,
Winchester

World Medical Association

SIR,—Understandably in the present financial climate the question is being asked whether the B.M.A. can afford to continue its membership of the W.M.A. I believe the B.M.A. can and must because never before has there been such a need for those who believe in professional freedom to stand together—not only in Britain but throughout the world. We may be struggling against Government interference in Britain but the position of our colleagues in many other countries is far more precarious, especially in developing countries where Governments, for compelling reasons, often have to assume dictatorial powers. The "honour and dignity" of the profession can be sustained only when there is a free and strong medical association. If this is essential on a national level it is just as essential on an international level. International agencies, the U.N., I.L.O., U.N.E.S.C.O., and of course W.H.O. in particular, are involved in matters which often have a direct impact on the way medicine is practised. It is therefore essential for the voice of the profession to be heard at this level. Just as the B.M.A. is the voice of the medical profession vis-à-vis the Government in Britain, so is it equally important that a similar authoritative body should exist at international level.

The B.M.A. was one of the founder members of the W.M.A. and has been a highly respected and staunch supporter ever since. Its subscription to the W.M.A. costs two Swiss francs per U.K. member, roughly 30p each, a very small contribution to make to a very important task.

May I take this opportunity to remind B.M.A. members that they are entitled to join the W.M.A. personally as associate members? Not only does this help to support the work of the W.M.A., but such membership can be useful to those who do much international travel. Associate members are also entitled to take part in the annual assembly. The subscription rate is at present £6 per annum, including subscription to the *World Medical Journal*. Anyone interested should contact the B.M.A.—I am, etc.,

H. A. CONSTABLE

Chairman,
British Supporting Group of W.M.A.

Ringwood, Hants

Effective Dosage of Tricyclic Antidepressants

SIR,—Continuing the debate on the clinical significance of tricyclic antidepressant plasma concentrations and the optimum "therapeutic range," to which Drs. A. J. Coppen and S. A. Montgomery refer (11 January, p. 91), we feel that further detailed comment may not be out of place.

There are now quite a number of published studies in which the relationship between tricyclic antidepressant plasma concentrations and clinical response has been examined. The findings, however, are by no means in concordance for the simple reason that the design of these studies conforms to no single pattern. Generalizations from the results of one study are therefore fallacious.

Firstly, there is little clinical consistency in the type of patients investigated. Some workers have considered only patients with "severe endogenous" depression, others have considered cases of

"moderate" depression, and one study specifically included patients with personality or environmental problems. It would seem illogical, if not foolish, to expect any sort of clear relationship between drug plasma concentrations and therapeutic response among such a diagnostic diversity of patients.

Secondly, not all of the studies have been devoted to the same drugs, some having been concerned with nortriptyline, others with imipramine, and yet another with amitriptyline. Since there are important pharmacological differences between the tricyclic antidepressants it is not always valid to compare the findings of studies conducted on different drugs.^{1,2}

Thirdly, the analysis of tricyclic antidepressant plasma concentrations is difficult to perform and the same techniques have not always been followed throughout. Thus the plasma nortriptyline levels reported in one particular study are quite at variance with the accumulated data on the pharmacokinetics of this drug in man.³⁻⁶

Fourthly, we understand that endogenous depression is a complex and biochemically heterogeneous disease, probably with a deficiency of at least two important neurotransmitter amines.⁷⁻⁹ Thus all the patients clinically classified as "endogenous depressives" in various studies need not be expected therapeutically to respond universally to antidepressant medication.

