secretory activity shows the influence of progesterone at this time. The mass of chorionic villi is proof of ovulation, though in the preliminary trimming of the block the ovum was lost.

Those cases of irregular and excessive uterine bleeding in which no local abnormality is detected are now regarded as determined by ovarian dysfunction, and are placed together under the term "metropathia." The histological picture in the endometrial glands of a large group of such cases is one of prolonged oestrogen activity and has been interpreted as evidence either of an excessive oestrogen phase or of an anovulatory cycle. In cases where examination of the pelvic organs has been made a cystic ovary has usually been found, and the underlying pathology has been considered to represent the repeated onset of a cystic degenerative process in the ripening follicle, before ovulation. Increasing attention has been paid to ovarian dysfunction of this type as a cause of sterility (Mazer and Zisermann, 1932; Mazer, Israel, and Kacher, 1937; Jeffcoate, 1935; Mason, Black, and Gustavson, 1938).

The present case shows that ovulation may occur in clinically and pathologically typical metropathia haemorrhagica, while the histology demonstrates a second possible cause for sterility in this condition. It shows that in addition to infrequency or total absence of ovulation, with its relative or absolute reduction in the chances of fertilization, nidation may be incomplete, and this inability of the fertilized ovum to embed itself may be due to the partially or completely unprepared state of the endometrium. In the later phases of a normal cycle pregestational changes take place both in the glands and in the stroma of the endometrium; but in this case stromal change was fairly well developed while glandular response was scarcely apparent. The importance of adequate concentrations of corpus luteum hormone for implantation of the ovum has been emphasized by several authors. Browne *et al.* (1939) state: "A short corpus luteum phase has been observed in some patients with sterility in whom no other cause for infertility has been detected." Allen and Corner (1929) first demonstrated the necessity for progesterone in the implantation of early embryos, and their observations have often been confirmed. The present specimen shows that in habitual abortion where the probable cause is inadequate progesterone production the administration of that hormone during the latter half of the cycle is probably soundly based on the pathogenesis of the condition. Progesterone is commonly stated to produce the pregestational changes in the endometrium, and these changes affect both the uterine glands and the stroma. The stromal reaction is marked in this case, but the glandular one lags far behind. In his monograph Hamblen (1939) calls attention to the evidence that "mixed" endometria probably represent partial inability of the endometrium to respond to the pregestational principle, but evidence is presented here that the response of the endometrium to progesterone can be unequally distributed as between the glandular elements and the stroma, as otherwise the two reactions must be assumed to be separately conditioned, and of this there is as yet no evidence.

Summary

A case is described of metropathia haemorrhagica in which the presence of chorionic villi shows that ovulation had occurred.

The suggestion is made that sterility in this condition may be due not to the absence of ovulation but to inability of the fertilized ovum to embed itself in an endometrium wholly or partially unprepared for its reception.

I am most grateful to Mr. H. A. Hamilton for allowing me to use his clinical findings, and to the medical superintendent, Farnborough County Hospital, for permission to publish this case.

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Before the war Mrs. R. G. Edwards raised a fund to provide the best means of combating primary tuberculosis in children by early treatment. It has been decided to devote this fund to the construction at Papworth of a home to be known as the Edith Edwards Children's Home.

TREATMENT OF SULPHONAMIDE-RESISTANT GONORRHOEA BY PENICILLIN

BY

ROBERT LEES, M.D., F.R.C.P.Ed.

This communication is based on observation of a large series of cases treated in the C.M.F. and a smaller number treated in the U.K. It has already been recorded by Campbell (1944) and Bell (1945) that a high proportion of cases of gonorrhoea in our Forces in Sicily and Italy proved resistant to routine methods of treatment with sulphonamides. On further investigation it was found that a considerable proportion of gonorrhoea cases were rendered "sulphonamide-resistant" by use of a dosage scheme which employed 4 or 5 g. of sulphapyridine or sulphathiazole a day for two days. Other cases were rendered sulphonamide-resistant by self-treatment, or by irregular dosage, or by taking a small number of tablets to obscure the diagnosis and thus evade the penalties of venereal infection. Prolonged treatment with high dosage of sulphathiazole or sulphadiazine (6 to 8 g. daily for 10 days), even when reinforced with non-specific "shock" and fever therapy with intravenous injections of typhoid vaccine, failed to produce more than 70% of cures. This must be ascribed to a high proportion of sulphonamide-resistant strains of gonococcus in the population, but no evidence could be found to support the popular theory that the Italian prostitutes were habitually taking small doses of sulphonamides which, although insufficient to cure gonorrhoea, were enough to minimize the signs and symptoms of the disease.

