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## THE DISCOVERY OF PENICILLIN

The discovery of penicillin introduced a new epoch in the treatment of disease. It has been followed by an intense search for other "antibiotics," and a whole range of bacterial infections have now come within the effective control of substances produced, for the most part, by moulds, among which *Penicillium notatum* holds pride of place not only historically but also therapeutically. We stand so close to a bewilderingly rapid sequence of discoveries that as yet we probably fail to understand fully the revolution in medicine that has taken and is taking place as a result of Alexander Fleming's discovery. It is natural that the world will acclaim a medical advance "great" in proportion to the curative benefits it brings, and on this count alone Sir Alexander Fleming has his place among the immortals. And close beside him will be Sir Howard Florey and Dr. Ernst Chain, who in a systematic investigation of antibacterial substances ten years later hit upon the technical ways and means of fulfilling the promise Fleming held out for penicillin in 1929. Fleming had the real naturalist's capacity for observation and the scientific imagination to see the implications of the observed fact—a capacity and an imagination which, it is true, only the prepared mind can compass, and which in the great discovery seem invariably to be joined to a mind that is essentially humble. As there have been some popular misconceptions of the part Fleming played in discovering penicillin it may not be inappropriate at this time of his death to recall in his own words some of the observations he summarized in his historical paper in the *British Journal of Experimental Pathology* for June, 1929:

"A certain type of penicillium produces in culture a powerful antibacterial substance."

"The active agent is readily filterable and the name 'penicillin' has been given to filtrates of broth cultures of the mould."

"The action is very marked on the pyogenic cocci and the diphtheria group of bacilli."

"Penicillin is non-toxic to animals in enormous doses and is not irritant. It does not interfere with leucocytic function to a greater degree than does ordinary broth."

"It is suggested that it may be an efficient antiseptic for application to, or injection into, areas infected with penicillin-sensitive microbes."

The discovery recorded in Fleming's paper is a milestone in the history of medical progress, and the "penicillin" he discovered and named has come nearer than any other remedy to Ehrlich's ideal therapia sterilisans magna.

## ANTICHOLINERGIC DRUGS FOR PEPTIC ULCER

During the past few years a spate of anticholinergic drugs have been introduced for the treatment of gastro-intestinal disorders, particularly peptic ulcer and enterospasm. Belladonna has had a time-honoured role, and these new preparations have sought to emulate its action but with fewer undesirable side-effects. "Banthine" (methantheline bromide) blazed the trail and has been followed by a bewildering number of other drugs, including "antrenyl," "bentyl," "centrine," "lergine," "lytensium," "merbentyl," "monodral," "pamine," "prantal," and "wyovin," and much has been written on both sides of the Atlantic about their pharmacological and clinical effects. In the *Journal* this week a special study of lergine (tricyclamol chloride) is presented by Drs. Pamela Aylett and A. H. Douthwaite.

All these drugs have much in common. Their chemistry is complex; they achieve an anticholinergic effect like atropine by blocking transmission either at autonomic ganglia or at the peripheral effector site; they reduce basal secretion, slow the emptying time of the stomach, and lessen intestinal muscular activity. Although side-effects are generally claimed to be slight, in practice the usual atropine-like disturbances of impaired vision and dryness of the mouth are quite common, and sometimes there may be constipation and difficulty in urination. Moreover, the response varies considerably between different patients and even in the same patient at different times.

The therapeutic contribution of these new drugs is not impressive, and they have not greatly advanced the therapy of peptic ulcer. Nor were they likely to do so, since atropine and related drugs, although undoubtedly beneficial for smooth-muscle spasm, have never been conclusively proved to give great benefit in cases of peptic ulcer, though most clinicians would agree that belladonna can help to relieve pain, particularly night pain, in duodenal ulcer. According to Nicol[1] even large doses of atropine had very

[1] Nicol, B. M., *Lancet*, 1939, **2**, 881.
[2] Rowlands, E. N., *et al.*, ibid., 1952, **2**, 1154.
[3] Friedlander, P. H., ibid., 1954, **1**, 386.
[4] Texter, E. C., and Barborka, C. J., *Postgrad. Med.*, 1954, **16**, 449.

little effect on the acid of the stomach when measured over 24 hours, and no better success seems to have been achieved by ganglion-blocking agents in this respect.[2] It has been postulated that slowing the stomach's rate of emptying would allow the more effective use of antacids, but this hypothesis is by no means proved. The distension of the stomach is itself an important stimulus to secretion, and slowing of the rate of emptying may well mean more prolonged secretion, which would offset the neutralization. However, using tricyclamol, Drs. Aylett and Douthwaite have prolonged the period of achlorhydria from $1\frac{1}{4}$ to $2\frac{1}{2}$ hours after a dose of aluminium hydroxide, but details of only two patients are given. Again, the inhibition of other intestinal secretions, particularly pancreatic, might offset any benefit to the duodenum from lowering of the gastric acidity. Indeed, in so far as these drugs are supposed to help the healing of peptic ulcer, the administration of them is still based on doubtful hypotheses and insufficient clinical study with control series.

