one was due to development of granulopenia while on a maintenance dose of thiouracil. One patient developed a malignant exophthalmos which necessitated evisceration of an eye.

Thiouracil Therapy v. Surgery

Thiouracil interferes with the production of thyroxine by the thyroid gland and, as shown by Himsworth *et al.* (1947), after the first three weeks there is no difference between the condition of patients so treated and those treated by thyroidectomy; and the risk of thyroidectomy is removed. With expert surgeons the mortality rate is 1% or less, and is probably nearer 4-5% when overall figures are taken. *A priori*, in cases with cardiovascular disease complicating thyrotoxicosis the figure is higher. In patients who refuse operation outright thiouracil provides an effective alternative method of treatment.

Thiouracil may also be used to assess the effect of thyroidectomy on the cardiovascular condition generally, and to bring the patient into a better state pre-operatively. This is so especially in cases in congestive heart failure. It is given for at least three weeks; it is then stopped seven to 10 days before operation, and iodine is substituted. This reduces the friability and vascularity of the gland resulting from the use of thiouracil, and substantially facilitates the surgical procedures. In patients who are sensitive to iodine, however, thiouracil may be used alone as a pre-operative measure.

Thiouracil may be used in the younger age groups in whom auricular fibrillation has occurred secondarily to the thyrotoxicosis alone. The heart in most cases will revert to normal rhythm spontaneously, and almost all of those which do not will do so when quinidine is combined with thiouracil therapy. The thyrotoxicosis may remit in time, and after adequate treatment over 12 to 18 months the thiouracil may be stopped with a fair chance of complete recovery.

Whenever thiouracil is used the risk of allergic or toxic complications arising is very real. The drug is stored in the bone-marrow in concentrations up to 16 times that in the blood, and it is this which causes the most lethal of all the ill-effects attendant on its use. Fowler (1946) has shown that of 1,573 cases collected from the literature toxic reactions of one kind or another occurred in 13.7% and serious complications in 4%; the mortality was 0.57%, and was decreasing. With the smaller doses needed when using methyl or propyl thiouracil complications are less likely to occur.

In cases with rheumatic, hypertensive, or arteriosclerotic heart disease neither thiouracil nor thyroidectomy will have any effect on the original heart condition. It will, however, improve prognosis by removing the toxic effect and the added load imposed on the already damaged heart by the thyrotoxic state.

Some cardiologists of repute have entirely abandoned the use of thiouracil as being too toxic and dangerous, and regard thyroidectomy as an equally safe method of treatment, with a more immediate and better cosmetic result.

Thiouracil should never be used when the gland is so enlarged or so placed as to cause tracheal obstruction; nor in cases in which there is the slightest suspicion of malignancy. In elderly people thyroidectomy is to be preferred. There is always a possibility of relapse on ceasing treatment or of complications, and such people will then be in a worse condition for thyroidectomy and their myocardium less well able to withstand either operation or thyrotoxicosis. In those whose temperament or economic condition will not permit them to face the long treatment with thiouracil under adequate supervision thyroidectomy is best performed at once.

Summary

An account is given of the use of methyl thiouracil in 10 patients with thyrotoxic cardiovascular disease.

The value of this treatment in auricular fibrillation, hypertension, and angina pectoris is discussed and the results are compared with those of other observers.

Treatment failed in five cases, the causes of failure being drug fever (2), malignant exophthalmos (1), granulopenia (1), and neurosis (1).

The considerations governing the choice between surgical treatment and thiouracil therapy in thyrotoxic cardiovascular disease have been reviewed.

I am much indebted to Dr. K. Shirley Smith for his encouragement and help and for permission to refer to his cases; also to Dr. H. A. Dunlop for permission to include two of his patients in this series.

