Rabbits injected intravenously with 20 ml. of a solution containing 60,000 units of sodium penicillin did not show any immediate or delayed reactions. Intracutaneous injections into the abdominal wall of rabbits and guinea-pigs did not cause any local inflammatory reactions, and the cutaneous swelling arising from the injection rapidly disappeared.

Morgan *et al.* (1944) when administering penicillin intravenously by the continuous-drip method noticed the development of thrombosis or thrombophlebitis in a large proportion of their cases. In view of these experiences intravenous application was not tried; the intramuscular route was employed exclusively. Usually 4 to 6 ml. of the penicillin solution (about 12,000 to 18,000 units) was injected every three hours. The continuous-intramuscular-drip method was also used in suitable cases, giving 80,000 to 100,000 units in 24 hours. Up to the present more than 40 patients suffering from various diseases due to penicillin-sensitive organisms were successfully treated in this way. Details of the clinical results will be published later. The injections of penicillin did not cause any immediate or delayed painful sensations, and no irritative or inflammatory reactions were observed.

Penicillin was also repeatedly injected intrathecally in two cases of pneumococcal meningitis and one case of streptococcal meningitis. The injections were therapeutically effective, were well tolerated, and did not cause any untoward symptoms.

Penicillin for Local Treatment

Crude culture filtrates containing as little as 2 to 10 units of penicillin per ml. have been used successfully by Pulvertaft (1943), Alston (1944), and Hobson (1944) for treatment of many localized infections. The clinical use of crude culture filtrates appears inadvisable and potentially dangerous for two reasons. First, such filtrates always contain large amounts of protein, which is also produced by the mould and secreted into the culture fluid. The repeated application of such fluids to large raw surfaces is likely to lead to sensitization—a point also made by Raper and Coghill (1943) in connexion with "home-made" penicillin. Secondly, culture filtrates from media which do not contain yeast extract or corn-steep liquor may contain notatin (Kocholaty, 1942; Coulthard *et al.*, 1942; Roberts *et al.*, 1943), a potent antibacterial substance of extreme toxicity.

Clutterbuck *et al.* (1932) found that by adjusting the fluid to pH 3.6 most of the protein and a considerable proportion of pigment could be flocculated and filtered off from the culture fluid without loss of penicillin. This method has been successfully employed for this purpose, and incidentally the gummy substances formed from the corn-steep liquor during autoclaving were precipitated out at the same time. Kocholaty (1943) found that notatin is not formed in cultures of *P. notatum* which contain corn-steep liquor.

The protein-free penicillin solutions were not toxic. Two rabbits, weighing about 1,600 g. each, were injected with 50 ml. intravenously in 10-ml. portions in the course of two days. The animals did not show any immediate or delayed reactions of any kind. The protein-free penicillin solutions have been used successfully in the treatment of extensive infected burns, wounds, abscesses, ulcers, discharging sinuses, throat and ear infections, empyemata, and gonococcal vulvovaginitis, and in selected cases of osteomyelitis and compound fractures. The penicillin solutions proved non-irritating and did not cause untoward symptoms in any case. Manifestations of allergy were not observed even when application of penicillin was continued for a month or longer.

Summary

A simple and efficient method of preparing purified penicillin for systemic treatment is described.

Intramuscular injections of penicillin solutions obtained with this method were therapeutically effective, were painless, and did not cause untoward effects of any kind.

This work has been done under the direction of Prof. P. L. Sutherland, to whom I am indebted for many valuable suggestions and for help and advice throughout the course of the investigation. Thanks are due to Sir Alexander Fleming for a subculture of the mould; to Dr. J. W. Trevan, of the Wellcome Research Laboratories, for a sample of standardized penicillin; and to Dr. D. Engel, medical superintendent of Staincliffe County Hospital, Dewsbury,

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THYROID HYPERPLASIA AFTER PROLONGED EXCESSIVE DOSAGE WITH THIOURACIL

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During the past year we have treated with thiouracil a total of 31 patients suffering from thyrotoxicosis. The results obtained are very similar to those noted by other workers. They are on the whole most encouraging, and comparable to those produced by successful thyroidectomy. Only one of the patients developed serious toxic reactions to the drug, consisting of leucopenia and signs of acute sensitivity. Another appeared relatively drug-resistant, and, in spite of prolonged treatment, thyrotoxic symptoms and signs persisted. With the exception of the case noted below no significant changes in the size of the goitres occurred as the result of treatment, though they usually became softer, and a transient slight increase in size was often noted at the menstrual period. It seems to be the general experience of other workers that thiouracil in therapeutic doses does not as a rule affect the size of the goitre significantly, but Himsworth (1944) has reported three cases in which the goitre increased considerably in size as the result of treatment with thiouracil—an effect which he attributes to overdosage.

