Drug Treatment of Disease

DRUGS IN THE TREATMENT OF SYPHILIS: PART I*

BY

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During the past fifty years drugs have played a predominant part in the treatment of syphilis; and within the past fifteen years short and safe methods of treatment have been substituted for those which were long and hazardous. The administration of these remedies is simple, but the management of the cases is still far from being so.

The diagnosis of syphilis is apt to provoke in the patient a disproportionate fear of the disease and its effect on himself and his family, and, in some cases, a profound sense of guilt and unworthiness. The doctor must deal with this difficult psychological problem and must strive to mitigate the stresses and strains in family life which, for the married patient, will certainly follow. He has responsibility not only for his patient, but for wife or husband, for other sexual contacts, and for the children of the marriage. He has a duty to trace contacts and to restrict infection in the interests of the public health. His problem is a bigger one than that of prescribing the right drug in the correct amount.

Preventive Treatment

A clear distinction must be made between preventive measures applied before and after the risk is taken. Those applied before are truly preventive measures, involving broad issues of education, public health administration, and, in some aspects, complex moral problems. Drugs play no part in these preventive measures.

Prevention applied after the risk is taken should, strictly, be called abortive treatment. There are two schools of thought about the use of drugs for this purpose. The World Health Organization has used penicillin extensively, and with some success, in certain attempts to control treponemal infections, including syphilis, in what McElligott (1954) has aptly called "the almost veterinary methods of the mass campaign." Whatever the virtues or faults of this procedure, the general view in Great Britain is that antisyphilitic drugs should not be used as abortive treatment for patients who have taken risks. To do so is tantamount to making a diagnosis of syphilis, and, in justice to the patient and his family, this should be followed by a period of observation and testing lasting at least two years, together with prohibition of sexual intercourse, which throws a great strain on the marital relationship. The patient is uncertain whether or not he has suffered from the disease, and prolonged uncertainty, together with recurring reminders in the form of clinical examinations and serological tests, can be most damaging to patients already obsessed by fear and anxiety. On the other hand, to withhold treatment means a probationary period of three months at most, a firm diagnosis, and in most cases a solution of all problems after the initial period of stress.

There are exceptional circumstances in which it might be expedient to depart from the rules of withholding abortive treatment. The case of a woman late in pregnancy who has been subjected to a serious risk is one in point. There may also be a case for such a procedure among backward peoples where medical services are deficient and co-operation is unlikely. But it should be emphasized that all such indications for making exceptions to an important principle should be carefully and critically examined. "Diagnosis before treatment" is still a golden rule.

Curative Treatment

Penicillin is the drug of choice in the treatment of syphilis in all its stages. It should be given by intramuscular injection and not by mouth, because of individual variations in absorption from the gastrointestinal tract, and the difficulty of ensuring that tablets are taken regularly by out-patients. There is no evidence of "penicillin resistance" on the part of *Treponema pallidum*, and there is considerable evidence to indicate that the addition of other remedies in treatment gives no additional curative effect. The use of organic arsenicals adds considerably to the hazards of treatment and is probably no longer justifiable. For effective treatment, a high level of penicillin in the blood appears to be unnecessary. A low level, such as 0.03 unit per ml. or more, is all that is required, but it should be present continuously and for a considerable time.

For this purpose the repository preparations of penicillin have proved thoroughly satisfactory. Their toxicity is low; they produce prolonged low levels of penicillin in the blood, and so avert the necessity for repeated injections and for in-patient treatment. Procaine penicillin in oily or watery suspension may be given daily intramuscularly in doses of 2 ml., containing 600,000 units. An effective level of penicillin is maintained for approximately 24 hours, and, if treatment is continued for 10 days totalling 6 million units of the drug, success in cases of early syphilis is to be expected in 95% of the cases. With this method of treatment there should be no interval. *Postponement of an injection from Sunday to Monday might turn the scale between success and failure.*

A later development of this method (Buckwalter and Dickison, 1948) was the addition of the water-repellent aluminium monostearate in concentration of 2% to the oily suspension of procaine penicillin (sterile procaine penicillin G with aluminium stearate suspension, or P.A.M.). This still further delays absorption, and a single dose of 600,000 units maintains an effective level for 72 hours or more. This is the standard remedy throughout the world at the present time. An injection may be given every second or third day with adequate effect, but, if the patient can attend, many prefer to give daily injections of 600,000 units of P.A.M. This

*Part II will be published next week, with a list of references.

facilitates strict control of the patient during a period of potential infectivity and has the added advantage that it builds up a considerable depot of penicillin in the tissues so that treatment may continue for a week or more after the injections are discontinued. One modification of this method, either with procaine penicillin or P.A.M., is to give a single large dose, such as 2.4 million units, on the first occasion. Should the patient discontinue attendance, he is likely to be rendered non-infectious and has a chance of being cured.

