Post-Graduate Medical Journal

LONDON, MAY 1, 1942

Recent Advances in Drug Therapy.

In the welter of war it is very difficult for practitioners to keep track of recent advances in drug therapy, and an article by Dr. GOODMAN[1] in the *Bulletin of the New York Academy of Medicine* is a very timely one. He divides his drugs into groups. In group 1 he takes those which are generally accepted and which are much used, and are shown to be successful. In group 2 he places those which are widely employed, but which need further investigation before being universally adopted. In group 3 are those which are in the doubtful category and whose position is not so far properly assured. In group 4 are listed those drugs which hold very little promise, and which the author considers are not rational and are destined for eventual discard.

Group 1 of course is headed by the sulphonamides. So much has already been written on the subject of the drugs that he says little about them, but he mentions sulphadiazine and sulphaguanidine. He remarks that these are valid additions to the family of the sulphonamides, and there will be few people who will disagree with him. He mentions a few special uses of these drugs. The local use he regards as being extremely important, and says that their value is difficult to exaggerate. The prophylactic use is also considered, and amongst the indications he mentions the quiescent stage of rheumatic fever, scarlet fever contacts when the Dick's test is positive, meningococcus carriers, and after severe accidents and before severe operations. We think him wise to have mentioned these points for, although these drugs are very extensively used in this country, their prophylactic use has not come to the same prominence.

Dilantin in epilepsy is mentioned, and it is considered that this drug possesses two outstanding advantages, firstly because it is not a sedative, and secondly because it is of value not only in the control of grand mal, but also in the treatment of seizures of the psychomotor variety.

Plasma is recommended as a blood substitute, especially in the treatment of burns and traumatic shock. Two drugs are next mentioned in the treatment of bronchial asthma, epinephrine, and theophylline. It seems doubtful whether epinephrine really comes into the category of recent drugs, but there are some new preparations of this drug, and its use by inhalation is a more recent introduction. Theophylline is especially recommended, in combination with ethylene diamine.

Some synthetic atropine substitutes are next mentioned, and especially eumydrin. These, of course, are anti-spasmodic, and are used in conditions which vary from spastic dysmenorrhea to ureteral colic. These substitutes have not the unpleasant effect of atropine and do not, for instance, affect the cardiac rate. One of these substitutes, syntropan, has been recently used experimentally in labour and preliminary results show that labour may be shortened in duration by as much as 50 per cent. This work requires careful study before it can be properly assessed.

Vitamins next come under review, and very rightly it is stated that thiamin or vitamin B1 and nicotinic acid, another member of the vitamin B family, should only be used where there are clear-cut deficiencies in nutrition, such as occurs in beri-beri and pellagra. Vitamin K is now used as a routine in jaundiced patients before operation, in haemorraghic diseases of the newborn, and is sometimes administered to pregnant women prior to delivery. Its physiological role in the body is of course concerned in the production of prothrombin.

Desoxycorticosterone is mentioned in the treatment of Addison's disease, and quinine in the treatment of myotonia congenita.

In the old days papaverine, one of the opium alkaloids, was always treated very like the other alkaloids of opium, and had the same uses. Within recent years, however, this is found to be a useful vasodilator, and has been used in the emergency treatment of embolism whether of peripheral or pulmonary distribution. It is injected intravenously, and the author is of opinion that it is of value in saving life.

Heparin is next mentioned on the list of drugs, and it is stated that it has been found to be of use in the surgery of blood vessels, blood transfusion, prevention and treatment of thrombosis and embolism, and in thrombophlebitis. As is well known, heparin has been the subject of many articles in the British and American medical press in recent years, and there is no

[1] Goodman, L. S., *Bulletin of the N.Y. Academy of Medicine*, **18**, 112, 1942.

doubt that it is of considerable value in the therapy of certain conditions where thrombosis and embolism are a feature.

This completes the author's list under group 1, and most people will probably agree that it is a very complete list, but that nothing has been included which should not be included. If one may be allowed to pick out certain drugs which have been mentioned as being outstanding in the sense that they are new and of use, one would include first of all the sulphonamides, secondly the blood substitutes, thirdly theophylline, fourthly Vitamin K, and lastly heparin.

Now we come to group 2, the group which, although promising, requires further study before it may be generally employed, and we propose to mention nearly all the drugs which are mentioned because they all have some particular use, although a great many of them are not of great use in the diseases and syndromes which are met with in this country.

