There are snags. The problem list, if not checked regularly, can give a sense of false security. Once, a haemoglobin result showing anaemia was slipped into the notes without appearing in the list. I have not solved the difficulty of arranging follow-up notes after the "data base" (basic data sounds more familiar) has been completed. I first tried running the problems horizontally across several sheets by sticking blank pages together and folding them back into the notes. I saw this used two years ago in Professor Ian McKay's department at Melbourne, where a similar method of note-keeping had been developed by V. X. Gledhill independently of the Weed system. Now we tend to allot numbered areas in the case notes, perhaps a whole sheet for one and a half sheet for another. However, the amount of space needed is unpredictable and chaos may occur. Then a colleague called into consultation may write his opinion in the wrong place, not being aware of the problem oriented record. Some, either young or old, are resistant to change. The system will probably never be universally accepted unless it is taught to all medical students when first they meet a patient.

The problem oriented is better than the disease oriented medical record. Anything that focuses attention upon the patient must be an improvement. It avoids one missing something important to the patient, but trivial to the doctor, who may otherwise become preoccupied with academic interest in the disease itself. Nevertheless, the greatest problem is how the hell to keep good follow-up case notes at all! More time is needed for the problem oriented record, though time is saved later on ward rounds and in writing letters. My H.P.s are excellent, but detailed notes are often impossible in a busy hospital admitting emergencies; so case notes are seldom full enough to go straight into a computer—if that were desirable.

How are follow-up notes best written? During a round with the H.P. sitting and having something firm to write on, or afterwards in sister's office or elsewhere? And what role should the hospital secretary play? Ideally she could join the round and type dictated notes later, but seldom are there enough secretaries for this. Or should one use a pocket tape-recorder? Professor Weed and his follower Dr. McIntyre preach the problem oriented medical record with the fervour of proselytes but sometimes seem to be aloof from these practical difficulties.—I am, etc.,

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Dangers of Corn Starch Powder

SIR,—Your useful review of the dangers of corn starch glove powder (2 June, p. 502) was confined to the peritoneal cavity, and one of us has seen pathological material from many cases of peritonitis produced by spillage of glove powder (7 August 1971, p. 369). We have now encountered evidence of tissue reaction in the ear to corn starch powder which may be derived from therapeutic insufflations as well as glove powder from the surgeon's hands.

A 24-year-old man had had four operations on the ear since the age of 8 years, when left radical mastoidectomy was performed. At a recent operation for revision of the radical mastoidectomy greyish tissue was seen in the facial and tympanic recesses, the facial ridge, the attic, and the hypotympanum of the middle ear and much of this was removed as well as the lining of the mastoid cavity. Histological examination of this material showed numerous typical starch granules embedded in a granulomatous mass composed of histiocytes, foreign body giant cells, lymphocytes, and plasma cells. In some places fibrosis was marked. This tissue was present in areas where there was columnar epithelium or where the epithelium was denuded. Areas covered by squamous epithelium were not affected. The patient's hearing improved after this procedure and symptoms of vertigo disappeared, suggesting that the starch granuloma had caused some hearing loss and vestibular involvement.

Apart from the possibility of starch powder dropping from the hands to the tips of instruments it is difficult to explain the presence of a starch granuloma following ear operations, since these are usually carried out by the non-touch technique. This patient had been treated from time to time by the insufflation of a variety of powders into his mastoid cavity and middle ear. We examined the insufflations commonly used in the treatment of middle ear infection at the Royal National Throat, Nose and Ear Hospital and found that streptomycin, chloramphenicol, Penotrane (hydrargaphen), colistin, and nystatin insufflations contain large proportions of starch, which is used as an "inert" base in the preparation of the powders. Polymyxin and boric acid insufflations do not contain starch.

A 17-year-old boy was treated for a week with daily chloramphenicol insufflations to the right ear, following which a mass of polypoid tissue arising from the tympanic membrane was removed. Histological examination of the material showed it to be covered by large numbers of starch granules which, in some areas, were infiltrated by numerous neutrophils that were phagocytosing some of the granules. Thus the corn starch granules in the chloramphenicol powder had induced an acute inflammatory reaction on the surface of the polyp.

In the case recently described by Dawes *et al.*,[1] the starch granuloma which appeared in the oval window following stapedectomy for otosclerosis may similarly have been related to the use of an antibiotic starch-containing insufflation. Though such a preparation is not mentioned in the report, these powders are often in routine use in otological practice. We would therefore like to suggest that starch powder may cause a pathological reaction across the columnar epithelium of the ear, especially where tissues are devitalized following surgery. The use of insufflations containing corn starch in this area should be questioned.—We are, etc.,

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1 Dawes, J. D. K., Cameron, D. S., Curry, A. R., and Rannie, I., *Journal of Laryngology and Otology*, 1973, **87**, 365.

Contraindications to Smallpox Vaccination

SIR,—Dr. A. S. V. Steele (2 June, p. 552) does not distinguish between vaccination as a routine procedure, vaccination for travel purposes, and vaccination because of exposure to smallpox.