A further development along these lines was the introduction by Szabo, Edwards, and Bruce (1951) of benzathine penicillin (N,N':dibenzylethylene-diamine dipenicillin G). O'Brien and Smith (1952) showed that a single intramuscular injection of 2.5 million units of this preparation would provide an effective level of penicillin in patients' blood for as long as two weeks or more. Recent evidence indicates that in the treatment of early syphilis a single injection of 2,500,000 units of benzathine penicillin is equally effective as a single course of injections of procaine penicillin G in oil totalling 4,800,000 units. Benzathine penicillin has great advantage in the treatment of patients unable to attend regularly even for 10 days, such as seamen who must rejoin their ship, or patients of low educational level in less advanced countries or elsewhere, who, from lack of proper understanding of the problem, are unlikely to co-operate in treatment after the first injection. Benzathine penicillin has the practical disadvantage that the injection is sometimes painful, and the theoretical disadvantage that it might cause more serious illness than a more rapidly eliminated drug, in patients who prove to have been sensitized to penicillin administered earlier.

Another possible substitute for procaine penicillin G in oil is benethamine penicillin (N-benzyl- β -phenylethylamine salt of penicillin G). It is available as an aqueous suspension and thus is easier to handle. It will produce blood levels of similar or longer duration to those produced by procaine penicillin G in oil. Unfortunately the injections cause pain.

Early Syphilis

For the treatment of early syphilis—that is, syphilis in the primary, secondary, or early latent stages—any one of these methods should prove effective in the great majority of cases. Treponemes disappear from the lesions within 24 hours, lesions heal promptly, and positive serological tests become negative within weeks or months. Further treatment with penicillin or other drugs is unnecessary and probably undesirable, because it might be expected to mask the tendency to relapse which is shown by a small proportion of the patients. It is for the detection of the latter that prolonged observation and testing is required in these cases. This should continue for at least two years and should include at least one series of tests of the cerebrospinal fluid a year or more after the completion of treatment. Relapses respond well to further administration of penicillin, but the patient who is prone to relapse may well continue to do so.

Late Syphilis

For the treatment of late syphilis of the benign or gummatous type, or of late latent syphilis, similar courses of injections of penicillin are effective, and

supplementary treatment is usually unnecessary. When treatment is started with penicillin, a slight danger attaches to the general and focal reaction which may follow the first injection, the Jarisch-Herxheimer reaction. This may endanger the patient if there is an undetected focus of infection in an important site, such as the opening of a coronary artery, the aortic wall, the wall of a cerebral or spinal artery, or the mucous membrane of the larynx. Serious accidents due to this cause are certainly rare, and perhaps the dangers have been overemphasized in the past.

Nevertheless, nothing is to be gained by speed in these cases, and some physicians in Great Britain prefer to start treatment with a few intramuscular injections of a suspension of bismuth metal or one of its insoluble salts, such as the oxychloride or the salicylate. The dose is 0.2 to 0.3 g., and injections should be given at intervals of a week for three to four weeks. They should not be given to patients with severe oral sepsis or with disease of the kidneys, because of the possible dangers of bismuth stomatitis or bismuth nephrosis. Care should be taken not to give the injection into a vein, because pulmonary embolism may follow.

The practice of attempting to avoid the Herxheimer reaction by starting with small doses of penicillin, and gradually increasing, is ineffective. The reaction is of the "all or none type." Very small doses may give no reaction, but once the "trigger" dose is reached the reaction is likely to occur with full force.

In the treatment of *cardiovascular syphilis* general measures are of great importance to prevent progression and to sustain a seriously weakened aortic wall with, perhaps, secondary damage to the myocardium. The evidence suggests that antisyphilitic remedies have an important place in treatment, and penicillin is the drug of choice. Herxheimer reactions have been uncommon and American experience has thrown doubt on the necessity for preliminary treatment with bismuth. Nevertheless, it is a reasonable precaution to give injections of bismuth during the first four to six weeks of treatment. Afterwards, penicillin may be given by standard methods. When procaine penicillin has been given daily in dosage of 600,000 units, a prevailing custom is to continue treatment in these cases for 14 days, giving a total dosage of 8.4 million units, but this is purely empirical and there is no evidence that four days' extra treatment is necessarily beneficial. It must be stressed that assessment of the efficacy of any form of treatment for cardiovascular syphilis is extremely difficult, because of the varied nature of the lesions and the considerable individual variation of prognosis in untreated cases.

For *neurosyphilis*, penicillin is an effective remedy and fever therapy or other adjuvant methods are seldom required. Daily injections are commonly given for 21 days with total dosage of 12.6 million units of procaine penicillin. The response to treatment is estimated by periodic tests of the cerebrospinal fluid. In some cases, especially those of general paralysis, further courses of treatment are required.

The treatment of *syphilitic pregnant women* with penicillin gives excellent results in the prevention of congenital syphilis at any stage of pregnancy. A course of injections of procaine penicillin lasting 10 days is fully adequate and should be given as soon as the diagnosis is made. It is common practice in Great Britain to repeat such a course in successive pregnancies,

though experience in the United States suggests that this is unnecessary in the great majority of cases.

