Schools and Convalescent Homes

Most children with asthma are capable of remaining at an ordinary school. An open-air school may help a few of them. It is, however, also important to them that their education is as good as possible. Boarding schools have certain advantages in that the frequency and severity of attacks of asthma seem much worse at home than when a child is away from home. This probably reflects more the attitude of the child and those around him to the asthma than any improvement in the disease itself. It is rarely, if ever, justifiable to suggest sending a child away from home for any length of time purely to keep him away from his parents. However, where life at home is grossly abnormal as the result of his asthma and it seems possible that he will be able to continue his education and live a more normal life at a boarding school, this should be considered. Some county educational authorities have residential schools for children with handicaps such as asthma; and some private schools are particularly sympathetic to children with this disorder. The Invalid Children's Aid Association has two schools for boys with asthma, one for the younger and one for the older child.

Convalescence away from home is only a short-term expedient which is sometimes necessary to give either the child or his parents a rest. A period in the Swiss Alps is undoubtedly beneficial from the purely physical angle, and can be arranged through the Chest and Heart Association.² It has the disadvantage of entailing separation from the family in a distant and somewhat artificial environment, but good results are claimed.

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TO-DAY'S DRUGS

Side-effects

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The spread of powerful therapeutic tools brings much good and also some harm. "Iatrogenic disorders" and "diseases of medical progress" have become familiar phrases, and some estimates of the amount of the harm which can be caused are alarmingly large. In one American University hospital the recovery of one patient in five is claimed to have been complicated in this way, and several other reports contain proportions not much smaller. Some of the diseases of progress result from various procedures adopted for investigation, but most of them are signs of the toxic effects of drugs. "Side-effects" is a fashionable expression, consoling in its implication of something relatively unimportant. Most of the diseases of medical progress are due to side-effects of drugs, and the narcotic phrase is itself a dangerous cover, hiding a wide selection of hazards to which patients are exposed.

What are side-effects? This expression, like the phrase "iatrogenic disorders," was not used until about ten years ago. Its grammar is a little rakish. Presumably side-effects belongs with sideboards, side-lights, side-lines, side-shows, and side-walks. Sometimes side effects manage without a hyphen, but sideeffects is unfamiliar. Unhappily, sideeffects will presumably be coined soon, if it has not been already, and then it will be too late to worry about the propriety of using the noun "side" as if it were an adjective. The point is not pure pedantry. The slovenly grammar goes with slovenly thought. Side-effects are effects at the side of . . . of what? The only clear answer is "at the side of the main effects," and the suggestion is that, by a heaven-sent providence, the main effects of drugs are all therapeutically desirable and the side-effects are unwanted but happily (being only side-effects, after all) irregular in appearance and relatively insignificant.

Consider some instances from notes on recently introduced diuretics in a standard source of reference about new products:

"Side Effects: Psychic disturbances may occur in patients with cirrhosis. Mild digestive disturbances avoided by taking

the tablets with meals. May increase sensitivity to digitalis." (A thiazide diuretic.)

"Side Effects: Nausea, vertigo, weakness, fatigue or skin rash may occur (can usually be controlled by reducing dose or correcting abnormalities of electrolyte balance)." (Another thiazide diuretic.)

"Side Effects: Electrolyte imbalance has been reported. Drowsiness, ataxia and skin rashes have occurred on large doses." (An antagonist of aldosterone.)

Notice that these effects *may* occur; *have been reported*; *can usually be corrected*. Notice that they are vague ("psychic disturbances," "fatigue," "electrolyte imbalance"). Notice, particularly, how uncertain is the boundary between side-effects and the action for which the drug is used. Diuretics increase the excretion of water, sodium, chloride, and other ions. Whatever electrolyte concentrations may have existed originally will almost inevitably be altered if the drug acts at all. It is difficult to attach an exact meaning to electrolyte balances of any kind, except between total cation and total anion. It is impossible to distinguish a pharmacological effect of creating electrolyte balance from a side-effect of creating imbalance. The story is nonsense, and a little plain thinking and plainer writing eliminates side-effects more thoroughly than the most specious blandishments of copy writers.

