warfarin therapy. Between 1961 and 1967 we started our first trial of oral anti-coagulants in patients with advanced cancers and 29 patients out of 96 responded for one to five years.⁴

In 1967-8 it was not possible to organize a controlled clinical trial because of the small number of suitable patients available to us and the multiplicity of factors in each case. As an alternative, however, we used patients as their own controls by starting warfarin therapy when their disease became resistant to cytotoxic therapy. The results were presented at the annual meeting of the Irish Association for Cancer Research in December 1971 and are being published. Briefly, 30 cases of lymphoma and chronic leukaemia being maintained on a single cytotoxic agent—busulphan, chlorambucil, or cyclophosphamide—were given warfarin therapy to double the prothrombin time when their disease became resistant. The same cytotoxic agent was continued in each case. Response was measured by calculating the total dosage of cytotoxic agent, per three month periods, required to maintain the patient in remission before and after the addition of warfarin. Twenty-one cases responded and the three-monthly average requirement of cytotoxic agent for these patients decreased to 25% of the pre-warfarin level after three months.

From our experience with warfarin in the treatment of human cancer it would appear to be a useful agent for maintenance therapy. This supports the observation of Michaels, quoted in your leading article, that mortality from cancer is lowered by oral anticoagulants. We found that morbidity is also lowered and this is usually the first sign of response to therapy occurring seven to 14 days after the prothrombin time is doubled.—I am, etc.,

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¹ Thornes, R. D., and Martin, W. T., *Irish Journal of Medical Science*, 1961, 6, 487.

² Lisnell, A., and Mellgren, J., *Acta Pathologica et Microbiologica Scandinavica*, 1963, 57, 145.

³ Thornes, R. D., Edlow, D. W., and Wood, S., jr., *The Johns Hopkins Medical Journal*, 1968, 123, 305.

⁴ Thornes, R. D., *Journal of the Irish Medical Association*, 1969, 62, 426.

** The reference to A. S. Ketcham *et al.*, should have read: *American Journal of Roentgenology*, 1971, 3, 42.—Ed., B.M.J.

Hospital Advisory Service

SIR,—When the Hospital Advisory Service's courteous teams visited one mental hospital in 1971 I found much of their advice instructive, stimulating, and helpful. I have also had the pleasure of reading Dr. A. A. Baker's Annual Report for 1970.¹ Nevertheless, I strongly endorse Dr. J. L. Crammer's plea (18 December, p. 746) that they ought to improve their methods of analysing work loads and the staff needed to labour under them; they should publish their standards, and key statistics of the hospitals they visit. Inadequate staff ratios may delay the closure of mental hospitals, but the greater risk is that the standard of care afforded existing inpatients will fall below an acceptable level.

Wing and his colleagues² have already established in three mental hospitals that the progress of earlier years has begun to slip back, and they emphasize how difficult it is

to sustain social innovations. One explanation is that because of the present steadily increasing work load "the attention that doctors can give to long-stay patients, and the number of staff who can be spared for rehabilitation, must inevitably diminish."

A logical strategy, where general hospital units have yet to open, is to arrange the existing mental hospital (or each catchment division within it) in two sections: admission wards and other wards. Each admission unit would look after the total inpatient load of its catchment area (and in doing so would not bequeath patients to the other wards) until the general hospital department opens.

To do this staff ratios similar to those of the general hospital units are essential. A common ratio for junior medical staff is three doctors (senior house officers or registrars) for 60 beds serving a population of 120,000. For the remainder of the mental hospital it would be inequitable if 100 patients had fewer than one junior doctor to look after them, particularly when the aim is to rehabilitate and support in the community as many as feasible. The numbers of other staff also need careful and local evaluation. For example the nursing load provided by incontinent severely demented patients, a proportion of whom are cared for in mental hospitals, is extremely high.³

If I understand the role of the Hospital Advisory Service correctly one of their main tasks is to consider staff ratios within the hospitals visited. Yet there is a notable lack of facts about these in the Annual Report for 1970. The mental hospital already mentioned has 18 junior doctors (below senior registrar grade), but on the unexceptional staff ratios outlined it needs about 30. Yet the Hospital Advisory Service considered that this hospital was relatively well provided with non-consultant psychiatric staff. The Advisory Service's standard was not revealed. Should it be revised?—I am, etc.,

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¹ Department of Health and Social Security. *National Health Service Hospital Advisory Service, Annual Report for 1969-70*, London, H.M.S.O., 1971.

² Wing, J. K., and Brown, G. W., *Institutionalism and Schizophrenia*, Cambridge University Press, 1970.

³ Hulten, A., Kerstell, J., Olsson, R., and Svanborg, A., *Scandinavian Journal of Rehabilitation Medicine*, 1969, 1, 117.