REFERENCES

- Ben-Ascher, S. (1945). *J. med. Soc. N.J.*, **42**, 401.
 — (1947). *Amer. Heart J.*, **33**, 490.
 Cookson, H. (1945). *Lancet*, **2**, 485.
 — and Staines, F. H. (1947). *British Medical Journal*, **2**, 759.
 Di Palma, J. R., and McGovern, J. J. (1946). *Amer. Heart J.*, **32**, 494.
 Fowler, E. F. (1946). *Int. Abstr. Surg.*, **83**, 313.
 Grainger, A., Gregson, D. A., and Pemberton, H. S. (1945). *British Medical Journal*, **2**, 343.
 Himsworth, H. P. (1944). *Proc. R. Soc. Med.*, **37**, 693.
 — Morgan, M. E., and Trotter, W. R. (1947). *Lancet*, **1**, 241.
 McGarack, T. H., *et al.* (1945). *J. clin. Endocrinol.*, **5**, 259.
 Nussey, A. M. (1944). *British Medical Journal*, **2**, 745.
 Raab, W. (1945). *J. Amer. med. Ass.*, **128**, 249.
 Wilson, A. (1946). *Lancet*, **1**, 640.

PENICILLIN AND GONORRHOEA

AN ANALYSIS OF 150 CASES TREATED BY THE SINGLE-INJECTION METHOD

BY

C. C. R. DOWNING, M.A., M.D. Cantab.

Medical Officer in Charge of Male V.D. Clinic,
Cardiff Royal Infirmary

It is now common knowledge that penicillin injected intramuscularly affords the best means of curing gonorrhoea. Like other treatments it has, however, certain disadvantages, and an analysis of 150 cases seen at the male V.D. clinic of the Cardiff Royal Infirmary may prove of interest. The cases were treated between October, 1946, and June, 1947. All except three showed typical signs and symptoms of acute gonococcal urethritis. In each case the diagnosis was confirmed by a microscopical examination of the discharge.

Details of the Cases

Their nationality was: British, 144; Greek, 3; Maltese, 3. 101 were single, 44 married, 3 married but separated, and 2 were widowers.

Age Incidence

16-20 years	..	..	9	36-40 years	..	..	8
21-25 "	..	..	50	41-50 "	..	..	7
26-30 "	..	..	44	51-60 "	..	..	Nil
31-35 "	..	..	31	61-70 "	..	..	1

The greatest number of cases occurred during the age group 21-25, and altogether 125 out of the 150 men were from 21 to 35 years old. The youngest patient seen was a boy aged 16 years and 11 months whose case is described below, and the oldest was a widower aged 63, who gave a history of having had gonorrhoea 30 years previously. This man was first seen on Nov. 11, 1946, after infection by a prostitute. He was free from discharge and other signs of gonorrhoea in 10 days after one injection. He then ceased attending. On Jan. 2, 1947, he returned, admitting to further coitus, and was found to have become reinfected. Again a single injection of penicillin cleared

him up. He then absented himself once more, only to reappear with a further infection on April 21. Thirty-five of the men were on demobilization leave. The rest were clerks, dock labourers, farm workers, seamen, and every conceivable type of worker found in a large seaport town. The sources of infection were: by friends, 60; by prostitutes, 56; marital coitus only, 4; risks denied, 2; not stated, 28. These figures show what is already widely known—that the prostitute is not the only source of infection.

Duration of Infection before Treatment

1 week and under	50	Between 1 and 2 months	1
Between 1 and 2 weeks	55	2 " 3 "	2
2 " 3 "	26	Over 3 months	1
3 " 4 "	6	Uncertain	9

The great majority of the men came to the clinic within two weeks of becoming infected. In the "uncertain" group were a number of sailors who had had treatment with ineffectual remedies on board ship. No doctor was on board to give them proper advice.

All the patients showed typical signs and symptoms of acute gonococcal urethritis, with the exception of the following three:

1. A man aged 31, who had had gonorrhoea while on active service in India in 1944. He said he had been cured. No gonococci were found in a specimen of pus which looked typical of a gonococcal infection. He had been married two years and denied extramarital coitus. He made an uneventful recovery after one injection of penicillin.

