ever, the advice to continue increasing the dose "until intolerable side-effects are provoked or a total daily dose of about 8 g. is attained" should be modified. Experience in starting three to five new patients weekly on treatment with L-dopa has shown that many months are needed to become familiar with the drug's actions, its foibles, and the range of patients' responses to it. Some of our patients have done well on as little as 1.5 g. per day, and only rarely was it necessary to exceed 6 g. per day. In a group of 88 patients we found the average effective therapeutic dose to be 4.5 g. per day. This is in agreement with the average dose used by Barbeau,¹ and was 1.3 g. less than that used by Cotzias, Papavasiliou, and Gellene.²

The therapeutic results of the first reported clinical studies in which large doses of L-dopa were used were so dramatic that, when using the drug for the first time, physicians now tend to overdose patients. During the first few months of our trial we aimed at increasing the dose gradually to an arbitrary upper limit of 8 g. per day, but even patients who were able to tolerate such a high dose without excessive nausea showed a high incidence of other severe effects, particularly involuntary bulbar and limb-muscle dyskinesias, which necessitated cutting back the dose. The dose was reduced from 6-8 g. per day to 2-3 g. per day in some patients without loss of therapeutic effect. It would therefore appear either that the maintenance dose of L-dopa is less than that required initially to achieve a therapeutic result, or a lower dose than the average of 5-6 g. per day reported in early papers becomes equally efficacious when taken over a prolonged period. As is the case with other chronic diseases, there is much individual variation in the drug requirements of Parkinsonian patients; furthermore, it is often necessary to adopt a compromise between a larger dose to attain a maximum therapeutic response and a lesser dose to avoid side-effects. In view of these facts, it is both untherapeutic and unkind to force the dose of L-dopa to an arbitrary maximum of 8 g. per day.

Improvement of Parkinsonian symptoms may continue for many months, so it is reasonable to delay increasing the dose of L-dopa beyond say 5 g. daily in any patient in whom significant improvement occurs within the first month. These individuals tend to show progressive and gratifying lessening of disabilities, and the dose can always be increased later in those with residual symptoms or signs but who have not developed disabling side-effects. Following preliminary laboratory studies, including an electrocardiogram, the majority can be started on L-dopa quite safely as outpatients. Small increments may give a lower incidence of side-effects, but increments of less than 250 mg. are rarely necessary, provided the rate of increase is not too fast. We start outpatients on 250 mg. tablets or capsules with food, as follows:

Day	Breakfast	Lunch	Supper
1st-3rd	1	1	1
4th-6th	1	2	1
7th-9th	1	2	2
10th-12th .. .	2	2	2
13th-15th .. .	2	3	2
16th-18th .. .	2	3	3

and so on, adding 250 mg. every fourth day.

New increments are begun with the second, then the third, and finally the first

dose, because experience shows that patients adapt poorly to the first dose of the day. Patients who become nauseated on this regimen are advised to divide the daily dose of L-dopa into four or more parts, and take each one with food. One to three non-phenothiazine anti-emetic tablets (dimenhydrinate, cyclizine, etc.) may be taken half an hour or more before taking the L-dopa. Many patients find it useful to take one tablet prophylactically each morning on rising.

Both trifluoperazine and haloperidol are useful antidotes to the involuntary movements in some patients, but it is essential to prescribe them in minute doses. When patients are given more than 1 or 2 mg. per day Parkinsonian symptoms tend to recur. If these are mild they may be acceptable, provided the involuntary movements are also alleviated, but in one patient an excellent therapeutic response to L-dopa was completely vitiated by only 1 mg. per day of either of these drugs.—I am, etc.,

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REFERENCES

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- 2 Cotzias, G. C., Papavasiliou, P. S., and Gellene, R., *New England Journal of Medicine*, 1969, **281**, 272.

Severe Dermatitis and "Biological" Detergents

SIR,—Acute oedema of the penoscrotal skin area of young boys in the absence of demonstrable infection or intra-scrotal pathology, while not a common condition, is probably better known to surgeons and casualty officers than mention in textbooks would suggest. It is described in three recent textbooks dealing with the surgery of childhood, but labelled "idiopathic".¹⁻³ To the best of my knowledge the possibility of an association with detergents has not been raised.

Over the last 12 years I have seen over 50 patients with this condition. Without exception their underclothes had been washed with one of three leading detergents. The association has been predominantly with one brand, to the extent that one may predict its use with considerable accuracy. In most instances the suspect detergent has been used for the family wash for more than a week before the episode of oedema, but there is some evidence to suggest that inadequate rinsing may have been a factor. Constitutional predisposition to allergic reactions has not been a feature of the affected patients. The suspicion that contact with certain detergents has been a factor has been strengthened by the absence from the case histories of any other common contact or systemic agent; the absence of known recurrence following advice to substitute a soap-based preparation for the detergent in washing undergarments; the recurrence, in two instances, following the re-introduction of the suspected brand into the wash, after more than a year; and positive results on patch-testing three recent subjects.