The clinical evidence of the value of methantheline in controlled observations is unimpressive apart from some reduction of pain, and P. H. Friedlander[3] did not find that the natural history of duodenal ulcer was improved. E. C. Texter and C. J. Barborka[4] followed 250 patients with proved peptic ulcer for two years. The patients were treated identically with diet and the usually recommended forms of treatment, the only difference being that half the patients received 100 mg. of methantheline four times a day, while the remainder received 0.4 mg. of atropine sulphate four times a day. After the two years these authors, without knowledge of which drug had been given, then assessed the patients' progress: they found that those taking banthine were symptomatically improved and had had somewhat fewer and milder recurrences than those taking atropine. The recurrence rates were high in both groups—75% in the banthine group and 90% in the atropine group. When the results were separated into mild, moderate, and serious cases, the best results occurred in the group whose ulcers had been classified as mild before treatment, whereas in the group with severe ulcers it mattered little whether atropine or banthine had been used. Complications and the need for surgery were of the same frequency in the two groups. Therefore the conclusion was that, although these drugs often gave symptomatic improvement, the eventual course of the disease was not altered.

But, while the natural history of the disease is not materially influenced, greater relief of pain is important to the patient and justifies the administration of any of these preparations during the phase of active ulceration, though it would seem reasonable to see whether the desired effect cannot be obtained with the traditional belladonna before prescribing the new, and much more expensive, preparations. The *tab. belladonnae et phenobarb.* of the *National Formulary* contains $\frac{3}{4}$ gr. (50 mg.) of phenobarbitone and $\frac{2}{5}$ gr. (26 mg.) of the dry extract of belladonna and is convenient to prescribe when some sedation is required as well.

It may be unfashionable to say so, but patients appreciate brand-new treatments, and it is an advantage to have a variety of compounds available for the management of a chronic and relapsing disease. Apart from some difference in side-effects, it is unlikely that any one of the many new preparations will prove to be superior to its rivals, and the family doctor need not feel that he must personally evaluate each preparation.

## EXCHANGE TRANSFUSION

No effective prophylaxis is yet available against maternal iso-immunization from rhesus and other blood-group incompatibility between mother and foetus. The problem of preventing stillbirths from this cause is still unsolved, in spite of attempts to reduce the effects of foetal haemolytic anaemia by cortisone administration to the mother[1–3] or inducing labour early in a few selected cases.[4] Treatment has therefore been concentrated on the 70% of affected babies who are born alive. The main complications in untreated infants are anaemia at birth in about two-thirds, which may be progressive, and kernicterus after 36 hours in up to a quarter. Adequate exchange blood transfusion with fresh compatible packed cells not only corrects severe anaemia without increasing blood volume but also reduces the risk of kernicterus by removing up to 1,000 mg. of bilirubin contained in over 85% of the infant's sensitized red blood cells. In our opening pages Drs. W. Walker and G. A. Neligan, of Newcastle, report the results of 250 exchange transfusions, with a remarkably low mortality of only 15 deaths attributable to haemolytic disease of the newborn. A follow-up of 200 of the survivors showed only 3 suffering from kernicterus, confirming the good long-term prognosis found by P. Armitage and P. L. Mollison.[5] They also discuss the modern indications for the procedure

[1] Hunter, O. B., Jr., *J. Amer. med. Ass.*, 1954, **154**, 905.
[2] Wiener, A. S., ibid., **155**, 63.
[3] DeCosta, E. J., *et al.*, *Obstet. Gynec.*, 1954, **3**, 131.
[4] Davies, B. S., *et al.*, *Arch. Dis. Childh.*, 1953, **28**, 466.
[5] Armitage, P., and Mollison, P. L., *J. Obstet. Gynaec. Brit. Emp.*, 1953, **60**, 605.
[6] Wiener, A. S., *et al.*, *J. Pediat.*, 1954, **45**, 546.
[7] Diamond, L. K., *Pediatrics*, 1948, **2**, 520.
[8] Mollison, P. L., and Cutbush, M., *Advances in Paediatrics*, Chapt. 5. 1954, London.