2. A Chinese cook on board ship aged 34, who had been given an unknown dose of sulphapyridine by the ship's steward. No obvious discharge was present. He was given one injection of penicillin and a "V.15" as he was going to sea again.

3. A man aged 34, who had a primary sore as well as gonorrhoea. He was given 20 g. of sulphathiazole concurrently with arsenic and bismuth injections. After 10 days he was given an injection of penicillin, as his discharge had not gone. It did so in a day or two after the penicillin. He is still under treatment for syphilis.

There were four cases of double infection: two had a typical primary sore as well as an acute gonococcal urethritis, and two proved to be double infections but the onset of the syphilitic infection was delayed by the penicillin. Reports of these two cases follow.

Onset of Syphilis Delayed by Penicillin

Case 1.—A married man aged 24, with no previous history of venereal disease, was first seen on Sept. 30, 1946. He had run risks a week before, and had had a urethral discharge for three days. It was a typical example of gonococcal urethritis, and cleared up completely after one injection of penicillin. He reported at proper intervals of time, and on Nov. 4 his Wassermann reaction was negative. At about 12 noon on Nov. 21 I noticed a small plaque-like swelling on the body of the penis bordering on the coronal sulcus. It had a tiny central pinpoint opening. By Nov. 28 it was a typical indurated hard sore. Dark-ground illumination failed to reveal spirochaetes, but his Wassermann reaction was ++ on Dec. 9. He had typical enlarged inguinal glands on both sides. He was at once given treatment, and is still attending. This would appear to be a delayed chancre. The man first noticed a spot on his penis about Nov. 20, thus the first appearance of a specific lesion was approximately 51 days after the date of infection.

Case 2.—This patient, a married man aged 26, was first seen on Oct. 14, 1946. He had been infected a week previously and discharge had been present for three days. He had a typical gonococcal urethritis. The discharge dried up in a week after one injection of penicillin. On Dec. 2 his Wassermann reaction was negative; on Feb. 3, 1947, it was +±—, and on Feb. 10 it was ++++. The only physical signs of syphilis were very typical enlarged inguinal glands on both sides. There was no trace of any primary sore, and the man was not aware that he had seen anything like a pimple on his

penis. He is now being treated with concurrent injections of arsenic and bismuth. The first evidence of syphilis appeared approximately 112 days after the date of infection.

Reinfections.—During the period September, 1946, to June, 1947, there were 17 patients who reappeared with a fresh infection of gonorrhoea—12 admitted the fact spontaneously; the other five, when pressed and confronted with a pathological report, left little doubt in my mind concerning the source of their acute urethritis.

Type of Penicillin Used, Dosage, and Technique

Two penicillin oil-wax suspensions (ethyl oleate and arachis oil) were used, and both proved very satisfactory. They were warmed up to blood heat and well shaken before being drawn up into the syringe. The dose given was 375,000 i.u. in each case. It was injected into the upper and outer quadrant of the buttock. None of the patients complained of more than temporary pain or stiffness at the site of injection. No time was lost at work and no patient had any allergic reaction. The discharge disappeared in most cases very quickly: 41 were free of discharge in under 1 week, 66 in 1 week, 5 in 2 weeks, 3 in 3 weeks, and 5 in 4 weeks. In 30 cases no definite time was stated.

Sulphathiazole tablets were prescribed in 5 cases in which the urine showed persistent pus cells but no gonococci after the penicillin injection. Irrigation of the urethra was not resorted to. In cases with balanitis and some phimosis a solution of 1 in 10,000 potassium permanganate was used for subpreputial lavage.

A single injection was given to 134 patients, 14 required two injections, one patient three, and another four. When two injections were needed, the patients failed to attend promptly after the first one. The period varied from one to four weeks, and purulent discharge was always present. In one case the discharge had cleared up completely in a week, only to recur three weeks later. I have a suspicion that it was a case of reinfection, although this was denied. The case requiring three injections is described below (Group 3, Case 1).

