Professor McMICHAEL: It can be symptomless, dry, or haemorrhagic.

Dr. STRADLING: Certainly when he first came to the Chest Clinic we did not think he had bronchiectasis; there were no physical signs to suggest it and we did not do any bronchograms, so that we have no positive evidence either to support or to refute your suggestion. I'm very sorry.

Dr. SCADDING: There is some evidence in those x-rays, though, isn't there? Some in the serial x-rays between the first one in 1950 (Fig. 3).

Dr. STRADLING: That it developed subsequently?

Dr. SCADDING: Yes, between the first one in 1950 and the subsequent one (Fig. 4) there had been gross contraction of the base of the right lung. It seems inescapable that the bronchiectatic condition was associated with the contraction of the lung which occurred between those two x-rays.

Professor McMICHAEL: Yes, but that does not say that these lungs were utterly and completely anatomically normal before 1950, as I feel sure they were not.

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PHARMACOGENIC DISEASE IN PSYCHIATRY

BY

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A patient visits his doctor complaining of epigastric discomfort; the doctor tells him there is nothing wrong, and he goes away without being helped. He goes to another doctor, who tells him he is suffering from "dyspepsia"; this he accepts, and in consequence can be treated and get better. He has been supplied with an iatrogenic disorder, dyspepsia, which to his mind signifies a weak stomach, liable to upset; and this has been substituted for the real disorder. This common and successful practice involves only one major danger—that the iatrogenic disorder may become fixed, leading to lasting hypochondriacal preoccupations.

This is a homely example of the way in which the physician may offer the patient an explanation of his symptoms that will be readily accepted rather than make a precise diagnosis that would be met with resistance or antagonism. Thereby he hopes that he will be giving the patient the support he needs, but he adds an iatrogenic disorder to the patient's troubles. Neurotic symptoms, such as those of anxiety or organ dysfunction, are easy to manage once the patient has come to rely on his doctor. When first experienced they are difficult to bear, and seem then to be the sign of some dangerous disease; when they are better understood they may be well tolerated. In such cases psychotherapy or specialized psychiatric treatment is not required, and it is enough that the patient trusts his doctor. But the physician must be careful about the ideas he allows the patient to pick up from him, and he should make sure that these ideas are of a realistic and appropriate nature. There may be a difference between what the doctor said and what the patient believes he was told, and this can

be the start of a psychogenic iatrogenic disease which greatly complicates the treatment of the real neurotic condition.

Pharmacogenic Side-effects

Similarly, pharmacogenic disease is nowadays taking on increasing importance. Most drugs used in neuro-psychiatry have side-effects that may fully replace the effects of the original disease for which they were given. The interest of both doctor and patient may then be insensibly transferred to the management of pharmacogenic symptoms. This is common in epilepsy. When attacks are not completely controlled by a moderate dose of anticonvulsants the dosage is increased to the point where the patient is dull, depressed, moody, or irritable. These excessive effects are then countered by the giving of amphetamine, tranquillizers, or other drugs, with the alleviation of some pharmacogenic symptoms and the production of others.

The symptoms of pharmacogenic disease are usually well tolerated, and they are amenable to therapeutic correction. In general, they allow the patient to enjoy a better life while he waits for the underlying disorder to clear up, and he is generally able to adjust himself to them. Obsessional and anxious patients prefer the emotional indifference, impotence, dryness of mouth, vertigo, and dysuria which are produced by imipramine, to the hypersensitivity and the ruminations of the untreated state.

Pharmacogenic disease is frequent in psychiatric practice because drug treatment is rarely based on aetiology. The direct effect of the drugs on the central nervous system is to produce the symptoms of pharmacogenic disease, and only by their indirect effect do the drugs act on the symptoms of psychological illness. Their use has to be continued beyond the period in which recovery has occurred in order to guard against relapse; and this greatly favours the development of a lasting state which may not be recognized for what it is.