Penicillin is the drug of choice in the treatment of *congenital syphilis* in all its stages. It is particularly effective in the first two years of life. Excessive dosage should be avoided. A good working plan is to base the dosage on body weight, giving 200,000 units per lb. (450,000 units per kg.) and to space administration over 8 to 10 days. Thus, for a child weighing 7 lb. (3.2 kg.) total dosage would be 1,400,000 units. This may be given in individual doses of 20,000 units of crystalline penicillin intramuscularly every three hours, missing one dose at night. Thus the amount given daily would be 140,000 units and treatment would continue for 10 days. Alternatively, 150,000 units of procaine penicillin may be given in single doses daily for 10 days. For older children dosage is similarly based on body weight and the method of administration is the same. In these cases a preparation of procaine penicillin is to be preferred to crystalline penicillin, because it requires fewer injections.

Good results have been obtained in prevention of damage to sight by *interstitial keratitis* by local applications of steroid hormones. A good routine is to instil drops of a suspension of cortisone acetate (5 mg. per ml.) into the conjunctival sac at intervals of one to four hours, depending upon the severity of the condition. Suspension of hydrocortisone (5 mg. per ml.), and cortisone ointment (15 mg. per g.) have also been used with effect. The steroids suppress the inflammatory reaction and hold it in check until spontaneous cure occurs, so that the amount of residual damage may be reduced to a minimum. Prolonged treatment is necessary, because relapse follows if treatment is stopped too soon. The frequency of instillation is gradually reduced, after the acute stage, but drops should be continued once or twice a day for many months.

OUT-PATIENT ADULT PSYCHIATRIC CLINICS*

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One of the greatest though not the most dramatic advances in psychiatry in the twentieth century has been the development of the concept of social psychiatry, the realization that cases of mental illness cannot be treated adequately in isolation from the community, and the growing awareness of the need for an integrated mental health service.

The first man to see this clearly was that very great psychiatrist Adolph Meyer, who in 1913 stated (Meyer, 1952):

"The great future of Psychiatry lies in the extension of the work beyond the hospital walls, but with the full experience that only hospitals can furnish. For this it will be necessary to look to the State hospitals not merely as Asylums but as centres of the Mental Health Work of the

Community. They must be manned by physicians trained to meet that task. To attract those who are in need of help they must establish out-patient departments to which teachers and physicians can send those who are not at their best but not in need of hospital care.

"We want to get out-patient departments and through them create a feeling in the community that our special hospitals are places for help, places from which to get the guidance of experience and directions as to prevention.

"In some communities it would be best to organize special mental organizations, using the available dispensaries as far as possible, doing emergency work and work in the form of after-care and placing of patients returned from hospitals, and serving as advisors in the decisions as to where to place patients or where to direct them.

"The ideal arrangement would be to have in connection with the dispensary at least one physician able to visit homes, assisted by Social Workers trained for investigation and for giving guidance to the patient and to the family and social unit.

"I want to urge upon you especially, that the numbers of physicians must be large enough for the hospitals to spare, once or twice a week, one or more members of the staff who will go out as dispensary physicians to community centres at distances from the hospital. My way of arranging that would be to have every ambitious hospital physician trained so that he can be sent out on certain afternoons to do extramural work in one of the centres of the district, where he will see the after-care and preventive cases together with local members of the profession who might take an interest in these conditions and work as local dispensary physicians."

Psychiatric Out-patient Clinics in Britain

Psychiatric out-patient clinics in Britain, however, were started independently of Meyer. So far as I am aware the only clinic of this kind in Britain prior to 1900 was at St. Thomas's Hospital, and, although there was a good deal of interest in the subject during the 1900s and several clinics were started, it was not until after the first world war that they became generally accepted.

Blacker (1946), writing of their history in England, states:

"The oldest and most active clinics were the spontaneous creations of voluntary hospitals where they were the product of the hospital's internal development. Attention had been drawn in the first world war to the successful treatment by psychological methods of what was then called shell shock. Neurotic illness in its various forms came to be recognized more clearly than formerly, and an optimistic view of the possibilities of treatment was prevalent. Cases of neurosis were usually referred to the neurological departments of hospitals, often by other hospital departments, but also by practitioners outside the hospital. Such patients sometimes caused embarrassment; there were few satisfactory facilities for treatment; adequate disposal was difficult, and these cases were apt to become chronic hangers-on, returning again and again for their bottle of medicine, varying little in their recital of symptoms and complaints, yet somehow sustained by a faith in the hospital. The predicament thus caused was frequently met by establishing a new Department of Psychiatry. With the establishment of such a department, facilities were created for dealing better with neurotic patients. Psychotherapy was arranged, a psychiatric social worker was often added to the staff, who furnished reports on the domestic and occupational background, and the psychologist often helped with intelligence tests. Under the Mental Treatment Act of 1930, local authorities began to make arrangements for providing out-patient treatment for psychiatric cases in their areas. The clinics thus

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