Drugs have actions. The actions are localized to certain cells, varying with the individual drug. The cells concerned are sometimes made more active than usual. Generally they are made less active. The duration of activity depends on how firmly the drug is bound by the cells, and on how quickly the drug elsewhere in the body is got rid of, by excretion or chemical change. Whether the action is beneficial or not depends on the state of the patient and the dose of the drug. Most tissues are essential for life, and arresting their activity

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for some time is disastrous. Even stimulated cells usually run out of one or more essential metabolites fairly soon, and fail. Either way, active drugs are lethal in excess. In less than lethal doses, the altered cellular activity may have useful consequences, as when the kidney excretes more urine after inhibition of some tubular cells or the brain becomes less reactive after depression by a barbiturate. But if a drug is non-toxic it is inert, though placebo effects often lead to the allegation of non-existent pharmacological properties.

Thiazides and Barbiturates

Even after optimal doses of an active drug the consequences are not necessarily all desirable. The particular way in which thiazides act on renal tubular cells reduces reabsorption of sodium, potassium, chloride, bicarbonate, and water. Most patients who are treated with thiazides benefit from the loss of sodium and chloride and water, but some of them also suffer from the loss of potassium. The loss is important because it is sometimes dangerous; it is easily made good by giving supplementary potassium salts. To call the loss a side-effect is to hide the fact that it is an essential part of the action of thiazides, and to encourage woolly optimism that the next thiazide on the market will have all the beneficial properties without this undesirable one. Possibly such a thiazide will be discovered, but the rate at which the market is flooded with new remedies precludes proper testing of any of them and claims in this direction smack more of the copy writer than of the clinical laboratory.

Similarly, a barbiturate or tranquillizer which makes a patient less sensitive to the disturbing experiences of life is likely also to make him less alert to the simple hazards of the home and the road. It may benefit a patient to make him less sensitive to all kinds of threatening stimuli, but it is silly to pretend, without extremely rigorous evidence, that a drug can so modify the activity of some nerve cells and not others as to achieve beneficial without disadvantageous protection. Drowsiness is not a side-effect of sedative drugs: it is a characteristic consequence of their use. There are, of course, differences between the actions of barbiturates and phenothiazines. There are differences between the actions of different barbiturates and different phenothiazines, but the differences are probably smaller than many claims suggest. The rate of metabolism certainly differs with different barbiturates, and the potency varies widely between phenothiazines. How far such differences result in different pharmacological actions remains unproved. The majority of alleged differences do not appear to be based on scientifically acceptable evidence, and the reported absence of side-effects is apt, especially with a new drug, only to mean that little search has been made for its less desirable properties.

Drugs with Multiple Actions

Quite often drugs act on more than one set of cells. Atropine acts on the smooth muscle of the intestine, the bladder, the bronchioles, the constrictor pupillae, the ciliary muscle and elsewhere, on the salivary and other glands, and on the pace-maker cells of the heart, in all cases blocking the effects of parasympathetic nervous activity. A physician administering belladonna to a patient with a peptic ulcer might call dryness of the mouth and dilatation of the pupil side-effects. An anaesthetist controlling bronchial secretion or an oculist inspecting the retina might think otherwise. The term side-effect is in fact meaningless for atropine, and for the extensive family of drugs with similar properties. Modest differences in relative potency at different sites in man have been shown between atropine, hyoscine, hyoscine methylbromide, and some others. The differences are useful but not absolute. They do not

suggest that any particular kind of anticholinergic activity can be divorced from the rest, or that any can be called side-effects. To do so is to risk dismissing the possibility of potentially harmful events when the drug is administered.

When a drug acts on more than one set of cells it may reflect the existence of two quite different biochemical mechanisms, into each of which the drug fits, or it may reflect the occurrence of similar mechanisms in cells with different functions. The different peripheral actions of atropine, all occurring at physiologically analogous sites, probably all involve the same kind of tissue mechanism. The central actions of the otherwise similar drug, hyoscine, perhaps involve a different kind of receptor. On the other hand, the diuretic and anti-convulsant activities of acetazolamide, not immediately suggestive of a common mechanism, are probably both signs of the inhibition of the same enzyme, carbonic anhydrase, and so indicate a single pharmacological mechanism. Often the exact mechanism on which a drug acts is unknown, and diverse actions of the same drug may indicate a common underlying event. Even the toxicity of thalidomide might have been predictable if enough basic biochemistry had been known both about the brain and about the developing embryo. Predictable or not, should one or should one not call teratogenicity a side-effect?