Case Requiring Four Injections.—This patient had had gonorrhoea in 1940 during his Army service and had been cured. He was admitted with an acute gonococcal urethritis and penicillin was injected. When he attended the clinic three weeks after the injection the discharge was still profuse. A second injection was given. This time he stayed away for five weeks, and when he reappeared the discharge was as free as ever. A third injection was given. Again he absented himself, this time for 10 weeks. Then on examination the discharge was still plentiful, and a fourth injection was given. Since then he has not attended.

End Results

Group 1.—This group consisted of 62 men who were discharged cured. No patient was under treatment and surveillance for less than three months. The average period of treatment for the whole group was about four months per patient. Every one of them was free from all signs and symptoms of gonorrhoea and, except in one case in which a double infection was present, the Wassermann reaction was negative. Tests of cure adopted conform to those advised by the Ministry of Health.

Group 2.—This group consisted of 56 men who had attended the clinic for less than four weeks and had then ceased attending. Twenty-five came only once, so it is impossible to say whether they were properly cured. It is not unreasonable to assume that at least their discharges were dried up. All the remainder were dry and free from signs and symptoms.

Group 3.—In this group of 30 patients who ceased attending after one to seven months only the following three showed any signs of infection.

Case 1.—The patient, aged 23, was infected two weeks before. He attended the clinic on four occasions between Dec. 23, 1946, and March 3, 1947. On admission he was found to have a typical gonococcal urethritis and penicillin was given. He absented himself for a month, and when he returned he was found to be still discharging freely. A second injection of penicillin was given, and he then disappeared for a further month, only to return again with a right-sided epididymitis and orchitis. A third injection of penicillin was given, followed by a course of sulphathiazole. When he turned up a fortnight later his discharge had gone and his testicle was less swollen though still tender. Since that time he has ceased attending altogether.

Case 2.—A youth aged 16 years 11 months had a typical gonococcal urethritis associated with phimosis and balanitis. He did not attend until two weeks after his first injection, and was then showing much purulent discharge. The second injection of penicillin cleared up the gonococcal inflammation of the urethra, but he still had a mild degree of balanitis. This showed no evidence of being gonococcal. He ceased attending after 11 weeks' treatment.

Case 3.—A man aged 31, who had served in the Army in the East, attended for 10 weeks, and when he ceased attending had been free from discharge for a long time. His urine, however, still showed some pus cells. His general health was poor. He had been a prisoner of war in Japanese hands and had had pellagra, beriberi, and dysentery.

Group 4.—The following two cases are still attending at the clinic.

Case 1.—A man aged 21 had typical gonococcal urethritis. The discharge and all other signs and symptoms cleared up in 24 hours. His gonococcal flocculation reaction, however, was positive.

Case 2.—A man aged 26 had had gonorrhoea in the early part of 1946. He had a typical gonorrhoeal discharge, which cleared up in a week after an injection of penicillin. His urine still shows some pus cells.

Comments

To analyse case records at a V.D. clinic is difficult and unsatisfactory. In the first place I feel that the patients' statements are often open to doubt. In the second place—and this is the main trouble—such a large percentage of patients cease attending before their surveillance is complete. However, from the facts and figures that emerge from this analysis I can say that penicillin given intramuscularly in an oil-wax suspension is the treatment of choice for gonorrhoea to-day. Its advantages are obvious. Easy to give, it causes no appreciable pain or discomfort. The patient is asked to spend the minimum amount of time attending the doctor and loses no time at his work. His discharge is quickly dried up, and if he co-operates he is certain of a quick cure. It is to be specially noted that complications such as orchitis, epididymitis, and vesiculitis are now very rarely met with.

As I said at the start, there are a few disadvantages: (1) It is almost too efficient. The patient gets well so quickly and so easily that some are tempted to run further risks. No longer is the cure worse than the disease. (2) As is already known, penicillin can mask and delay the onset of primary syphilis. (3) Because of this the necessity for repeating the Wassermann test over a period of months is unfortunate. So many patients fail to realize the importance of having more than one blood test.