Immune Suppression, Gliomas, and Tuberculosis

SIR,—The possibility that some cancers may be due to defects in immunological surveillance has been widely discussed of late.¹ The theory states that many thousands of cell divisions occur each day within the human body and a number of faults in the mitotic process are inevitable as the copying or template mechanism for DNA replication must break down from time to time. Some of these "mutants" may well be "potential tumours," and it is suggested that the immune system recognizes and destroys them. Thus several potential cancers may occur in an individual every day but these are usually completely suppressed. It is envisaged, therefore, that the immune system has two main functions—its classically recognized role as a defence mechanism against external attack by foreign organisms, mediated usually by humoral antibody, and the problem of internal security, perhaps

effected by the cellular immune system. Within the complex ecology of the body involving massive cell populations the latter role of internal security may well be the more important.

Evidence for this hypothesis has been admirably documented and discussed by Burnet in his book on *Immunological Surveillance*. Two of the most important pieces of evidence are, firstly, that there is a high risk of malignancy, particularly intracerebral lymphomas, after immunosuppression in transplant recipients, and, secondly, that neoplasms are a common complication in certain immune deficiency states of genetic origin. It therefore occurred to us that it might be worthwhile looking into the medical histories of patients with cerebral gliomas to see whether there was an increased incidence of conditions likely to be associated with a deficiency in the immune system.

We accordingly determined the previous medical history of 26 patients with cerebral gliomas, and as a control series took 52 patients with other conditions. The positive finding related to the incidence of old tuberculosis as defined by the history and/or radiological changes. There were six cases of old tuberculosis among the 26 gliomas compared with 5 cases among the 52 controls. The difference is not statistically significant, but the finding that nearly a quarter of the patients with gliomas had a previous history of tuberculosis is certainly impressive. Also of interest is the fact that among the 26 gliomas there were two cases of diabetes (one also had tuberculosis), one of hepatic cirrhosis, and one of long-standing chronic chest infection—this last in a female. Thus a third of the patients with gliomas had a previous medical history containing a major disease which could conceivably be associated with some alteration in immune response.

This is a small and preliminary study and the results could well be due to chance, but, if confirmed in larger series, the results would carry some very interesting implications. They would provide further evidence that infection with tuberculosis is in large part governed by the resistance of the host, and that many patients with this disease may have occult immune deficiencies. They would also provide evidence in support of the theory that neoplasia is, at least in part, due to a deficiency in immunological surveillance.—We are, etc.,

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¹ *Lancet*, 1971, 2, 143.

² Burnet, M., *Immunological Surveillance*. Oxford, Pergamon Press, 1970.

International Convention on Psychotropic Drugs

SIR,—The new international convention on psychotropic substances adopted at a United Nations conference in Vienna in 1971¹ raises some fundamental questions about the control of scientific research—particularly research that requires possession of controlled drugs for research purposes. Some of the clauses of the new convention are open to a wide range of administrative and legal interpretation.

One clause in the preamble reads: "Recognizing that the use of psychotropic

substances for medical and scientific purposes is indispensable and that their availability for such purposes should not be unduly restricted"

In contrast, part of Article 7 states that in respect of substances in Schedule I, the parties shall: "(a) prohibit all use except for scientific and very limited medical purposes by duly authorized persons, in medical or scientific establishments which are directly under the control of their Governments or specifically approved by them; (b) require that manufacture, trade, distribution, and possession be under a special licence or prior authorization; (c) provide for close supervision of the activities and acts mentioned in paragraphs (a) and (b); (d) restrict the amount supplied to a duly authorized person to the quantity required for his authorized purpose; (e) require that persons performing medical or scientific functions keep records concerning the acquisition of the substances and the details of their use, such records to be preserved for at least two years after the last use recorded therein"

When a country ratifies this new convention the responsibility for control and all of the legal and administrative interpretations will undoubtedly be vested in the national government. Moreover—if history is any guide—this power and authority will be given to governmental officials, whose prime interest is in control of the drugs—with relatively low priority given to science. For example, our sad experience with cannabis, whereby a tremendous hedge of legal and administrative controls virtually precluded the development of bona fide scientific investigations, is a classic example of an unbalanced system that should never again be allowed to develop. Admitting the need for appropriate measures of control through the national government, the major policy questions that must be clarified are: Does the government by virtue of its responsibility for the control of drugs also retain control of scientific investigations that require supplies of the controlled drugs for research purposes? Who is going to determine the kinds of research and the priorities—the control officials or the scientists?

An appropriate answer to these questions is crucial to the development of responsible scientific work. Moreover, in the case of the United Kingdom they should be debated and settled before the new international convention is ratified by Parliament. In my opinion, the determination of research priorities and investigations should be vested in the appropriate scientific body, not in the administrative officials.—I am, etc.,

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¹ United Nations, *Conference for the Adoption of a Protocol on Psychotropic Substances*, E/Conf. 58/6, February 1971.

Camphorated Oil

SIR,—We feel that the "over the counter" purchase of drugs on the market gives easy access to some very dangerous pharmaceutical preparations. Recently a man was admitted to the Regional Poisons Unit following an attempted suicide with an overdose of 150 ml of camphorated oil (B.P.