"Idiosyncrasy"

Sometimes patients are unusually sensitive to drugs. They may show an ordinary response to an exceptionally small dose, as when a patient is paralysed for a long time after injection of suxamethonium. Or some abnormal event may occur, such as haemolytic anaemia after the administration of primaquine, or coma and death after a conventional dose of pethidine. In any such case the patient may be said to have an idiosyncrasy to the drug. This is a verbal escape from the difficulty. In the instances chosen the actual reason for the sensitivity is known, and the untoward reaction is not inexplicable, not an obscure side-effect, but a straightforward consequence of the particular biochemistry of the individual patient at the time. The first two are genetic in origin. A lack of cholinesterase, genetically determined, results in a slower than usual hydrolysis of suxamethonium, and in the meantime the usual paralysis of all voluntary muscle is prolonged. A lack of glucose-6-phosphate dehydrogenase in red cells is normally symptomless, but has some as yet unknown consequence which makes the cells vulnerable to a variety of drugs, including primaquine, with consequent haemolysis. The last is "therapeutic" in origin. A monoamine oxidase inhibitor, administered with the objective of ameliorating depression, inhibits enzymes which normally inactivate pethidine, so that the effects of pethidine are exaggerated in a way similar to the exaggeration of effects of suxamethonium where there is a congenital lack of cholinesterase. All these "idiosyncrasies" could also be called "side-effects which may occur." Neither label is helpful in preventing unwanted consequences of the drugs. Accurate knowledge of the actions of the drug, of its fate in the body, and of individual biochemistry, together provide complete protection against the disasters of misguided therapy.

In the present state of knowledge, particularly of individual biochemistry, we are still a long way from being able to use drugs safely. There remain a large number of miscellaneous reactions to drugs which are not readily explicable by known biochemical mechanisms. Agranulocytosis after phenylbutazone, exfoliative dermatitis after gold salts, diabetes after thiazides, are all uncommon "side" (or unwanted) effects. As more basic knowledge is acquired about the fate of drugs in patients and about individual biochemical variation, most of these effects will probably become explicable. Whether the knowledge of their mechanism will make it possible to prevent them is less certain. The lure of novelty, the urge of experi-

ment, the desire to leave no stone unturned, the pursuit of fashion, or the pressures of a system of commerce persuade many doctors to use new remedies and to discover their hazards by the hard way of actually doing harm with them. As long as this is so, the early recognition of ill effects is vital. Machinery for collecting and dispersing information about possible or definite ill effects is rapidly being elaborated by the Dunlop Committee and other bodies. Such machinery can be effective only if it is properly supplied with facts, and these must come from the early prescribers. Any drug less than five years old almost certainly has some undiscovered toxic effects for at least some people, and even older drugs may have unpleasant properties which are still unrecognized. How soon these properties are discovered depends on the alertness and the general pharmacological knowledge of everyone who prescribes drugs. All drugs are either ineffective or dangerous, just as all knives are either blunt or sharp. To use a potent

drug without knowing which organs it will go to and how long it will stay there is like using a knife blindfold.

Correction.—In the "To-day's Drugs" article on "Fibrinolytic Enzymes" (20 March, p. 775) a word was omitted in error. The last sentence of the paragraph headed "Streptokinase" should read "After treatment streptokinase *antibody* levels rise steeply. . . ."

Book of "To-day's Drugs."—This book is now available through booksellers at 30s., or from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1, at 32s. 6d., including postage. It is based on the series of review articles which were printed in the "To-day's Drugs" section between January 1963 and May 1964. The articles have been edited and brought completely up to date so as to form an authoritative and practical guide to modern therapeutics. The book is designed to cover the drug treatment of those common conditions which are met with in general and hospital practice.

ANY QUESTIONS?

We publish below a selection of questions and answers of general interest.

