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Analgesics in Terminal Disease

SIR,—We would like to endorse Dr. P. B. Schofield's plea for a more liberal attitude to the giving of analgesics (26 June, p. 773). Too often we admit patients from both hospital and home who have severe pain which has not been adequately relieved. We would, however, like to point out that it is usually of benefit to have some kind of time schedule, albeit a rather relaxed one. Our own feeling is that we should give the patient a dose which will be sufficient to control his pain for a slightly longer time than the interval between regular drug rounds. This should prevent pain from occurring at all and will also prevent clock watching. We find it is important to combine our analgesics, narcotic or otherwise, with a mild tranquillizer in most cases. This helps to control the reactive element of pain and may thus reduce the dose of analgesics. We may still sometimes need to be bold in the doses we use but we do not find we have problems of tolerance and dependence on this regimen.

Although we do not normally leave narcotic analgesics by the bedside we frequently leave drugs of other groups. This is valuable in giving patients some control of their medication and in giving them some-

thing in reserve. It sometimes seems to help the sudden pain on movement common with bone metastases rather better than an increase in the routine dose of the stronger drug.

May we emphasize the importance of recognizing and trying to understand the various components of pain. Much of it can be controlled by measures other than the use of analgesics alone if we will only listen to the patient's story. The listening itself can be therapeutic and relieve the anxiety and depression, which are often so marked. Suitable medication for this is frequently needed.

We have deliberately omitted any discussion of the pain relief from nerve blocks, cytotoxic drugs, steroids, and the control of infections, which may still be useful when the time for palliative radiotherapy, internal fixation, or other more active measures is over. Terminal pain can be regarded as an illness in itself and there is need for more teaching in its proper diagnosis and treatment.—We are, etc.,

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Halothane Hepatitis

SIR,—Professor W. W. Mushin and his colleagues (3 July, p. 18) present a statistical study to support the hypothesis that repeated halothane anaesthesia may cause liver damage. They conclude that "halothane should if possible be avoided in patients who have had it before, particularly if this was within the previous four weeks." This statement from such an authoritative source must give rise to considerable concern. For this reason, and

because of the possible medicolegal implications of their conclusion, careful scrutiny of the material presented is mandatory.

Their paper reports a statistical comparison of three groups of patients; a general surgical population, 54 patients reported to the Committee on Safety of Drugs, and 74 patients recorded in the literature. These latter two groups had developed post-operative jaundice after repeated halothane

anaesthesia. On a point of detail, Figures 2 and 3 relate to Committee on Safety of Drugs and literature reports and are limited to a 10-year period. It is misleading, therefore, to include in Figure 1 a large group of patients (23% of the total) who had received an anaesthetic more than 10 years previously—almost certainly in the pre-halothane era.

Professor Mushin and his colleagues draw attention to the fact that halothane "now forms a part in nearly 90% of all general anaesthetics." The data obtained from the Committee on Safety of Drugs covers the period 1964–69. Inquiry¹ establishes that up to the present time, 126 reports of jaundice related to anaesthesia have been received by the Committee on Safety of Drugs, of which only 103 pertain to halothane—a reminder that postoperative jaundice is not peculiar to halothane. It would seem, therefore, that the appropriate control for the two groups of jaundiced patients should be patients subjected to multiple non-halothane anaesthetics, and it is questionable whether it is valid to use a "general surgical population" for this purpose.

This consideration apart, the recommendation that repeated halothane should be avoided is based on the finding of an "excess" of jaundiced patients who had had a previous halothane anaesthetic within four weeks. Professor Mushin and his colleagues base their study on the hypothesis that "halothane hepatitis" is caused by sensitization, and therefore no clinical details of the Committee on Safety of Drugs patients are provided. However, the crux of the matter is whether the jaundice of these patients was unexplained. It must be recalled that the United States National Halothane Study² reported 82 cases of fatal postoperative hepatic necrosis, but the expert panel decided that an adequate explanation, other than anaesthesia, existed for all but nine of these.

Extrapolation from this data suggests that only some 10% of postoperative liver damage is likely to be attributable to anaesthetic agents. Furthermore, we are currently engaged in a study of postoperative jaundice occurring in Great Britain and Eire. Up to the present time, in the majority of cases investigated, the jaundice is probably due to factors other than the anaesthetic agent used. However, it can be seen from Table IV on p. 21 that every case reported to the Committee on Safety of Drugs has been included in Figure 2, p. 19. It is highly unlikely, therefore, that all of these cases are unexplained, and an "excess" of cases in which a cause and effect relationship is attributable to halothane may not exist. The high incidence of jaundice after operations repeated within a month remains of interest and concern. (Similar arguments may be applied to Figure 3.)

We endorse the view that "the rare occurrence of jaundice after halothane anaesthesia is of much concern to anaesthetists." Regrettably, however, we conclude that the paper by Professor Mushin and his colleagues does not reduce the uncertainty as to whether or not halothane hepatitis exists. Indeed, the statement that "this complication could be avoided if the use of halothane were stopped altogether" is open to misinterpretation by non-anaesthetists who may not appreciate that most anaesthetic agents and techniques have been incriminated following the occurrence of postoperative liver damage. It may well be that, if the advice not to repeat halothane is taken "because of the possible greater overall safety of administration of two halothane anaesthetics as opposed to administration of one halothane followed or preceded by one non-halothane anaesthetic, the epidemiologic consequences of withholding halothane from almost all patients returning for a second surgical procedure might well be the opposite of those intended."³—We are, etc.,

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¹ Inman, W. H. W., 1971, Personal communication.
² National Halothane Study. *Journal of the American Medical Association*, 1966, 197, 775.
³ Dykes, M. H. M., *Journal of the American Medical Association*, 1971, 216, 641.