For many reasons, therefore, we at least would hesitate to propound a "therapeutic range" of plasma levels for all tricyclic antidepressant drugs that might be used in a diversity of patients superficially diagnosed as suffering from "depression." From our experience over a number of years now in offering a service for the measurement of tricyclic antidepressant drugs in plasma we in this unit would agree with the views of Asberg² that in patients who do not respond to seemingly adequate doses of antidepressant drugs and in those who suffer from serious side effects the measurement of plasma levels is a way of increasing the efficacy of treatment. In addition, the regular monitoring of these levels may also prove useful in those patients receiving long-term medication for the prophylaxis of recurrent endogenous depression.¹⁰ Patients with properly diagnosed endogenous depression, carefully managed in this way, must be distinguished from that vast population of people prescribed antidepressant medication for mental "depression" of no clear-cut aetiology, for whom, we would admit, the performing of plasma level analyses is of doubtful value.—We are, etc.,

ROBIN BRAITHWAITE
ROY GOULDING

Poisons Unit,
Guy's Hospital,
London

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- 2 Asberg, M., *Clinical Pharmacology and Therapeutics*, 1974, 16, 215.
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Fluorescent Drumsticks in Human Female Polymorphs

SIR,—The presence of a sex specific nuclear appendage, called "drumstick," was first reported in human polymorphonuclear leucocytes by Davidson and Smith.¹ In normal

1 Home Office and Department of Health and Social Security, *Interim Report of the Committee on Mentally Abnormal Offenders*, Cmnd. 5698. London, H.M.S.O., 1974.

2 Department of Health and Social Security, *Revised Report of the Working Party on Security in N.H.S. Psychiatric Hospitals*. London, D.H.S.S., 1974.

females it is generally believed to originate from one of the X chromosomes (like the Barr body). Brightly fluorescent "drumstick-like" nuclear projections (that is, structures similar to typical drumsticks in shape but generally smaller in size) in male polymorphonuclear leucocytes have also been reported and a causal relationship between these projections and the Y chromosomes has been suggested but not yet proved.^{2,4} We have previously reported that the X as well as the Y chromatin body in interphase nuclei of various types of cultured and uncultured cell could be unambiguously identified by their characteristic size, location, and bright fluorescence.^{5,6} We now report that a proportion of drumsticks in female polymorphonuclear leucocytes, similar to the drumstick-like nuclear appendages in male leucocytes, exhibit bright fluorescence when stained with quinacrine mustard solution.

Our preliminary fluorescent study of blood samples derived from three normal males and three normal females showed that both brightly fluorescent and very weakly fluorescent drumsticks (in females) and drumstick-like (in males) appendages existed in polymorphonuclear leucocytes of all six individuals. From 500 to 1000 cells were examined in each case. About 77-92% (varying in different individuals) out of 121 drumsticks in female leucocytes and 68-86% out of 215 drumstick-like nuclear appendages displayed distinctive bright fluorescence.

Brightly fluorescent "drumstick-like" body in male (left) and typical drumstick in female (right) polymorphonuclear leucocytes.

The remaining drumsticks and drumstick-like appendages showed very weak fluorescence. The brightly fluorescent appendage in the male and in the female leucocytes could be readily distinguished from each other by their characteristic shape and size, being much larger in females than in males (see fig.). Bright fluorescence of sessile nodules and intranuclear bodies was also seen in about 21-25% of female and 13-27% of male leucocytes. One of the females had brightly fluorescent double drumsticks in about 4% of her polymorphs. The fluorescent banding patterns and chromosome constitution of all six individuals were found to be normal.

The sex chromatin body in the interphase nucleus of various cell types of mammalian species is known to be directly formed by the condensation of the genetically inactive X chromosome. We found⁶ that all the sex chromatin bodies in human cultured fibroblasts, amniotic fluid cells, and other cell types exhibit bright fluorescence. Since all drumsticks do not exhibit bright fluorescence the fluorescent property of the inactive X chromosome in polymorphonuclear leucocytes may be different from that in other types of tissues. Alternatively, the drum-

stick in normal females may not be formed directly by the condensation of the inactive X chromosome and thus could represent a sex-specific nuclear structure in the nature of a secondary sexual character. These and other aspects of the possible origin of drumsticks are now being investigated by the fluorescent method and will be reported later.—We are, etc.,

ASIT B. MUKHERJEE
JUAN SAN SEBASTIAN

Department of Biological Sciences,
Fordham University,
Bronx, New York,
U.S.A.