The author heads his list with the newer digitalis glycosides. The author states that the three native glycosides of digitalis are known as lanatosides A, B, and C. He agrees that when all three are employed they provide an acceptable digitalis preparation for oral use, but he states that this does not necessarily mean that such a preparation possesses any overwhelming advantages. Lanatoside C has been employed for intravenous administration, but his view is that this is only warranted when the digitalis effect must be produced in minutes rather than hours. He therefore compares it with such substances as strophanthin, and his view is that this drug may be comparable in the future with strophanthin. A fairly long and well thought out paragraph follows in which the author compares these lanatosides, especially lanatoside C, with the older digitalis drugs and strophanthin. On the whole, his view is that the older drugs may be as effective as the newer ones and with considerably less cost. He says that the powdered digitalis leaf is easy to administer, is readily absorbed when given by mouth, is effective in its action on the myocardium, has a fair margin of safety, and keeps up a satisfactory maintenance of effect for a long period. His view is also that the burden of truth for a new digitalis substitute must be borne by those who make such a claim. The practitioner will do well for the present to select therapeutic agents from standard preparations, and will be wise to leave the final evaluation of the glycosides to the experimental investigator, as both he and his patients can gain thereby.

Benzedrine next comes under review. It is treated as an adjuvant in epilepsy and Parkinsonism. As is well known, this is one of the newer members of the epinephrine family, and has been put to crucial tests in the two conditions mentioned above. Perhaps the most interesting remark that the author makes is that benzedrine may prove to be a valuable adjuvant to phenobarbital in the treatment of epilepsy.

It appears that the concomitant use of benzedrine obviates untoward effect, and allows doses of phenobarbital which would otherwise be impossible. It also appears that benzedrine is a valuable adjuvant to the alkaloid of belladonna in the treatment of Parkinsonism.

Rather unfortunately this effect can only be produced in that type of Parkinsonism which is postencephalitic, and not in the type which is arteriosclerotic, and which of course is much more common in ordinary practice. Nevertheless any aid which can be given in the treatment of this condition is very welcome, and although personally we have no experience of this method of therapy, we feel that it should be put to its uttermost useful limit.

The author next refers to the use of picrotoxin in barbiturate poisoning. Until recently this substance was largely a laboratory curiosity. It is now found, however, that it is capable of lessening the degree of depression and stimulating respiration in patients poisoned by certain anaesthetic agents, especially the barbiturates. It is too early to say yet whether it can replace other analeptic agents, but it is felt that this may be possible, although picrotoxin must not be employed in the treatment of morphine poisoning.

The next paragraph deals with curare and curariform drugs. This drug is full of historical interest, and is of course one of the oldest of the so-called nervous poisons.

As is well known, curare acts principally on neuro-muscular junctions, and this action has been used principally for the treatment of schizophrenia. The treatment of schizophrenia has lain in the production of shock, and this shock may be produced either by electrical methods or by insulin, or sometimes by other methods, such as cardiazol. Whatever method is used there are dangers attaching to this treatment, and one of the principal dangers is the production of injury to the patient during his seizure. It is no uncommon feature to find that fractures have been sustained by the patients during their treatment. This indeed is no reflection on the treatment, but it is an unfortunate concomitant. Curare has been used during the course

of these treatments, and by its action on the neuro-muscular junctions has reduced the incidence of these casualties. In consequence of this curare has come back into medical notice, and some measure of success has been obtained in patients with other nervous disorders, particularly perhaps in those with spastic paralysis and with torticollis. It would seem that a possible method of advance would be that some curare-like preparation could be found with a selective action on abnormal muscles. It is quite evident that in this way it might be possible to relieve certain conditions in which spasticity is a clinical and rather distressing feature.

Although it is fairly well known in this country that the mercurial diuretics have been administered by the rectal route, it is not, we think, generally known that a preparation of salyrgan combined with theophylline has been given by the oral route. It appears that satisfactory diuresis has been obtained in this way in approximately 70 per cent of patients in whom it has been used. It is generally agreed that the mercurial diuretics are 95 per cent successful when given by the intravenous route, so that the oral figures are not so far as good as the intravenous ones. In addition to this certain untoward gastro-intestinal symptoms are found to occur, such as epigastric discomfort and diarrhoea, but it is said that these are not found frequently. We shall therefore look forward to the release of this combination of drugs as it is evident that the oral route would be far more convenient in most cases. It must, however, be remembered that these drugs must not be used by mouth any more than they must be given intravenously, if renal function is impaired.