Functions of the G.M.C.

SIR,—Dr. J. Fry (10 July, p. 116) paints too complacent a picture of the present situation of the G.M.C. As one who, so far as I know, was entirely unsponsored in the recent election, I feel entitled to say something about sponsorship. If the B.M.A. opts out it leaves the field open to others who do sponsor, and while this may result, as Dr. Fry modestly states, in a reasonable choice it does not necessarily represent the profession but is loaded in favour of those groups who sponsored candidates. It strikes me as odd that the largest and most important association of doctors should abandon the field, particularly when it has policies to pursue and perhaps even more important has the responsibility to advise the profession on the vexed questions of the retention fee and postgraduate registration.

Dr. Fry seems satisfied with the Brynmor Jones Report. I am not, and in this respect I am in agreement with Dr. J. F. G. Pigott (3 July, p. 52). The G.M.C. is already too big and although the majority of elected members has been accepted in the report, it would mean a council of about 70 as a start, with an extra two for each new medical school or college that is accepted in future.

The arguments for each university having a seat are much weakened by the firm views of London University to stick to only one representative for all the medical schools in London. It strikes me as incongruous that the universities for whose standards of medical education the G.M.C. is responsible should be so heavily represented on the only body which can call them to account. If it is seriously suggested that they are needed to such an extent, then medical schools in India, Pakistan, and Egypt, whose degrees the G.M.C. accept as registerable, should also be represented. Some, because of the large numbers of graduates they send here, may even claim a greater entitlement.

We really need a much smaller G.M.C., with less but still an overall majority of elected members. If the universities and the colleges feel so strongly about membership, one could be accommodating, but at a price. They should make a proportionate contribution to the finance of the G.M.C. It is entirely unfair that the registered doctors should be asked to subsidize privileged classes. The Government should also be asked to make its contribution on behalf of Privy Council members. This would not give us the most efficient G.M.C., but at least the financial burden would be shared.—I am, etc.,

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Lymphocyte Sensitization

SIR,—We have read the recent study of lymphocyte sensitization in sarcoidosis by Dr. E. A. Caspary and Professor E. J. Field (17 April, p. 143) as shown by inhibition of macrophage migration. These authors also report two other patients who repeatedly failed to "convert" to tuberculin sensitivity after B.C.G., and who had lymphocytes sensitized to the same cell antigens as patients with sarcoidosis. This finding leads them to suggest that an extended study might show that "non-converted," although apparently healthy, subjects may exhibit the immunopathology of sarcoidosis.

We have investigated the phenomenon of apparently healthy subjects who remain "non-converted" to tuberculin sensitivity following two vaccinations,^{1,2} using both liquid and freeze-dried B.C.G. vaccine; each of our subjects showed satisfactory vaccination scars. In our first study¹ 7 out of 10 subjects who were vaccinated twice and who remained non-converted had positive Kveim tests. These seven subjects also showed marked depression of delayed-type skin hypersensitivity following intracutaneous tests with a *Candida albicans* suspension. Further tests three years later showed marked regression of Kveim reactivity. A similar waning of the Kveim response with persistence of tuberculin anergy is frequently seen in regressing clinical sarcoidosis. However, none of these seven subjects

had a history suggestive of erythema nodosum or arthralgia or showed any other evidence of sarcoidosis on physical examination. Moreover, miniature chest radiographs extending back to the initial B.C.G. vaccinations 10 years previously, and chest radiographs taken within six months of the positive Kveim tests, were normal. Serum calcium, IgG, IgM, and IgA were normal and all the ABO blood groups were represented.

The lymphocyte transformation test carried out in four of these seven subjects showed no response to Kveim material used as antigen after five or seven days' culture, or to tuberculin or B.C.G.³ A similar lack of response was reported by Brandt, Bouveng, and Norden⁴ on a healthy "non-converter," using tuberculin as antigen.

No tests were made on our subjects using a migration inhibition technique. In this context it is of interest that Lockshin and Bombardieri⁵ using tuberculin and *Candida albicans* antigens, found that the macrophage migration inhibition test was sometimes positive in subjects with reduced skin reactivity to these materials. The dissociation between cell sensitization of cutaneous reactivity disclosed by Dr. Caspary and Professor Field would appear to be in line with these findings. Hardt and Wanstrup,⁶ also using a migration inhibition technique, were able to mediate a specific response to sarcoid spleen suspensions, and more recently Willoughby and Mitchell⁷ have found inhibition of leucocyte migration in sarcoidosis and Crohn's disease, with sarcoid but not with normal spleen suspensions.

In discussing our own findings² we suggested that healthy "non-converted" subjects seem most likely to represent a minute proportion of the healthy population who reflect an unusual immunological change brought about by B.C.G. itself and in some way related to tuberculin sensitivity, being especially prominent among subjects with persistent tuberculin anergy. We still favour this hypothesis.—We are, etc.,

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Vitamin B₁₂ and Metformin

SIR,—We welcomed the paper by Dr. G. H. Tomkin and others (19 June, p. 685) for its convincing demonstration of the causative association between malabsorption of vitamin B₁₂ and long-term therapy with metformin. These authors showed that 30% of 71 diabetic patients on such treatment had