looked in the drug addiction film "The Man with the Golden Arm."

Then at my outpatient clinic another patient suffering from neurotic depression told me how very ill she felt after stopping her regimen of phenelzine and haloperidol to go on to lorazepam. The lorazepam made her excessively drowsy and she stopped it after a day or so but then she felt depressed and irritable and also described this feeling of cold and shivering.

This last symptom is quite reminiscent of the "cold turkey" reaction to the withdrawal of narcotics from the habituated, and the reaction followed so swiftly the discontinuation of the drug that I wonder if it might not represent a genuine physical response to deprivation of the drug rather than a purely psychological one or the return of the depression. The medical adviser to the manufacturers tells me that no such withdrawal symptoms have previously been reported but I wonder if any of your readers can record similar experiences?—I am, etc.,

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Malaria in the United Kingdom

SIR,—In your epidemiological report (5 January, p. 43) you mention 84 cases of malaria in immigrants to the U.K. in 1972. The adult populations of countries where malaria is endemic are generally considered to be immune to malaria in the sense that they do not suffer overt attacks of the disease.

It would be valuable to know if there is any record of the proportion of immigrants in whom malaria was considered to be the cause of their illness rather than simply a concomitant finding, the number of adults, and whether any factors were found, such as acute infections or steroid therapy, which might have been responsible for a temporary lowering of resistance to malaria.—I am, etc.,

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Intensive Care: Allocation of Resources

SIR,—Your issue of 23 March (p. 567) contains an article by Dr. K. Astvad and others on the effect on mortality from cardiac infarction of the establishment of an (intensive) coronary care unit. *Health Trends* for February 1974 includes a report by Dr. Eva Alberman on stillbirths and neonatal mortality in England and Wales by birth weight during 1953-71.

The first article suggests that intensive care makes little difference to the overall mortality of patients with coronary heart disease; the second makes it clear that provision of adequate neonatal care, including intensive care, in maternity hospitals makes a great deal of difference to mortality in newborn infants, as it has also done to morbidity.^{2,3}

The moral as regards allocation of resources is obvious, but it is not obvious that it has been drawn, nor that it will be while the British Paediatric Association

remains a poor relative of the royal colleges with no direct representation, for instance, on the Central Health Services Council and similar bodies.—I am, etc.,

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- ¹ Alberman, E., *Health Trends*, 1974, 6, 14.
- ² Stewart, A., in *Perinatal Medicine*, ed. H. Bos-sart, J. M. Cruz, A. Huber, L. S. Prod'hom, and J. Sístek, p. 181. Bern, Huber, 1973.
- ³ *Lancet*, 1972, 1, 437.

Thromboembolism and Oral Contraceptives

SIR,—Your leading article (9 February, p. 213) suggests a difference in the possibly thrombogenic effect of unnatural oestrogenic compounds and natural oestrogens.

A normal content of fibrinolytic activators in the vessel walls is important for counteracting thrombosis.¹ In an earlier investigation we found that ethinyloestradiol in a large dose (250 µg daily for 10 days) depressed the fibrinolytic activity in the venous vessel wall in post menopausal women about to be operated upon for uterine prolapse.² We now have given 17-beta-oestradiol to a similar group of 16 women in a biologically equivalent dose (10 mg daily for 10 days). Biopsy specimens of superficial veins were obtained before and during the last day of treatment and were examined histochemically for their content of fibrinolytic activators. In contrast with the findings during treatment with ethinyloestradiol, no significant depression of the fibrinolytic activity was found, which is in accordance with your editorial suggestions.—We are, etc.,

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- ¹ Isacson, S., and Nilsson, I. M., *Acta Chirurgica Scandinavica*, 1972, 138, 313.
- ² Åstedt, B., *Acta Obstetrica et Gynecologica Scandinavica*, 1971, 50, 279.

Skin Reactions to Practolol

SIR,—Since the report by Rowland and Stevenson¹ in 1972 of a patient with exfoliative dermatitis who was taking practolol we have been concerned at the increasing number of patients we have seen who have developed a rash caused by this drug. Although a minority of patients presented with either an eczematous eruption or exfoliative dermatitis, the majority have presented with a distinctive psoriasiform eruption, further details of which will be the subject of a full communication.