Vaccination as a routine is no longer recommended in Britain, and contraindications are therefore irrelevant.

For travellers from one smallpox-free country to another, say from England to Canada, a letter stating that the traveller suffers from a condition which is a contraindication to vaccination will usually be accepted by immigration authorities. This may not be the case for travellers going to countries where smallpox is endemic; nor may such a letter always be accepted if the traveller comes from a country where there are cases of smallpox, as was the situation recently in England. I heard of at least one such holiday traveller from England, an "infected" country, who was not allowed to disembark at his holiday resort in spite of his letter, but was sent back to England. Epidemiologically this may have been absurd, but it did conform with international agreements. The patient may have to choose between being vaccinated or staying at home.

When a patient has been exposed to an infectious case of smallpox and may therefore have inhaled smallpox virus there are no contraindications at all to vaccination. One must choose between the danger of vaccinia and the danger of smallpox. Vaccinia is *usually* the milder disease. Its effects can be modified, and the danger of smallpox perhaps diminished, by the administration of vaccinal immunoglobulin. Neither primary nor revaccination is a completely safe procedure.—I am, etc.,

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Psychiatric Symptoms in Typhoid Fever

SIR,—With reference to your leading article (26 May, p. 436), I suspect that the presumed contrast between the prevalence of psychiatric symptoms in developed and undeveloped countries is more apparent than real. In my copy of the 1892 edition of Osler's *Principles and Practice of Medicine*, I read under "Typhoid Fever" that:

"The following are the most important deviations [from the normal mode of onset]: (a) *Onset with pronounced nervous manifestations:* Headache, of a severe and intractable nature, is by no means an infrequent initial symptom. Again, a severe facial neuralgia may for a few days put the practitioner off his guard. In cases in which the patients have kept about and, as they say, fought the disease, the very first manifestations may be pronounced delirium. Such patients may even leave home and wander about for days. In rare cases the disease sets in with the most intense cerebrospinal symptoms, simulating meningitis—severe headache, photophobia, retraction of the head, twitching of the muscles and even convulsions. Occasionally drowsiness, stupor and signs of basilar meningitis may exist for ten days or more before the characteristic symptoms develop; occasionally the onset is with mania. . . ."

Osler's experience came in part, at least, from Philadelphia, where in those days a busy physician that I knew years ago saw 1,000 cases a year on the wards of one hospital, prior to the installation of filtration of the city water supply. Under such circumstances neuropsychiatric problems of differential diagnosis were familiar. So was "brain fever"—an endemic disease of young heroes and heroines in nineteenth century novels which Osler says was actually to a large extent typhoid fever. But the present-day physician in the Western world may not see more than 10 or 20 cases of typhoid fever in a lifetime; hence any comparison between typhoid fever here and in the developing

countries is bound to be fraught with uncertainty.—I am, etc.,

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1 Osler, W., *The Principles and Practice of Medicine*. New York, Appleton, 1892.

SIR,—I was interested to read your leading article (26 May, p. 436) in which the different presentations of typhoid within developed temperate countries and undeveloped African countries was attributed to variations in infective, emotional, cultural, and religious backgrounds. Several years ago I had the opportunity of working in a mixed European and Asian community during an outbreak of typhoid. Psychiatric symptoms occurred in no more than 10% of cases, and there was no apparent difference in the incidence of these symptoms between the two racial groups.

One patient presented initially with severe anxiety and agitation accompanied by pain in the neck and thoracic spine, another presented with hypomanic symptoms, and three others with the more characteristic mental confusion and delirium, associated with headache and pyrexia. As you point out, the true diagnosis may be obscured by these psychiatric manifestations and the management of the case made more difficult.—I am, etc.,

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Infection with E.B. Virus

SIR,—We would like to comment on one point in your leading article (31 March, p. 757) in which you state that "a common virus aetiology for [infectious mononucleosis and acute lymphatic leukaemia] appears to be improbable, for more than half of leukaemic children examined have been found not to show antibody to E.B. virus." While we do not dispute the conclusion expressed, we feel some comment should be expressed about this line of reasoning.

At the 42nd Annual Meeting of the Royal College of Physicians and Surgeons of Canada in January of this year we presented a case of acute childhood leukaemia in which a patterned inverse relationship in fluctuation between serum IgM and the absolute blast count in the peripheral blood was frequently observed. We had speculated that this might represent a faltering response in the humoral immune system to specific leukaemia antigen (? virus). This is in line with the theories of Schwartz *et al.*,[1] who have postulated that the absence of antibodies in patients with acute lymphoblastic leukaemia to leukaemia antigens is part of the disease syndrome. It is interesting that these patients may have an impaired ability to mount an IgM antibody response to poliovirus.[2]

In proving or disproving the thesis that inability to produce antibodies to leukaemia antigen is an integral part of lymphoblastic leukaemia, experience with an out-bred strain of animals (for example, cats) might prove useful—if, that is, one can draw analogies between these situations. The sequential estimation of anti-FeLV titres in cats naturally and experimentally infected with leukaemia might help to elucidate this point. The assistance of our veterinary colleagues might be valuable.—We are, etc.,

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1 Schwartz, S. O., Greenspan, I., Brown, E. R., *Journal of the American Medical Association*, 1963, **186**, 106.
2 Ogra, P. L., Sinks, L. F., Karzon, D. T., *Journal of Pediatrics*, 1971, **79**, 444.