"Biological" detergents have been freely

available, and no doubt extensively used, in Northern Ireland for several months, but it is only during this last week that I have seen a patient with severe penoscrotal oedema whose clothes had been washed in one. The oedema was unusually severe affecting the scrotum, penis, upper medial thighs, and suprapubic region, but predominantly (and characteristically) affecting one side of the scrotum and penis, the skin of which appeared thickened to almost $\frac{1}{2}$ in. (1.25 cm.) and almost translucent. A dull carmine, macular rash extended from below the umbilicus to mid-thigh, and he had pyrexia (38.5°C) and vomiting and complained of headache and general malaise. It was quite the most severe reaction of this type I have seen, and for this reason he was given a single dose of hydrocortisone in addition to the anti-histamines and bed rest usually employed. Signs and symptoms rapidly subsided to near normal in less than 48 hours. Like Dr. G. A. G. Peterkin (28 March, p. 818) I was reluctant to risk provocation of reaction by patch testing.

Impression and suspicion are not enough to establish a clear relationship of cause and effect, and more information is required to establish or refute the relation of detergents to this condition. The present incidence of penoscrotal oedema would not constitute an argument for restriction in the use of strong detergents even if they were proven to be a cause, but I feel it is only prudent to advise the parents of affected children against the use of detergents for underclothes in these children until more is known about the cause.

It seems to me that the incidence of penoscrotal oedema is increasing, and that the condition should be known to doctors concerned in the emergency treatment of children to a greater extent than it is at present, so that parents can be reassured and advised and unnecessary treatment (including surgery) avoided. There must be, however, no doubt about the diagnosis, for it can never be emphasized enough that torsion of the testes (or the rare epididymo-orchitis of childhood) may present with very considerable unilateral scrotal oedema.—I am, etc.,

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- 1 Nixon, H. H., O'Donnell, B., *Essentials of Paediatric Surgery*, p. 102. London, Heinemann, 1961.
- 2 Dennison, W. M., *Surgery in Infancy and Childhood*, 2nd Ed. p. 304. Edinburgh, Livingstone, 1967.
- 3 Johnston, J. H., in *Paediatric Urology*, Ed. D. I. Williams, p.45, London, Butterworth, 1968.

Corticosteroids and Pituitary-adrenal Function

SIR,—Dr. J. R. Daly points out in his letter (14 March, 1970) that the depression of plasma cortisol levels which is seen following the injection of methylprednisolone is a normal consequence of corticosteroid administration, and therefore one may question the interpretation of pituitary-adrenal function tests during this period. This argument implies that amounts of exogenous steroid sufficient to inhibit

A.C.T.H. release are still circulating for very considerable times after injection of methylprednisolone.

Studies on our own patients and observations by Jacombe *et al.*¹ suggest that after 17-20 days the resting plasma cortisol had returned to within the normal range, presumably because by this time there is little or no circulating exogenous steroid. Nevertheless, in our own study the adrenal response to A.C.T.H. remained suppressed beyond this time, and even in patients studied for 60 days did not regain its former levels. We therefore considered that this degree of depression of adrenal response represented a recovery phase following the disappearance of exogenous steroid from the plasma.

It seems important to re-state the conclusion which we drew in our paper—that is, that this small degree of suppression would probably be unimportant if only two doses of methylprednisolone were given. A more prolonged course of treatment though might produce correspondingly greater effects.—We are, etc.,

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REFERENCE

- ¹ Bain, L. S., Balch, H. W., and Jacomb, R. G., *Annals of Physical Medicine*, 1967, 9, 43.

Breathlessness and Anxiety

SIR,—We read with much interest the paper by Dr. N. C. Oswald and others (4 April, p. 14), relating respiratory disability and personality attributes. As we are engaged on similar work, though with asthmatics only, may we refer to three points from their careful study?

While data on, *inter alia*, 51 male and 58 female asthmatics was reported, the proportions of these that were attending for the first and for follow-up consultations were not mentioned. We believe that conclusions must be drawn only warily from cases who attend clinics regularly—anxiety may be as important a determinant of such attendance as the severity of pulmonary disorder.

In 1956, Professor Linford Rees¹ reported a study of a large number of asthmatics, and found that more of them were obsessional, sensitive, anxious, and under-confident than controls. We have just reported² confirmation of this observation, but in a study of a much smaller number of patients drawn randomly from a register, and of normal and neurotic controls. We noted that these are the very traits which might be associated with failure to adapt to distress, and with a tendency to reiteration of complaint. Conclusions about psychopathology in bronchial asthma (or indeed in bronchitis or in any other disease) can be made only from studying a sample as truly representative as possible of the whole asthmatic population. Failure to attend to this principle has produced much worthless speculation in psychosomatic medicine.