Some forms of pharmacogenic disease hardly need special discussion. The toxicomanias make a well-known chapter; and insulin treatment, cardiazol, and sleep therapy cause dramatic pharmacogenic disorders limited in duration to the time of application in hospital. On the other hand, the appearance and the rapid expansion in the use of stimulant amines, neuroplegics, tranquillizers, and antidepressives have greatly increased the frequency of pharmacogenic disease in psychiatric practice. In times when the use of a drug is rapidly expanding its side-effects are not fully known; and in this age of excessive medical specialization patients may go to one doctor for the treatment of, say, a neurotic condition, and to a second doctor for the treatment of the pharmacogenic symptoms caused by the first. Drugs whose main effect is on the nervous system may cause side-effects elsewhere, such as the liver damage produced by hydrazine derivatives, or the hypotension of imipramine. These are well known, and it is to the less-known psychological symptoms that I wish to call attention.

These symptoms are often very similar to the symptoms of the illness for which the drug is given. The perseveration, retardation, and limitation of interests which will be seen with the administration of phenobarbitone in adequate dosage for the treatment of epilepsy are difficult to distinguish from similar symptoms produced by epileptic personality change. Neuroplegics are the cause of lack of drive, loss of

interest, depression, fatigue, and impotence, which can also be the initial symptoms of a schizophrenic process. Neuroplegics are commonly used in anxiety depression because of their quick effect on anxiety; but they may lead to a vicious circle if the patient reacts with diminution of anxiety but increase of depression. The hydrazine derivatives are the cause of impotence, constipation, insomnia, dysphoric tension, and restlessness, which may also be the symptoms of endogenous depression. It may be difficult, though not so much so as with the neuroplegics, to distinguish in the final phase what is pharmacogenic disease and what is mental illness.

Good Management

The possibility of obtaining a therapeutic effect depends in many cases on good management of the pharmacogenic disease. This has to be accepted. The dosage of these drugs has to be highly individualized; and to get the best results we may have to work at the level bordering on intolerance, helping ourselves where the need arises by the use of antidotes for the more troublesome pharmacogenic symptoms. Chronic depressives, asthenics, those liable to phobic anxiety, and insecure obsessive and oversensitive people have benefited from the protracted use of these drugs. We may compare such treatment with the use of hypotensive drugs in essential hypertension. In such patients, and generally where we are treating constitutional deviations, personality problems, or the symptoms of ageing, the part played by pharmacogenic disease has more than usual importance.

In the integrative action of the nervous system, physiological and psychological factors may be supraordinated and subordinated to one another in many ways. In many cases psychogenic symptoms owe their persistence to neurophysiological mechanisms. On the other hand, neurotic illnesses of neurophysiological origin acquire psychological motivations. Such a process of secondary building up of a psychological structure may indeed permit of an easier psychotherapeutic approach; but often enough it tends towards the fixation of neurotic symptoms. It may activate primitive neurotic experience and root itself deeply in the personality. Drugs may be effective at the personality level; and psychotherapy may help to relieve the symptoms of organic disease. An overcompensatory effect at one level of activity of the nervous system may be the way to true recovery from symptoms derived at other levels. At other times all we can do is to damp down at one level the reverberations of dysfunction at another. It is possible that the majority of drugs capable of producing pharmacogenic disease have such an overcompensatory action.

The New Drugs

The new drugs, especially the stimulants, the energizers, and the tranquillizers, certainly have a future of increasing importance in the life of the normal man. They can be expected to supplement and to some extent to replace such traditional drugs as tea, coffee, and alcohol. The intensity of modern life brings with it a natural wish to rise to the heights, and afterwards to relax and escape the persistence of the excitement that follows effort. Though the new drugs will be helpful, it is well that a man should not live too much of his life out of his normal register or that he should find in these drugs pleasures that take him away from reality—in the

side-effects of the drugs, or in the power they give to transcend natural limits or to reduce inner life to a blank.