20%). The potential lethal dose in an adult is 20 ml. He was in peripheral circulatory shock and severely dehydrated owing to vomiting. After immediate resuscitation gastric lavage was carried out under general anaesthesia using a cuffed endotracheal tube. Soon after admission he developed three attacks of severe and prolonged grand mal, which subsided with intravenous diazepam. Following intensive supportive treatment he was fit and well 36 hours later. To the best of our knowledge this is one of the highest doses to be survived.

Camphorated oil has in the past been used for the purpose of abortion because the substance crosses the placenta. It causes death due to respiratory depression. There is no specific antidote. However, haemodialysis utilizing soyabean oil has been employed in the past.

In this day and age camphorated oil has lost its former medical indications. Its danger as a poison by far outweighs its usefulness, if any, and we do not think that camphorated oil now has a place in the open market.—We are, etc.,

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Pharmacologically Active I.U.D.s

SIR,—At a time when concern at the increase in iatrogenic disease is both opportune and fashionable I should like to draw attention to and deplore a recent new development in contraception. This is experimentation with pharmacologically active intrauterine devices, notably those wound with metallic copper wire.

The rationale behind their development is that, whereas for inactive devices pregnancy rates appear to be roughly proportional to surface area and large devices carry compensating disadvantages, copper ions have a directly contraceptive effect, so that devices can be kept small to minimize other inconveniences, leaving the copper to take care of the risks of pregnancy.

Where a major gain in efficacy is at stake clearly we must be ready to accept a temporary increase in uncertainty regarding the safety of a new device or drug. No progress is possible otherwise. In this instance, however, this is not the case. The more advanced of the inert I.U.D.s (the Dalcon shield, for example) have, if the results of trials so far available are a guide, rates of pregnancy, expulsion, and medical side-effects low enough so that no improvements could be classified as major advances. Improvements should of course be sought continually, but there must be a limit on their price. Pharmacologically active I.U.D.s introduce a new dimension of unknown long-term hazards, and I suggest that this is too high a price for the small gains remaining to be made.

We know nothing of the properties of the endometrium as a route for medication nor of the effects of continuous exposure to a weak solution of copper salts on it, on myometrium or cervix. We have no experience of intermittent massage with such a solution of vagina, glans penis, and urethral meatus. We shall have to await with uncertainty the outcome of pregnancies that will take place with the device in situ and to speculate on the performance of a possibly

damaged myometrium during labour even in pregnancies occurring after its removal. Allergic reactions, as with the topical use of copper salts elsewhere, are to be expected. An added source of anxiety regarding carcinogenesis, this time in both male and female genital tracts, will have to be studied for 20 years or more.

In addition, it should be recognized that the advantages of the active I.U.D.s are fairly gold. With present copper devices, after a relatively short period the active substance becomes exhausted or inactivated, and removal and reinsertion is necessary. However, I understand that promising work is in progress to extend the life time of the device. Until this has been achieved the application of copper I.U.D.s to mass programmes in developing countries is likely to give rise after a short period to unacceptably high pregnancy rates. The difficulties and costs of attempting to arrange for regular renewal of all I.U.D.s in such settings are virtually insurmountable.

The introduction of pharmacologically active I.U.D.s is gratuitous *furor medicandi*. I suggest we should continue to have confidence in the steady progress being made towards the perfection of inert devices and have nothing to do with this complex, hazardous, and unnecessary new industry.—I am, etc.,

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Phenformin Overdose

SIR,—Phenformin is an oral hypoglycaemic agent related to the biguanide group and is in increasing usage. In 1969 156,000 National Health prescriptions for phenformin were made.¹ Combined with an oestrogen it has recently been used experimentally in fibrinolytic therapy.² One of the presentations of phenformin is as a 50 mg slow-release capsule and the therapeutic range is up to 3 capsules daily.

On 31 August a white male aged 30 years presented with collapse, having vomited about a pint and a half (800 ml) of altered blood, with fresh blood, during the evening and morning before admission. When examined he was in peripheral circulatory failure, but apart from some midline epigastric tenderness and fresh melaena stool in the rectum there were no physical signs.

During a medical examination for a job abroad 10 months before he was found to have glycosuria. Subsequent blood sugars were raised above normal and he was given soluble insulin. His insulin requirements were low and he was changed to phenformin 50 mg slow-release capsules and a 200 g carbohydrate diet.

Throughout the 6 months before admission he took his capsules according to his urine testing with Clinitest tablets. This meant he took 6–8 capsules per day (2–2½ times the maximum effective therapeutic dose). He lost 2 stone (12.7 kg) in weight in the four months before admission, and had anorexia with central low epigastric discomfort but no symptoms of gastric reflux. He dated the onset of symptoms from when he started phenformin. There was no previous history of peptic ulcer nor a family history.

He was transfused a total of four units of whole blood and treated medically with antacids, antiemetics, and analgesics. A