We have been struck by the uniformity of this type of eruption, particularly in its distribution on the hands and bony prominences, the main features of which are scaling and thickening of the skin of the palms, soles, and sides of digits with atypical psoriasis-like plaques over the knees. The remainder of the rash is widely scattered over the body, being red and characterized by margined scaling. In our opinion the clinical features produce an easily recognizable diagnostic picture.

These patients have been taking practolol

for periods ranging from three weeks up to two years, with a mean duration of treatment of 10 months, before the onset of the rash. As this drug has now been available for over two years this latent period before the onset of the rash may be one explanation for the apparent increased frequency of the practolol-induced rashes that is our impression at present. We therefore consider it timely to draw the attention of the medical profession to this entity.—We are, etc.,

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F. A. IVE

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- ¹ Rowland, M. G. M., and Stevenson, C. J., *Lancet*, 1972, 1, 1130.

Drugs Affecting Oral Contraceptives

SIR,—Ever since oral contraceptives were introduced, their efficacy has almost been taken for granted. By both the doctor and the patient they have been regarded as being almost infallible. In the very rare cases where a pregnancy occurred the blame was first laid against the patient for having forgotten the pill and then only rather grudgingly against the pill. Recent publications have, however, started to accumulate to show that neither the patient nor the pill may be at fault. It may in fact be that the patient is taking other medicines and that these may be preventing the pill from producing the proper contraceptive effect. This effect appears to act mainly against the oestrogen content and may explain the strange finding that the average age of the patients who became pregnant while taking the pill was 35¹. This was found to be occurring predominantly on sequential-type oral contraceptives.

The most marked effect on oral contraceptives would appear to come from the antibiotic rifampicin. This antibiotic is one of the recently introduced antituberculosis drugs and it has gained wide usage in many countries as it is very effective and easy to administer. Unfortunately, since it is given to ambulant patients many of these may also be taking oral contraceptives to prevent unwanted pregnancies during their treatment period. The first indication of this interaction came from Reimers *et al.*,² who found that of 88 patients with pulmonary tuberculosis who were taking oral contraceptives in addition to rifampicin, 75% suffered from cycle disturbances and five became pregnant, whereas in another group, who received streptomycin, only 4% showed any cycle irregularity and there were no pregnancies.

Though other workers³ found no cycle disturbances or pill failure, it was felt by Reimers that rifampicin might influence the biogenesis and metabolism of the oestrogens and that this might lead to failure of action. Other antibiotics have also been shown to affect oestrogen metabolism, for ampicillin given to healthy mothers in the latter weeks of pregnancy decreases the urinary oestriol levels by as much as 69% of the pretreatment level.⁴ It was felt that ampicillin also could give rise to unexpected complications with oral contraceptives by affecting the enterohepatic circulation of the oestrogens. This type of work has been confirmed by other workers.⁵

The second most common therapeutic group to affect the mechanism of action of oral contraceptives are the barbiturates. This could have been expected, as it was reported in 1968 by Levin⁶ that in animals chronic treatment with phenobarbitone could reduce the uterotropic effect of oestrogen and progestogens. Other workers⁷ reported that barbiturates stimulate the metabolism, by enhancing the hydroxylation, of all steroids, and it was confirmed^{8,9} in vitro and in vivo in animals that the conversion of mestranol to ethinyloestradiol could be increased as much as three times by pretreatment with barbiturates.

Perhaps the most important paper on this subject is that by Hempel, Bohm, and Carol,¹¹ who studied the incidence of menstrual irregularities in 200 patients on oral contraceptives and the case histories of 25 patients who became pregnant on the pill. They also studied three groups of patients who, in addition to hormonal contraceptives, had taken aminophenazone or phenobarbitone. Their findings were as follows: (1) Many drugs can accelerate the metabolism of hormonal contraceptives, thus reducing their biological effectiveness. This occurs via the mechanism known as enzyme induction. (2) Breakthrough bleedings, spotting, and in some cases pregnancy correlate with these periods of enzyme induction in spite of regular intake of hormonal contraceptives. (3) It can be proved by an experimental test-cycle that certain individuals will have a tendency to such enzyme induction and that the beginning of bleeding is the most useful indication that it has occurred. This work, with that of the other investigators, has highlighted a new problem, for as the doses of oral contraceptives are reduced enzyme induction by the other drug taken becomes increasingly significant.