Stimulating amines excite, but they limit or disperse mental activity. Hydrazine derivatives increase energy but disinhibit. Patients have told me, "I felt well, but my friends said I was almost mad"; "I felt well, but I lost my head with a professional woman." The wife of one patient said, "He got well; he had no more anxiety and insecurity. But he has become cynical and egocentric, and he thinks only of pleasure. He is not so honest." We have seen neurotic behaviour change to psychopathic behaviour, and patients who had felt very well indeed disown their past actions once the drug was stopped. Lasting changes of personality may result from the experiences and the life that these drugs make possible. In the delicate equilibrium of opposing drives that makes the personality these drugs cause a shift of balance that may permit unforeseen developments. The most careful assessment of the personality structure is required to avoid disagreeable surprises. The tranquillizers and thymoleptics may cause emotional and intellectual dulling, irresponsibility and decline in interest, impulsive behaviour and instability. The inner life is limited, and loses depth and amplitude when guarded against suffering.

The effect of these drugs is at the core of the personality, below the level accessible to insight. It is easy for the patient to be unaware that there is a drug effect, and he may become aware only when the drugs have been stopped and he can appreciate the change in retrospect. In all attempts at orthopsychiatry and at prevention one must remember the basic principle of *primum non nocere*; for it is in this field that corrective drug treatment may be the source of the greatest iatrogenic suffering. The existence of such powerful drugs provides a temptation to use them without consideration of their inherent risks. Similar temptations to excessive therapeutic intervention arise with the modern treatments of constitutional diseases, such as essential hypertension and arteriosclerosis.

Deeper motivations underlie this, in doctors as much as in patients. To be ill is to be guilty, and expiation is due. Nowadays it is not easy to make atonement; and patients and their families go to the doctor expecting him to be the priest at propitiatory sacrifices, or even to be the master of masochistic rituals. Suffering must have a positive meaning to be successfully integrated into life's pattern. The patient who comes to the psychoanalyst and is told that his symptoms are an expression of his aggression towards his father finds it easier to accept them in this light; feeling that he is atoning by his illness for the wrongs of the past, he is the more willing to get better. The doctor must understand such strong and natural feelings. He must avoid cultivating them; but compromises are often necessary.

The Power to Adjust

Man is the measure of all things: he reduces or amplifies what happens to him to his own measure. The common man may go through extraordinary circumstances almost without noticing them, and in the terror of a cataclysm continue to live at the everyday level. There have always been powerful forces for maladjustment—the fear of devils, the pressure of hunger, insecurities of all kinds. But when we observe the life of people in epidemics or under

political or spiritual tyranny we see the majority go on living as if nothing was happening; the realities that menace them have not the impact to take them out of their absorption in living from day to day. It is when the individual loses this power to reduce or amplify internal responses to external realities that a mere trifle becomes capable of producing neurotic breakdown.

Tradition and a common ideal do not have to-day the old power over the individual, and he cannot now lean so securely on his family and his group and their standards and values. Greater tolerance, an actual increase in freedom, allow the individual greater potential development, but also constitute a source of instability and insecurity. Technical advances and the fluidity of the modern world call for unremitting competitive effort and a differentiated adjustment, while at the same time man is subjected to a variety and strength of stimulation beyond his capacity to assimilate. The study of experimental neurosis finds that factors like these are demonstrably the cause of disorganization of nervous function. In the nervous machine with which man is endowed he does not have any ideal instrument, so plastic and flexible that it is completely self-adjusting or so balanced that, barring physical damage, its operation can be ignored. The student of human nature must face the limitations that the machine places on the mind.

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Phenacetin

Chemistry.—One of the *para*-aminophenol derivatives, this "coal tar analgesic" is a white odourless and nearly tasteless powder slightly soluble in water (1:1,310).

