capacity to synthesize this enzyme—though they do not entirely lack it—is not inconsistent with the Oxford report. Temporary suppressions of the already deficient enzyme, and the quantitative relationship between it and the substrate (gluten), could account for the episodic nature of multiple sclerosis; and in a population subsisting on a high gluten-containing diet the differences between normal subjects and heterozygotes in remission may be too subtle to be discerned by the immunological tests.—I am, etc.,

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Possible Retroperitoneal Fibrosis and Methysergide

SIR,—Following the initial report by Graham¹ of retroperitoneal fibrosis in two of 500 patients under prophylactic treatment with methysergide (Deseril) for various forms of severe recurrent migraine, Utz *et al.*² have recently described three cases of this condition in patients on long-term methysergide administration in varying dosage over 20 months, 22 months, and two years respectively. Utz *et al.* state: "A direct causal relationship between methysergide and retroperitoneal fibrosis has not been established by the presentation of these three cases."

The association, if there be one, is at present puzzling and is complicated by unpublished information from the United States which reports that, in cases treated with methysergide, symptoms and pyelographic changes suggestive of retroperitoneal fibrosis may disappear within a few days or weeks following drug withdrawal. Such patients have all been under continuous treatment with methysergide for eight months or longer.

Retroperitoneal fibrosis, a rare condition of uncertain aetiology, was first described by Ormond in 1948³ when methysergide was not available. It typically presents with persistent loin or flank pain and urinary symptoms of oliguria and/or dysuria. Impaired venous return and/or thrombophlebitis in lower limbs may be seen, and very rarely arterial insufficiency is described. In this event pyelographic evidence of hydronephrosis should be sought and renal function examined. If the patient is on methysergide therapy, drug withdrawal is mandatory.

It is advised, in view of this possible complication, that urinary tract dysfunction should form an additional contraindication to drug administration. Continuous methysergide administration should not at any time exceed six months without a drug-free interval of at least one month for reassessment. Review of patients already treated continuously for periods longer than this would be wise, and regular clinical supervision in all patients is recommended.

Investigations in experimental animals are being carried out to clarify this problem. In

the meantime we draw it to the medical profession's attention and request that any available information on this subject be brought to our notice.—I am, etc.,

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REFERENCES

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Behaviour Therapy

SIR,—The recent comparative analysis of the results of behaviour therapy by Drs. J. E. Cooper, M. G. Gelder, and I. M. Marks, appearing in the *B.M.J.* (8 May, p. 1222), provides a timely warning that some aspects of neurotic illness may be resistant to this treatment approach. Some of its more ardent protagonists have claimed that *all* neurotic symptoms are due to learning (or the failure to learn), which has led to overreaching claims for therapy based on learning theory. Such claims have aroused not only scepticism but also antagonism, and have endangered the wide acceptance of a therapeutic tool which is of undoubted value if applied selectively.

The condition called "agoraphobia," on which the authors have based much of their work, is a case in point. It is evident that this term, coined by Westphal in 1872 and meaning literally "fear of the market place" has led to much confusion. The term is generally applied to widespread fears of being away from a "secure" environment, and the suffix phobia places it squarely alongside other phobic conditions, such as animal phobias. The majority of "agoraphobic" patients suffer from generalized (=free-floating) states of anxiety, whereas the sufferers from true phobias as a rule do not. In most cases the symptoms of "agoraphobia" are best explained as a mere heightening of generalized anxiety in situations in which a patient already suffering from continuous anxiety and apprehension feels himself to be even more insecure; if this view is accepted it is clear that such a condition does not usually arise through "learned" mechanisms, and that a pure "unlearning" technique of therapy cannot be expected to succeed, except in so far as it incidentally provides environment and relationship, which tend to inhibit the generalized anxiety state.

Assessments of the results of behaviour (learning theory) therapy must concentrate on only those symptoms and syndromes which can fairly be thought to be learnt. There is much clinical material available on which to make such an assessment. The authors claim that "monosymptomatic" phobias are rare conditions; this is not my experience and I have recently found a dozen such patients to treat within the space of six months in a psychiatric service covering a population of less than 100,000.

One further comment: future assessments of behaviour therapy must include many more details of the actual technique. For instance, I have found that hypnosis as opposed to simple muscular relaxation based on Jacobson's techniques is a valuable adjunct and may even shorten treatment; not only can

the patient "imagine" the feared situation far more vividly under hypnosis, but instant calming can be produced by mere word of command as soon as tension is manifest. A further example: the authors give no details of their approach to the treatment of obsessional neurosis; yet there has been a recent suggestion¹ that behaviour therapy of this condition requires a two-pronged attack, not only to the compulsive behaviour, but also to the underlying anxiety-elevating factors; and that treatment of one without the other is likely to produce only a spurious and unstable improvement.—I am, etc.,

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REFERENCE

- ¹ *Experiments in Behaviour Therapy*, edited by H. J. Eysenck, 1965. Pergamon Press, Oxford.