Hatching of *Schistosoma* Ova

Q.—*Can the miracidia be liberated from the *Schistosoma haematobium* ova in the human bladder in a case of schistosomiasis and be excreted with the urine as freely swimming miracidia? If so, are these miracidia able to invade a fresh-water snail to develop into sporocysts and produce cercariae?*

A.—It is uncommon for miracidia to be excreted in the urine, though it is not absolutely impossible. Eggs in urine which has been allowed to stand outside the body may hatch into miracidia, and these are perfectly capable of infecting snails. Exposure of the eggs to fresh water aids the rupture of the egg-shell as a result of osmosis.

Cleaning for Hygiene

Q.—*I am thinking of building new surgery premises on to my house and using for domestic purposes the rooms that have served as consulting- and waiting-rooms for the past 15 years. Is there any risk of infection to my family in this, and, if so, what measures should be taken to obviate it?*

A.—I do not think that there is any risk of infection to the family from using for domestic purposes rooms that served as consulting- or waiting-rooms. Even if there were any risk it would be eliminated by normal cleaning and redecoration.

Intradermal T.A.B. Vaccine

Q.—*Is phenol-killed T.A.B. vaccine suitable for intradermal inoculation?*

A.—In theory acetone-killed T.A.B. vaccine is perhaps preferable, but in practice

there has been no evidence that phenol-killed vaccine is unsuitable for intradermal inoculation. For many years now it has been used thus in the Services, and more recently intradermal inoculation has been adopted in civilian practice, because both local and general reactions tend to be fewer and less severe than those following subcutaneous administration.

Blood by Post

Q.—*What effect does delay have on the accuracy of haemoglobin estimations in blood sent in sequestrene bottles to the laboratory by post?*

A.—Provided that the blood sample remains uncontaminated by bacteria the haemoglobin concentration will remain unchanged for at least 3-4 days, and probably longer, and the accuracy of its estimation is unaffected. Indeed, in the cold haemoglobin in solution may remain relatively unchanged for many months and retain its usual electrophoretic behaviour.

Delay in the examination of a blood sample longer than a few hours will vitiate the results of estimations other than measurement of the haemoglobin concentration. The red cells start to swell and the mean corpuscular volume rises, as does the haematocrit. Leucocyte and red-cell morphology is well preserved in blood films made 2 to 3 hours after collection of the sample, and a reliable total white-cell and platelet count can be obtained up to 12 hours after collection.

On the other hand, it is not uncommon to receive postal specimens in which there has been marked degradation of haemoglobin, and examination shows an abundant bacterial flora. Disposable polystyrene 2 ml. bottles for blood specimens are widely used to-day. These are generally not sterile and they would be quite unsuitable for the dispatch of blood samples by post.

Corticosteroid Treatment and Smallpox Vaccination

Q.—*What precautions are necessary in vaccinating or revaccinating against smallpox a patient who is on steroid therapy?*

A.—Corticosteroid therapy is recognized as one of the contraindications of smallpox vaccination. If vaccination is not essential or urgent it should be forgone or postponed. If the corticosteroid therapy can be interrupted for four to eight weeks without undue embarrassment to the patient smallpox vaccination (or revaccination) may be effected about two weeks after stopping the treatment. A gap of about two weeks should be allowed after the effects of vaccination have worn off before starting treatment again. If the corticosteroid therapy cannot be interrupted and the need for vaccination is pressing (as in the case of a smallpox contact or a person going overseas) anti-vaccinal gamma-globulin (1.0 to 1.5 g.) may be injected (in the other arm) at the time of vaccination. Some authorities recommend its injection 24 to 48 hours after vaccination in order to avoid interference with the mechanism of active immunization, but others have shown that the gamma-globulin does not in fact interfere with the maturation of the vaccination.

Prophylactic Antitetanus Serum

Q.—*If it is considered advisable to give prophylactic antitetanus serum what is the optimum dose?*

A.—Most authorities in the United Kingdom are agreed that the optimum dose of equine tetanus antitoxin is 1,500 units. In the United States many surgeons give 3,000 units, and a few even 5,000 or 10,000 units. Boyd¹ believes that 1,500 units give adequate passive protection and that a higher dose is unnecessary in routine prophylactic practice. When there is a history of horse serum having been given on a previous occasion (and therefore a risk of rapid elimination of the second injection), or if a tetanus-prone wound is slow to heal, the dose of 1,500