Pharmacology.—By its action on the thalamus and hypothalamus it is effective in relieving mild pain. By influencing the temperature-regulating centre it has an antipyretic effect. It has no action on the cerebral cortex.

Therapy.—The dose of phenacetin is 300 to 600 mg., but it is generally prescribed in combination with aspirin and other analgesics. It is used to relieve headache, dysmenorrhoea, and milder aches and pains, but is ineffective in relieving severe visceral pain.

Toxic Effects.—The present interest in this old drug centres on the toxic effects—usually after prolonged and excessive dosage. Until recently the best-known one was methaemoglobinemia showing as a dusky cyanosis. Because of a new manufacturing process phenacetin now contains 4-chloranilide as a contaminant, and this may be responsible for the cases of renal damage reported in recent years.¹ The lesions produced are necrosis of the renal papillae and chronic interstitial nephritis. Animal experiments have failed to produce these lesions possibly because dosage was not sufficiently prolonged, but a significant rise in the Addis count of red cells and leucocytes in the urine has been found in patients taking phenacetin. Another toxic effect is anaemia not of renal origin and almost certainly due to haemolysis.² The mechanism is either an inherited enzyme defect or the result of red cells becoming antigens when combined with phenacetin and so giving rise to autoantibodies.

REFERENCES

- ¹ *Brit. med. J.*, 1960, 1, 714.
- ² *Ibid.*, 1959, 1, 841.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Medical Aid to Developing Countries

SIR,—I was indeed glad to read your leading article, "Medical Aid to Developing Countries" (August 26, p. 572, just arrived), and especially glad that the horrid phrase "under-developed countries" has been thus dropped. No one, least of all my Ethiopian colleagues, denies the lack of development here, but the whole emphasis now is not upon the deficit of the past but upon the possibilities of the future. There is a tremendous upsurge for development as fast as resources permit, in this country as in the rest of Africa. As a foreigner it is a unique privilege to have even a small part in helping to guide this surge forward and more than adequate recompense for the difficulties, frustrations, and hard work involved.

The United Kingdom has lagged behind other countries in coming to the assistance of Ethiopia in this crucial period of expansion. The ex-colonial territories rightly claim much governmental support, but it is precisely in the areas not previously under British rule that there is the most need to demonstrate the value and achievements of British medicine.

Medicine in Ethiopia is not British or German or Italian or French or American or Yugoslav or Russian or Swedish or Indian or Chinese, but is a blending of all elements. Nearly twenty years after the re-liberation of the country it is only just being realized that we need to weld these many influences together and at the same time Ethiopianize the product. For, as we cannot argue directly from animal experiment to human application, so we cannot argue that disease processes in one country are the same as in another. Much can be learnt by study of disease in a different setting, especially at 7,000 ft. (2,134 m.) above sea-level. The need for experimentation and research in Ethiopia remains paramount and must be done on the spot by qualified investigators who are able to share and collaborate with other workers, both indigenous and foreign.

It does not take very long for a well-trained practitioner here to establish a reputation for good sound work, purely because there is such a vast need and so few who are well qualified to meet this need. My colleague from New Zealand, Dr. R. Hamlin, M.R.C.O.G., is at the moment operating upon about 100 vesico-vaginal and recto-vaginal fistulae per year, and is the only one doing so on such a scale. My own work among the polio and other cripples is, regrettably, so far unique in Ethiopia. Other international colleagues are concentrating on public health medicine, paediatrics, tuberculosis, cardiology. In every field of medical endeavour there are vast tracts waiting for the pioneer to give the lead. British medical practitioners have a wonderful opportunity to contribute to this phase of medicine in Ethiopia and other developing countries. It is imperative, however, that they be well trained with a strong mixture of realism and idealism. In the ten years since this hospital was established by voluntary funds raised in Britain and Ethiopia there has been a succession of British personnel some of whom were better than others. Those who do come should always be such as would add to the lustre of British medicine.