SIR,—Drs. J. E. Cooper, M. G. Gelder, and I. M. Marks claim (8 May, p. 1222) to have conducted a controlled study of behaviour therapy in 77 patients manifesting various phobic and obsessional symptoms. However, "In addition, all patients were subject to the usual hospital influences and were given a variety of drugs, supportive interviews, and other treatments." The presence of so many variables which could have been controlled is surely undesirable.

The tone of the article suggests that the authors are sceptical of the value of behaviour therapy. Such an attitude cannot be criticized so long as it does not interfere with the methods employed. The fact that the above-mentioned treatments were not denied the patients suggests either poor design or lack of faith in the treatment on trial. As the influence of suggestion cannot be eliminated from either behaviour therapy or psychotherapy, neither being suitable for the double-blind control type of trial, perhaps the negative attitude in respect of behaviour therapy on the part of the authors accounts for the poorer results they obtained than did Wolpe.

An interesting minor theoretical point is raised by the question of training of behaviour therapists. In reply to Wolpe's criticism¹ of Cooper's earlier study²—viz., that the therapists were unskilled—the authors point out that similar results were obtained after treatment by both therapists with extensive knowledge of learning theory and by student psychologists and psychiatric registrars, and they "consider that the relevant skills are derived more from clinical experience in treating neurotic patients than from detailed knowledge of learning principles." Does this latter statement mean that all neurotic patients receive a form of behaviour therapy? If so, the controls are no longer controls.—I am, etc.,

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REFERENCES

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Abuse of Digitalis

SIR,—Please accept my heartiest congratulations on your leading article about the abuse of digitalis (8 May, p. 1208). What a pity somebody did not write it 20 years ago.

History does not repeat itself in every detail but it does move in cycles. The use of digitalis in the witch doctor's brew was intuitive and empirical. Withering made its use respectable. However, he continued to use it indiscriminately for dropsy whether due to heart failure or kidney failure. Sir James Mackenzie, that master of general practice as well as of English prose, put the use of the drug on a scientific basis early in this century. He showed that digitalis will relieve the heart failure of a patient with rapid auricular fibrillation. It delays conduction through the bundle of His and slows the rate of the ventricle. Thus that chamber has time to fill before it pumps out the blood during each contraction.

Anybody who has perfused the heart of an animal knows that the cardiac glucosides when given in toxic doses cause the ventricle to contract more forcibly for a little while. However, if the dose is sufficient to stimulate, the initial stimulation is in all cases followed by spastic paralysis of the heart muscle. This toxic effect occurs sooner in the damaged heart than in the healthy heart.

The "modern" advocates of digitalis for all kinds of heart failure seem to have learned from the pharmacologists about its initial stimulating action only. How many people have died because doctors who did not study medical history and who lacked a broad knowledge of medicine did not know the toxic properties of digitalis on the heart?

History should not depress us. Rather should we study it so that we can avoid past mistakes and escape blame by the future. When all doctors rode horses they knew that you can make the lame or tired animal go faster for a little while if you beat him. However, if you abuse the poor dumb animal in this fashion he will fall going over the next jump or even drop dead before reaching it.—I am, etc.,

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Sodium Fluoride and Cell Growth

SIR,—Armstrong and colleagues (20 February, p. 486) found that *circa* 15 p.p.m. fluoride is required to inhibit growth of human epithelial cells *in vitro*, whereas Berry and Trillwood¹ had previously indicated that as little as 0.045 p.p.m. fluoride reduced the multiplication of HeLa cells in culture. Dr. Berry and Mr. Trillwood entered a rejoinder (20 March, p. 793) that our cells did not multiply at a rate sufficient to allow the inhibitory effect of fluoride to be revealed. While not acceding to the validity of this criticism of our work, we now present the results of experiments which should satisfy the objections to our first study, and we report new findings confirming the low order of effect of fluoride on HeLa-cell growth.