There seems to be general agreement that the optimum dosage during the initial period of treatment should be 0.6 g. daily. This dosage should be kept up for from three to four weeks, at which time a fall in the basal metabolic rate has usually become significant. No increased effect is obtained by doubling the dose, as any additional quantity appears to be immediately excreted in the urine. There is as yet no definite consensus of opinion as to the dose required for maintenance treatment. There can be little doubt that 0.2 g. daily is adequate. We have never noticed any evidence of "escape" from the control of the drug when a reduction in the dosage has been made from 0.6 to 0.2 g. daily. There is no definite evidence, however, that 0.2 g. is the minimum dose required. We have latterly treated a number of patients with a maintenance dose of 0.1 g. daily, and it is our impression that this dose is quite sufficient. One case, through a misunderstanding, received an excessively large maintenance dose for a period of five and a half months.

Case Record

A female patient, aged 33, suffering from classical thyrotoxicosis, had experienced her first symptoms one year before admission to hospital. A small primary goitre was present. She was treated

with 0.6 g. of thiouracil daily for 20 days, and was then given a maintenance dose of 0.2 g. daily for a week. She was discharged from hospital feeling very well. Her weight had increased by half a stone in a month, and her B.M.R. had fallen from +55 to +8. A mild tachycardia was the only residual sign of her thyrotoxicosis. She was told to continue to take 0.2 g. of thiouracil daily, but owing to a misunderstanding she actually took 0.4 g. As her home was in the far North of Scotland it was impossible for her to report to us regularly, and she was seen once a month by her own doctor. The first three reports from him were most satisfactory, but the fourth stated that she was not quite so well, though no specific symptom was noted beyond some lack of energy. By the fifth month this symptom had become pronounced, and a swelling of the neck was reported. The patient was immediately sent for, and on readmission, five and a half months after her discharge, was found to have a very large soft goitre. This was associated with a mild degree of myxoedema. Her weight had increased by one stone since discharge from hospital, her B.M.R. had fallen to -20, and her blood cholesterol had risen from 220 to 266 mg. per 100 c.cm. Her white blood count of 5,600 showed no significant alteration. Thiouracil was immediately stopped, and in two weeks' time she felt considerably better, her B.M.R. having risen from -20 to -3. No change had occurred, however, in the size or consistency of the goitre, and thyroidectomy was undertaken, principally for cosmetic reasons. At operation the thyroid was obviously enlarged, and was firm though not hard. The cut surface was typical of the hypertrophy associated with a primary toxic goitre which had not been treated by iodine. A section of the gland is shown in the accompanying photomicrograph. It can be seen that

there is extreme parenchymatous hyperplasia and an almost complete absence of colloid, the picture being similar to that produced by Mackenzie in animals treated with goitrogenic substances. After the operation the patient made an uninterrupted recovery, and was discharged home feeling well.

Comment

It is thought worth while to record this case as providing another instance to those noted by Himsworth of thiouracil causing a great enlargement of the goitre in a previously thyrotoxic patient. It gives practical proof of the theoretical assumption that if the pituitary is stimulated to produce excess thyrotrophic hormone by overdosage with thiouracil an increase in the size of the goitre will occur similar to the hyperplasia of the thyroid produced in experimental animals by thiourea and its derivatives, and by sulphaguanidine. A rapid and significant enlargement of the goitre in a patient under treatment with thiouracil may thus be evidence of overdosage.

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Medical Memoranda

A Method of Administering Systemic Penicillin

Owing to the shortage of rubber tubing systemic penicillin is being administered by 3-hourly intramuscular injections, and it has been found that a good many patients complain of the pain and discomfort, and "come to dread the needle." The following method has been adopted and found satisfactory.

Pressure-tubing, outside diameter $\frac{1}{4}$ in., length $\frac{3}{4}$ in., is worked over the intramuscular needle and a glass cap applied to seal off (Fig. 1). The intramuscular needle is fixed in a suitable site with elastoplast strapping. Another strip of elastoplast is applied over the first, the projecting rubber tubing with glass cap is wrapped in sterile gauze, and the elastoplast is fixed in place. 15,000 units of penicillin in 1.5 c.cm. are drawn up into an all-glass syringe, and the needle removed. The nozzle of the syringe is inserted into the rubber tubing, which is steadied by forceps, injection given, and a sterile glass cap applied. Sterile gauze is wrapped round and elastoplast is reapplied (Fig. 2). The intramuscular needle can remain in place for four days without changing to a new site.

FIG. 1

FIG. 2

I wish to thank Mrs. W. K. Somerton for the illustrations, Mr. Garner of the pathological department for the suggestion of the glass cap, and Dr. Shepherd, the medical superintendent, for permission to publish.

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A Case of Meningococcal Meningitis Treated with Penicillin

Since little is at present known about the effect of penicillin in meningococcal infections this case is considered worth recording.

CASE RECORD

A male child aged 18 months was admitted with a four-days history of repeated vomiting after all feeds. Previously he had been quite well. On the day before admission his mother had noticed that he felt hot and had a rash on his chest. There was no urinary retention and the bowels were normal. He had had gastro-enteritis at 2 months and at 6 months of age. The gain in weight had been good. On examination the child looked ill, being pale and lethargic. The anterior fontanelle was closed. There was slight diminution of skin elasticity. Some fading petechiae could just be seen on the thorax. The posterior cervical muscles were rigid, opisthotonos was