All cases of unintended pregnancy should in future be investigated not only from the point of view that the patient or the pill might be to blame but that the cause might lie with other, unrelated therapy. It is also of increasing significance where the medical and contraceptive care is the responsibility of two different physicians, as at the present time few realize the possibility of such interaction.—I am, etc.,

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- 1 Rutenskold, M., *Acta Obstetrica et Gynecologica Scandinavica*, 1971, 50, 203.
- 2 Reimers, D., and Jezek, A., *Praxis de Pneumologie*, 1971, 25, 255.
- 3 Mohr, M., and Sehm, G., *Praxis der Pneumologie*, 1971, 25, 23.
- 4 Tikkanen, J. M., Adlercreutz, H., and Pulkkinen, M. O., *British Medical Journal*, 1973, 2, 369.
- 5 Willman, K., and Pulkkinen, M. O., *American Journal of Obstetrics and Gynecology*, 1971, 109, 893.
- 6 Pulkkinen, M. O., and Willman, K., *American Journal of Obstetrics and Gynecology*, 1973, 115, 1153.
- 7 Pulkkinen, M., and Willman, K., *British Medical Journal*, 1971, 4, 48.
- 8 Levin, W., Welch, R. M., and Conney, A. H., *Endocrinology*, 1968, 83, 149.
- 9 Swidler, G., *Handbook of Drug Interactions*, p. 228. New York, Wiley, 1971.
- 10 Kappus, H., Bolt, H. M., and Rimmer, H., *Acta Endocrinologica*, 1972, 71, 374.
- 11 Hempel, E., Bohm, W., Carol, W., and Klinger, G., *Zentralblatt für Gynäkologie*, 1973, 95, 1451.

Atropine Poisoning

SIR,—Atropine was formerly a well-recognized cause of poisoning but now tends to be overlooked, attention having shifted to newer synthetic drugs.

A 22-year-old horticultural student was admitted as an emergency after his father, on collecting him from College, observed him to be staggering, replying to non-existent voices, irrational, somnolent, and behaving oddly—for example, donning his pyjamas to go out. Examination revealed slurred speech, ataxia, olfactory hallucinosis, disorientation, and widely dilated pupils. Atropine poisoning was suspected—especially as his mother had been prescribed Neutradonna—but he vigorously denied drug-taking, and comprehensive urinary testing for drugs was negative. Next day he had recovered fully and admitted taking the seeds of *Datura stramonium*, a plant related to deadly nightshade, growing in the college's nurseries. He was subsequently discharged.

Referred to a psychiatrist in 1968 for behaviour disturbance attributed to inability to attain his school's and his parents' expectations of him, he had been diagnosed as an aggressive psychopath. Keenly interested in chemistry, he later made explosives, injuring his hand in an accidental explosion, and habitually took quantities of opiates obtained from home-grown poppies and several

patent medicines containing opiates, chloroform, and ephedrine.

Atropine poisoning should be suspected in an acutely confused patient with dilated pupils and other neuropsychiatric abnormalities, particularly when the personality is deviant, the occupation "at risk," and urinary screening for drugs unhelpful. Atropine can probably cause symptoms in concentrations too low to be detected by gas chromatography testing of the urine.—I am, etc.,

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Laxative-induced Diarrhoea

SIR,—The interesting article by Dr. J. H. Cummings and others (23 March, p. 537) describes secret and excessive purgation with laxatives in seven women, resulting in severe physical illness and eluding early diagnosis. The patients were a heterogeneous group psychopathologically but included one (case 3) and possibly two others (cases 4 and 6) suffering from anorexia nervosa.