The culture medium was that previously used. HeLa cells from a 4-day monolayer were dispersed by trypsin and diluted in growth medium to give two cell suspensions of known cell count. Replicate flasks (30 ml., Falcon Plastics) at each fluoride concentration (0.0, 1, 5, and 10 p.p.m. added fluoride) were prepared to contain 4.5 ml. medium and 0.5 ml. cell suspension (108 cells in one series and 215 cells in a second series). The pH of the media was maintained at 7.3

during incubation by an atmosphere of 2.5% CO₂. The flasks were examined microscopically after 24 hours of incubation and the positions of 5 cells in each flask which had divided once were marked. The number of cells in each of these clones was recorded at 24-hour intervals but clones which had not divided into 4 cells on day 2 were abandoned. Cell counts were discontinued after the fifth day when the cells were too numerous for accurate enumeration. All counts of cell population and number of clones were made by one of us (M. E. P.) without knowledge of the fluoride contents of the media, which did not change during an 11-day period.

Each point in the Graph gives the average cell count of 36 to 54 clones and these counts were not affected by the size of the inoculum. The results obtained with media containing 1 and 5 p.p.m. fluoride were also indistinguishable from those of the controls. The generation times of the cells in the four media were: 0 F—1.1 days; 1 p.p.m. F—1.1 days; 5 p.p.m. F—1.1 days and 10 p.p.m. F—1.2 days, and are to be compared with a doubling time of about 30 hours obtained by Dr. Berry and Mr. Trillwood (20 March, p. 793) with media not containing added fluoride. We regard these results as confirmation of those of our previous study (20 February, p. 486) and to be a further demonstration that much higher concentrations of fluoride than those reported by Berry and Trillwood (0.045 to 4.5 p.p.m.) are required to reduce the growth of HeLa cells in culture.

Dr. Berry and Mr. Trillwood now suggest (20 March, p. 793) that attachment of HeLa cells to a glass surface may be the step at which the cells are most sensitive to the action of fluoride. This suggestion is made even though they originally reported that 4.5 p.p.m. fluoride did not reduce the number of clones formed on *plastic* surfaces, while finding that 0.045 p.p.m. fluoride reduced the number of cells. In the present experiments the mean number of clones in the flasks which had contained media of 1 and 5 p.p.m. fluoride equalled or exceeded the mean clone count of the control flasks with the same size of inocula. However, the mean number of clones formed from media with 10 p.p.m. fluoride were 84% and 79% of the control clone count for the larger and smaller inocula, respectively. Thus, there is a possibility that concentrations of fluoride of the order of 30 to 50 times that of human body fluids may affect HeLa cells, or the vessel surface, to impede attachment of cells to glass or plastic surfaces. Nevertheless,

alteration of HeLa-cell multiplication by fluoride, which is the feature of biologic significance and that originally claimed by Berry and Trillwood as an effect of fluoride, requires, according to the results of our two studies, a concentration of fluoride greatly in excess of that given in the original report of the Oxford workers.

Dr. Berry and Mr. Trillwood now indicate that they have never interpreted their results in respect to the safety or hazard of public water fluoridation. This clearly stated disclaimer will do much to counteract the unintended but unfortunate implications of some statements in their original report.—We are, etc.,

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REFERENCE

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Department for Venereal and Sexually Transmitted Diseases

SIR,—For many years I have been anxious about the narrowness of the classification of the nomenclature of diseases treated at so-called "Venereal Disease Clinics." These were, of course, formed following the passing of the Venereal Diseases Act of 1916. I welcome therefore most heartily the new Department for Venereal and Sexually Transmitted Diseases at the Middlesex Hospital (15 May, p. 1305).

It is known that experienced workers have in many cases ignored the "official" position and have diagnosed and treated these diseases at such clinics, merely including such infections under the large group of "other infections." This camouflage is not good enough and I am delighted that the necessity for a new approach has been more widely recognized.

It was for this reason that when the London Lock Hospital was the principal hospital for this type of infection its consultants had each to be on the staff of another hospital as either a genito-urinary surgeon, a dermatologist, a general surgeon, or a gynaecologist, and possessed of a higher qualification, either the F.R.C.S. or the M.R.C.P.

It is to be hoped that this far-seeing action of the Middlesex Hospital will be followed by others.—I am, etc.,

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C.S.F. Protein in Multiple Sclerosis

SIR,—Professor Henry Miller, in making an unfortunate mistake in an otherwise good review of an excellent book (27 March, p. 847) on multiple sclerosis by Drs. McAlpine, Lumsden, and Acheson,¹ may have misled some clinicians. He has stated that a simple colorimetric method for measuring spinal fluid gamma-globulin "represents" a real diagnostic advance and that such a method is in routine use at a teaching hospital not a hundred miles from Leeds. This is, indeed, surprising, because no simple colorimetric method for the estimation of gamma-globulin has yet been devised.