Duration of Action of Beta-blocking Drugs

SIR,—Dr. S. G. Carruthers and others (21 April, p. 177) draw attention to the duration of action of beta-adrenergic blocking drugs and present useful data comparing the decay in blood practolol level with the decline in beta-blockade.

Under the circumstances, however, we wonder whether their use of the term "pharmacological half-life" is appropriate. After the distribution phase practolol levels decline exponentially and the rate of this decline may be expressed as a half-life. If there was a direct relationship between practolol level and response, then the decay of beta-blockade would also be exponential. However, their data and those of others[1 2] show a near-linear relationship between response and the logarithm of practolol concentration. It follows that if the blood level falls exponentially, the response will diminish at a constant rate—that is, as a zero order process. In this type of decay process the time taken for response to fall from 20% to 10% would be twice as long as the change from 10% to 5%.

The decay of pharmacological effect would be better expressed as the decrease in response per unit of time.—We are, etc.,

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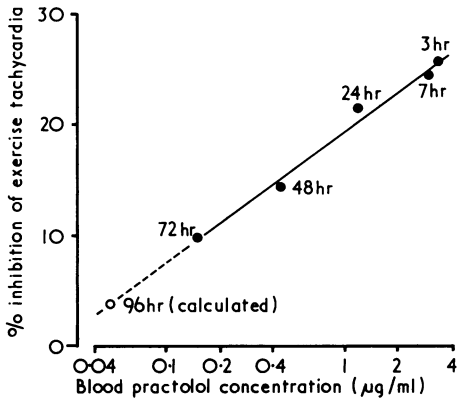
1 Gibson, D. G. *Postgraduate Medical Journal*, 1971, supplement (January) **47**, 16.
2 Schneck, D. W., Aoki, V. S., Kroetz, F. W., and Wilson, W. R., *Clinical Pharmacology and Therapeutics*, 1972, **13**, 685.

SIR,—Dr. S. G. Carruthers and his colleagues (21 April, p. 177) have produced valuable evidence that in man the action of beta-blocking drugs is more prolonged than had been suspected hitherto, and they rightly point out that practolol need be administered only once daily to achieve its therapeutic effect. They draw attention, however, to an apparent discrepancy between the blood practolol level and the reduction in exercise tachycardia achieved in a group of healthy volunteers following administration of a single dose of 400 mg.

On the theoretical basis, the effect of any drug ought to be a function of the logarithm of its concentration, a fact which seems to have been ignored in many published correlations between blood levels and drug effects in man. A log. concentration/effect plot of the data given by Dr. Carruthers and his colleagues (3-72 hr), shown in the figure, yields an almost perfect straight line ($r = 0.99$) in support of the theory. This relationship is also seen in the individual data, which have been kindly provided by the authors. Furthermore, calculation of the drug's blood



elimination half-life (15·1 hr) enables one to predict that the mean blood level at 96 hr after dosage should have been 0·049μg/ml (presumably below the sensitivity of the method used). On the basis of the log. concentration/effect plot shown, this should have produced 4·2% reduction in exercise tachycardia. This is close to the value actually observed (2·3%).

These observations indicate that the effect produced by practolol is consistent with its blood level. The reported discrepancy disappears and it is therefore unnecessary to implicate tissue binding to explain its prolonged action. Indeed, tissue binding is unlikely because the drug's distribution volume (100 l.), derived from the blood concentration data, is just that which would be predicted from its basic nature, its ionization constant (pKa) of 9·1, and its distribution into body water alone. It is apparent that measurement of a blood practolol level should provide a reliable prediction of its therapeutic effect.—I am, etc.,

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Outpatient Maintenance of Chronic Schizophrenics with Long-acting Fluphenazine

SIR,—The letter from Drs. G. R. Daniel and A. A. Schiff (28 April, p. 244) raises an issue of importance concerning the extent to which results of therapeutic drug trials can be generalized. In each of the studies cited by them we were able to supplement the results of a controlled trial by data which gave some indication of the proportion of patients to whom the results might apply.

In the trial of oral phenothiazines[1] our conclusions were not based solely on the results of the 35 schizophrenic patients in the trial, as implied by Drs. Daniel and Schiff, but on a consideration of the outcome in all 116 acutely ill patients who were admitted to hospital during an 18-month period. For example, two groups of patients were not allowed by their doctors to enter the trial. Of the 11 who were thought to need no preventive medication only three relapsed whereas out of the 15 who were thought to need (and did actually receive) continuous medication 10 relapsed. We concluded that maintenance medication was clearly useful in the group of patients with an intermediate prognosis who did enter the trial, but that the trial results could not with confidence be applied to all acutely ill schizophrenic patients. We discussed the choice of therapeutic strategies in our paper