A brief note appears about the short-term massive arsenotherapy of early syphilis. The original investigators outlined a method of continuous intravenous therapy, and so far very little has been written about it by other people. It seems a little early yet to say what the result will be, but so far as can be told, in early syphilis it appears to be a successful procedure.

A note follows on the oral treatment of syphilis with bismuth. Not a great deal is known so far about the results of this therapy, but if successful it will certainly be taken up.

A preparation made from the derris root is being used for certain conditions, such as scabies, in the United States, but so far it is only under trial. Benzyl benzoate is of course well known, and is said to be extremely successful.

Next comes three drugs used in human parasitic infection. They are phenothiazine gentian violet, and atabrine.

Synthetic morphine substitutes next come under review, and it may be recalled that dilaudid has been now used for some time in this country with fairly successful results. Now a methyl derivative of dilaudid has been synthesised and named metopon. Favourable reports have been received as to its action, but it is only available so far for trial.

In 1939 Dubos *et al.* isolated a crystalline principle from the soil, or rather from an aerobic soil bacillus. This kills Gram-positive cocci. It has therefore been named gramicidin. In the test-tube as little as ·005 of a mgm. of gramicidin kills 1 billion pneumococci or group A haemolytic streptococci. Unfortunately at the present time gramicidin is water-insoluble and is also haemolytic. There is however some reason to believe that water-soluble and not-haemolytic fractions of the drug may soon be available. If this is so there is little doubt that very much more will be heard of gramicidin ere long.

The next section deals with penicillin and its use in bacterial infection. Penicillin is said to differ from the sulphonamide drugs in three important ways. Firstly, it is more potent, secondly it completely inhibits bacterial growth even when the cultures are heavily inoculated, and thirdly penicillin is not inhibited by tissue fluid. It is water-soluble and can be administered to patients by almost every possible route. It has been used in Oxford in a variety of conditions including osteomyelitis, large carbuncles, and conjunctivitis. It has also proved of use in cases which failed to respond to the sulphonamides. The author's view is that its ultimate status in relation to gramicidin and the sulphonamides remains to be determined, and there are few people who will disagree with him.

The last two sections in group 2 deal with diethylstilboestrol and progesterone therapy. We are so familiar in this country with these two methods of treatment that nothing further need be said about them.

Next we come to group 3, which includes those newer drugs which are of questionable value. The following drugs are mentioned. Histamine, adrenal cortical hormone, renal antipressor extract, and lastly the shock treatment of schizophrenia.

Of these the only one which calls for mention is the shock therapy of schizophrenia. Rather surprisingly the author's view is that such treatment is questionable, and certainly of limited

value, and is not without serious danger. He says that so many so-called cures of schizophrenia have been endorsed enthusiastically only to be discarded after long-term study. This cautious view would not we think be held by most physicians who specialise in the psychoses in this country, nevertheless it may be of value and will act as a check on over-enthusiasm.

Group 4 includes those newest drugs which in the author's opinion are either extremely questionable or irrational.

A simple list will probably suffice for these. The author mentions pyridoxine in the treatment of Parkinsonism, alpha-tocopherol in the treatment of the muscular dystrophies, and testosterone in the treatment of prostatic hypertrophy. Histaminase and potassium salts in the treatment of allergy, and Bulgarian belladonna in the treatment of Parkinsonism complete the list.

We think that most of our readers will appreciate this brief survey of the newer drugs. It will also give them an idea of the sort of work which is being done in new treatments, and the sort of success that is likely to be expected from them. Although the war has interfered to a very large extent with research and trial of these drugs in this country, it will be as well that readers should keep an eye open on the drugs which have been mentioned as they may come into popular regard quite quickly.

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3. Slow respiration.

(i) Respiratory depression due to morphia given too soon before operation.
(ii) Increased resistance to breathing (slow and deep).
(iii) Deep anaesthesia (slow and shallow and jerky).

4. Periodic Breathing.

(i) Recovery stage from hyperventilation apnoea.
(ii) Oxygen want.

5. Alteration in length of expiration compared to inspiration.

Expiratory phase longer than inspiratory phase in deeper anaesthesia, and vice versa.

6. Irregular breathing.

(i) Reflexly in light anaesthesia.
(ii) Deep anaesthesia—impending death.

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POST-GRADUATE
MEDICAL JOURNAL

Official Organ of the Fellowship of Medicine

1 WIMPOLE STREET · LONDON · W.1 *Telephone*: LANGHAM 4266

VOLUME XVIII NUMBER 198 MAY 1942

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