I would like to express my thanks to my colleagues, Dr. H. Sheasby and Dr. J. Rebeiro, for their help in preparing this paper, and also to acknowledge much assistance given me by Mr. R. D. Vanstone, the clerk to the clinic.

Medical Memoranda

Penicillin, Beeswax, and Allergy

The following two cases of allergy occurring in general practice are described to illustrate the severity of reaction to penicillin and the possibility that some component of the beeswax-oil suspension, other than the penicillin, was the exciting factor.

CASE 1

A man aged 58 complained of persistent boils, and as no previous treatment had allayed the condition it was decided to give a course of penicillin. Injections of 250,000 units in distilled water were given twice daily on June 16 and 17, 1947, and one on the 18th. The patient then defaulted. However, the furunculosis improved considerably.

On June 25, the ninth day after the first injection of penicillin, I was asked to see the patient. He stated that while driving home that day he had felt itching, first of the left foot where his boot-laces pressed, and then of the right foot in the same situation. He felt very drowsy and could hardly keep awake to drive the car home. Within half an hour he began to itch all over. He also complained of severe pain behind the sternum and of severe indigestion. An examination showed the body to be covered with large urticarial weals about the size of the palm of the hand. The feet, hands, and face were swollen. This condition persisted for seven days in spite of treatment with "benadryl," 50 mg. thrice daily, later increased to 100 with adrenaline, 10 min. (0.6 ml.), twice daily. After seven days the condition gradually subsided, but during this time the itching was intense and the patient had only very fitful sleep with the aid of morphine.

CASE 2

The patient, aged 33, was the wife of an ardent bee-keeper, and she helped with the manipulation of the bees from time to time. At first the patient had little reaction to stings until the summer of 1941, when she was stung on the lip. This became very badly swollen. In the summer of 1944 she was stung on the leg. The leg became very swollen, and she stated that the sites of previous stings also became swollen. In February, 1947, she had a small carbuncle on the face, which was treated with penicillin, 150,000 units, in distilled water, given eight-hourly for five days. This cleared up the carbuncle. On Oct. 25 a carbuncle began to develop on the chin, and next day injections of 250,000 units of penicillin in wax-oil suspension were started. These were given twice daily into each buttock alternately at the "site of election." The injections were continued until the morning of Oct. 29, six injections in all being given. On Nov. 2, the eighth day after the first injection of penicillin, the patient began to feel the site of the old bee-sting on the leg itching and a weal developed. Within half an hour the sites of injection of penicillin on both buttocks became itchy and red. For a week the sites of the injections were covered with a ring of urticaria and there was considerable swelling of the underlying tissues. During the same period the site of the old bee-sting on the leg was irritated and became swollen from time to time. The patient also averred that the taking of honey led to an increase in the local symptoms of allergy shortly thereafter. All symptoms were controlled to some extent by benadryl.

COMMENTARY

Case 1 is described to illustrate the severity of the allergic reaction to penicillin. The patient avers that he had never before had penicillin in any form whatsoever.

The second case is the more interesting in that it would seem more likely that the local allergic reactions were due to some component of the beeswax suspension. This is deduced from the facts that the bee-sting on the leg was re-activated. The other interesting factor is that the patient was quite definite that the ingestion of section-honey caused an increased irritation of both the site of the bee-sting and the sites of penicillin injection. It may be argued that the sting of a bee has no relation to beeswax. The firm which produced the beeswax was contacted. They stated that the beeswax used in the suspension is the natural product, but that in their opinion it is impossible for formic acid or other component of a bee-sting to be present in the wax. On the other hand, a well-known naturalist, who is also a bee-keeper, is of the opinion that it is quite possible for formic acid to be present in nectar and that natural beeswax could quite easily be polluted with nectar.

J. WATSON, M.D.