Partly on account of its fluctuating nature, the severity of asthma as an illness is notoriously difficult to grade. We are not confident that subjective answers to questions on severity of breathlessness are appli-

cable in the present context. One arbitrary criterion of severity is whether corticosteroid treatment is required. In an extended sample of our own, women requiring such treatment had lower Eysenck Personality Inventory (E.P.I.) neuroticism scores (mean 10.6, s.d. 4.7, $n=26$) than those not on these drugs (mean 14.1, s.d. 4.6, $n=19$) ($p<0.02$). This was in contrast with the men on steroid treatment who returned scores (mean 9.4, s.d. 5.7, $n=9$) which were similar to those not so treated (mean 9.4, s.d. 5.9, $n=14$). In a smaller sample we found² that a group with severe pulmonary disorder—in terms of more likelihood to have been in hospital for treatment, a poorer F.V.C., and a greater need for corticosteroids—displayed less neurotic traits at interview, had lower psychophysiological activation (particularly in amount of hyperventilation), and less abnormal scores on psychometric tests. The implications of these observations are contrary to the relationship between breathlessness and anxiety suggested by Dr. Oswald and colleagues. We believe that the more prone a patient is to anxiety, the more he will be distressed by breathlessness—and that this is determined by more than pulmonary disease.

Dr. Oswald and his colleagues advocated the use of psychometric tests to screen clinic attenders for neuroticism. The E.P.I. is a poor test for reliably discriminating the abnormal individual. From data in the E.P.I. manual, the average neurotic patient's score on neuroticism lies at only the 89 percentile of a normal sample. While we advocate a broader approach to assessment of psychopathology^{2,3} we support wholeheartedly Dr. Oswald and colleagues' plea that emotional factors should be taken into account in the management of patients with bronchial asthma or bronchitis—or indeed with any other distressing disease.—We are, etc.,

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- ¹ Rees, L., *Journal of Psychosomatic Research*, 1956, 1, 98.
² Zealley, A. K., Aitken, R. C. B., and Rosenthal, S. V., *Scottish Medical Journal*, 1970, 15, 102.
³ Aitken, R. C. B., Zealley, A. K., and Rosenthal, S. V., *Journal of Psychosomatic Research*, 1969, 13, 289.

Depressive Illness in General Practice

SIR,—May I reply to Dr. M. J. Wooldridge and Dr. P. J. V. Beumont (18 April, p. 175)? I share Dr. Wooldridge's concern about classification. In the original draft of my paper I included case histories to show the type of patient I had admitted and—more important—the type I had not admitted; unfortunately this section had to be left out because of lack of space. I submit that the length and complexity of Dr. Wooldridge's observations about classification confirm the original wisdom of admitting patients who said they were depressed, and went on saying it, rather than those who seemed to conform with psychiatric classifications—I could identify the former, but not the latter.

May I comment on some other points in Dr. Wooldridge's letter? I excluded 11, not 33, patients from the trial of imipramine

(Table VI, p.775); 33 patients failed, for various defined reasons, to contribute useful data to the trial. Dr. Wooldridge writes: "the failure to fall sick more frequently in the premenstrual period is puzzling. . . ." I did not attempt to define where in the menstrual cycle patients "fell sick," only when they "reported sick." It was the day of presentation which was related to the menstrual cycle. Again Dr. Wooldridge writes: "I would finally criticise an assessment of a tricyclic drug over such a short period given in a standard dose of 75 mg./day." In the section entitled "Tablets and Dosage" (28 March, p. 776) I wrote: "If at the end of the first week the response to treatment was indifferent the dose was increased to two tablets three times a day;" the strength of the tablets (25 mg.) was defined in the text and the daily intake for these patients was, therefore, equivalent to Dr. Wooldridge's recommended minimum dose of 150 mg.

In reply to Dr. Beumont's inquiry, one patient only in my series succumbed to depression within six weeks of delivery. The demographic distribution of my depressed patients (women more than men, married women particularly, spinsters rarely) is puzzling. It might be explained by postulating that sexual fulfilment and sexual ignorance protect, but repeated sexual experience without orgasm, predisposes. Other factors are social isolation and the wear and tear of caring for a young family.

In the controlled trial of imipramine 19 patients were overt defaulters (failed to reattend or admitted a failure to take tablets); 14 of these had been allotted to the imipramine group. It has been pointed out to me that if these patients lapsed because they had in fact got better and saw no point in reattending, then their exclusion from the assessment might bias the results against the drug. The reasons for lapsing have been analysed elsewhere¹ and probably only four out of the 19 lapsed because of improvement. Their inclusion in the assessment seemed neither desirable nor important.—I am, etc.,

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REFERENCE

- ¹ Porter, A. M. W., M.D. Thesis, University of London, 1968, p. 164.

Crohn's Disease and Pregnancy

SIR,—In view of the evidence presented by Drs. J. F. Fielding and W. T. Cooke (11 April, p. 76) that pregnancy does not have any adverse effect on the course of Crohn's disease, it seems pertinent to add a note of caution to their optimism. We have seen two patients suffering with Crohn's disease who have had rare, life threatening complications associated with their pregnancies.

A 24-year-old woman with no known gastrointestinal symptoms was well during her first pregnancy in 1968 until 37 weeks. Pain then developed in the region of the right hip and a large, soft-tissue swelling, bluish in colour, appeared above the right iliac crest. The swelling was incised and a mixture of pus and gas released. Bacteriological culture of the pus grew *Clostridium welchii* and she was treated with anti-gas-gangrene serum, penicillin, and hyperbaric oxygen. A stillbirth occurred 24 hours later. Subsequently extensive debridement