Secret addiction to excessive quantities of laxatives, often in association with self-induced vomiting behaviour, is quite commonly a feature in patients with chronic primary anorexia nervosa. This disorder may be construed as a psychosomatic avoidance response to psychosocial maturation, mediated through weight loss in association with dieting behaviour. Appetite is very often retained and some patients submit to their impulse to overeat, sometimes in a bulimic form. They may then evoke purging and vomiting mechanisms as ways of preventing gain in weight. As they become entrenched in this behaviour they can develop serious physical complications often associated with metabolic imbalance, especially hypokalaemia, which may further mask the underlying disorder. Excessive purging and vomiting behaviour is nearly always secretive and denied, for patients with weight phobia are terrified at the prospect of their weight being restored to a normal level. The diagnosis of anorexia nervosa is one that should be considered in patients who appear to be addicted to laxatives.—I am, etc.,

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Chronic Mucocutaneous Candidiasis

SIR,—In your leading article (1 December, p. 504) it was reported that some forms of chronic mucocutaneous candidiasis are associated with latent iron deficiency. Hence it was suggested that iron deficiency must be looked for and treated in many of these cases.

Since chronic mucocutaneous candidiasis characteristically occurs as a complication in patients with immune-deficiency syndromes, especially those with T-cell defects,¹ it is of interest to mention the recently reported defects of cell-mediated immunity in patients with iron deficiency anaemia.² Thus iron deficiency might have been either the cause or a contributing factor of the chronic infection through the depressed immunity which it brings about. Since iron ions and

iron compounds such as haemin are known to enhance protein and DNA synthesis,^{3,4} this could be taken as the explanation for the mechanism by which iron affects immunity.

On the basis of this hypothesis replenishment of iron stores in patients with chronic mucocutaneous candidiasis might indeed cure them by correcting their immunological impairment. However, it is equally well established that iron promotes infections and is essential for bacterial growth, probably also by its effect on protein and DNA synthesis.⁵ Thus replenishing the iron stores of patients with this disease could have an equivocal effect. On the one hand it might restore, at least partially, the impaired cellular immunity which is probably responsible for the candidiasis. On the other hand such treatment might expose these patients, especially if their humoral immunity is also impaired, to bacterial infections.—I am, etc.,

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Israel

- 1 Kirkpatrick, C. H., Rich, R. R., and Bennett, J. E., *Annals of Internal Medicine*, 1971, 74, 955.
- 2 Joynson, D. H. M., Jacobs, A., Murray Walker, D., and Dolby, A. E., *Lancet*, 1972, 2, 1058.
- 3 Mathews, M. B., Hunt, T., and Brayley, A., *Nature New Biology*, 1973, 243, 230.
- 4 Hershko, Ch., Karsai, A., Eylon, L., and Izak, G., *Blood*, 1970, 36, 321.
- 5 Bullen, J. J., Rogers, H. J., and Griffiths, E., *British Journal of Haematology*, 1972, 23, 389.

Coping with Minor Casualties

SIR,—I am sure that many casualty officers and consultants in accident and emergency departments will agree wholeheartedly with some of the views expressed by Mr. C. Bagley (6 April, p. 55). In general we are all too well aware of the number of patients attending such departments who could well be treated by an occupationally based health service or indeed by their own general practitioners.

Three points, however, should be considered. Firstly, in many areas where there is an industrial health service patients are frequently sent to hospital by the staff of that service only because they require a tetanus toxoid injection or course of injections, their injuries in general not being of a serious nature. Surely the establishment of a population actively immunized against tetanus is the province of either the family doctor or industrial health services.

Secondly, many patients sent up by the industrial health services are patients who have had a condition which has persisted for some time, but apparently it is easier to send them up to the accident and emergency department than to refer them back to where they rightly belong—to the care of their family doctor.

Thirdly, a great many cases of industrial injury, in some areas at any rate, involve foreign bodies in the eyes and heavy objects falling on toes, etc. Such conditions occur in most cases because adequate safety measures had not been used, and it is very noticeable that very often the same patient will come up on several occasions with the same complaint. These industrial accidents are almost certainly, in the main, preventable, given adequate education by the firm's safety officer or equivalent, but often there