1 Davidson, W. M., and Smith, D. R., *British Medical Journal*, 1954, 2, 6.

2 Lamborot-Manzur, M., Tishler, P. V., and Atkins, L., *Lancet*, 1971, 1, 973.

3 Polani, P. E., and Mutton, D. E., *British Medical Journal*, 1971, 1, 138.

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5 Mukherjee, A. B., Moser, G. C., and Nitowsky, H. M., *Nature*, 1972, 235, 226.

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Large Y Chromosome Found in Polymorphs by a C-staining Technique

SIR,—Large Y chromosomes with extended heterochromatic regions on their long arms are known to be quite common familial variants which appear to be without phenotypic effect, though an association with certain types of mental retardation has been suggested.¹ Ricci *et al.*² pointed out that the polymorphs of individuals with large Y chromosomes often show nuclear projections which are larger than those usually encountered in males and resemble the drumsticks of polymorphs in females. Using quinacrine, Lamborot-Manzur *et al.*³ were able to confirm that in polymorphs the prominent fluorescent bodies due to large

B.S.G. staining technique⁵ for constitutive heterochromatin. A, blood smear showing large chromosome (arrow) in polymorphs ($\times 1815$). B, lymphocyte culture. No. 1 and G group chromosomes, including the Y chromosome with an extended heterochromatic region, from two cells. No. 1 chromosomes show a moderate degree of polymorphism ($\times 3374$).

Y chromosomes were often situated in nuclear projections.

We have recently noted⁴ that in individuals with an extended heterochromatic region on one of their No. 1 chromosomes a large chromocentre was present in over 50% of polymorphs after staining with a C-banding technique.⁵ This chromocentre was usually situated in contact with the nuclear membrane of one of the larger lobes (a number of smaller chromocentres presumably representing other C-staining chromosomal regions were also seen).

Using this technique we have recently screened a series of blood smears for possible heterochromatin variants. Among these we encountered one in which the large chromocentre was generally situated in a nuclear projection rather than in one of the main lobes of the polymorph (see fig. A). The patient, aged 69, was being treated for cervical and lumbar spondylosis. Chromosome studies on peripheral blood showed that a large Y chromosome was present (see fig. B).

Thus the possible usefulness of the C-staining technique for the detection of heterochromatin variants may be extended to the detection of large Y chromosomes by virtue of the situation of the large chromocentre in a projection rather than in one of the main lobes of the polymorphs.

We thank Dr. J. G. P. Williams for his help in this study and Mr. P. J. Whyer for providing the blood smears. This work was supported by a grant from the Cancer Research Campaign.—We are, etc.,

N. B. ATKIN
V. J. PICKTHALL

Department of Cancer Research,
Mount Vernon Hospital,
Northwood, Middlesex

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All Change

SIR,—Dr. H. R. Rollin's letter (9 November, p. 341) is most timely and apt, especially as it comes from a psychiatrist. I am a general practitioner and have experienced similar difficulties from the other side of the fence.

I have a patient, a young woman, for whom I needed psychotherapeutic advice. An appointment with psychiatrist Dr. X at hospital A, to which I normally refer most of my patients, was refused as the patient was said not to live within the catchment area of the hospital's psychiatric outpatient services. An appointment with psychiatrist Dr. Y at hospital B, also situated in my borough, was also refused and my patient was advised to make an appointment at hospital C, where psychiatrist Dr. Z holds outpatient sessions. Dr. X, Y, and Z are probably equally competent psychiatrists. There were, however, good medical reasons why I had chosen Dr. X and, in the second place, Dr. Y and why I did not wish to consult Dr. Z in this particular case.

In some specialties, assuming equal competence and qualifications of consultants,