The high incidence of V.D. in the Allied Forces in C.M.F. with the low percentage of cure in gonorrhoea led to the accumulation in hospital of very large numbers of chronic and resistant cases of gonorrhoea, and on arrival in Italy in March, 1944, I found there were over 2,000 such cases. Hospital accommodation was overtaxed; the men were urgently needed for the battles of Cassino and Anzio; accommodation had to be provided for battle casualties.

A series of 1,737 cases of sulphonamide-resistant and chronic and complicated cases of gonorrhoea were treated with penicillin. Many had been treated for weeks or even months without cure, and several had genito-urinary complications of gonorrhoea such as prostatic-vesiculitis and epididymitis. No case of metastatic complication of gonorrhoea was included in this series. The worst cases were chosen. The treatment was done with such amounts of penicillin as were available after the needs of war wounds and urgent medical and surgical cases had been met. The diversity of the dosage scheme is to be explained by the shortage of penicillin and the desire to obtain the maximum number of cures with the minimum consumption of the drug. Supplies were available irregularly at that time. It was also urgently necessary to return key-men to full duties as quickly as possible. These factors governed and modified this therapeutic experiment.

Dosage.—Penicillin was given in every case as 10,000 units dissolved in sterile distilled water or saline and injected intramuscularly at intervals of three hours. No pain or abscess formation resulted from the injections.

Results

The results are analysed according to dosage:

Dose	No. of Cases	% Cured
100,000 units	344	98.0
60,000 "	1,383	94.3
50,000 "	100	92.0
30,000 "	50	80.0
Total treated by various doses . .	1,737	93.9

Results of re-treatment with penicillin of the cases (6.1%) noted above as failures are available in 73 cases, and all but one were cured. Such cases were re-treated as soon as possible by penicillin in the same individual dose (10,000 units at three-

hour intervals), but the duration of treatment was prolonged until a larger total had been given, as follows:

120,000 units	..	..	..	..	..	..	..	14 cases
150,000	"	..	..	..	..	..	..	23 "
200,000	"	..	..	..	..	..	..	34 "
240,000	"	..	..	..	..	..	..	2 "

Subsequent experience with subjects not in this series has shown that all cases of gonorrhoea are not cured by re-treatment even with 240,000 units given as 15,000 units or 20,000 units at intervals of three hours. In all such resistant cases it was our custom to cultivate the organism, identify it, and test its resistance to penicillin *in vitro*. In no case was a penicillin-resistant strain of gonococcus found. Such cases are probably explained by persistence of gonococci in a closed focus of infection such as a prostatic abscess or a sealed-off infection of a seminal vesicle.

Notes on a number of patients treated with 50,000 units indicate that this amount is below the optimum dosage. For example, Case 207 relapsed with acute epididymitis twelve days after penicillin treatment, and Case 200 had gonococci in the para-urethral ducts on completion of the five injections of penicillin. Cases 295, 296, 298, and 299 showed gonococci on the third, fourth, ninth, and fifth day, respectively, after penicillin treatment. These cases were all cured ultimately with local treatment and sulphonamides.

Disappearance of sulphonamide resistance seemed to occur in several instances after unsuccessful penicillin treatment. Several patients who had been treated (perhaps badly) with sulphonamides and had acquired a chronic "sulphonamide-resistant" state were not cured by penicillin in the doses employed. But subsequent re-treatment with sulphathiazole produced a rapid and permanent cure. This procedure is not advised in preference to re-treatment with larger doses of penicillin, and success was by no means invariable.

Synergic Effect of Penicillin and Sulphonamides.—A small series of cases were treated with sulphathiazole, 5 g. a day, and 30,000 units of penicillin on the fifth day. The results were not good, and we could not confirm the published reports that there was a marked synergic effect and that 100% cures could thus be achieved quickly. It was considered that such schemes of treatment were unlikely to have much future value, and the experiment was not pursued.

Speed of Action.—The speed of action of penicillin is of some importance in deciding the precautions necessary, such as isolation of patients and sterilization of fomites. In this series it was the practice to take a urethral smear before the fourth injection was given—that is, after the patient had received 30,000 units and nine hours had elapsed since penicillin treatment began. This was also done after 60,000 units and after 100,000 units had been given. Typical results are those recorded (by Major Priest) in one series of 186 cases: after 30,000 units, 16 gonococcus-positive; after 100,000 units, 3 gonococcus-positive. Two of these cases showed gonococci in slides for 12 to 24 hours after treatment, but the organism disappeared without further treatment. The gonococci were swollen and atypical in appearance and did not grow in cultures.

Effect of Higher Dosages of Penicillin.—A smaller series were treated at a later date with 20,000 units of penicillin every three hours until 100,000 units were given. In a series of 204 cases cure was achieved in 97%. This scheme of five doses is much more convenient than ten doses, for treatment can be completed within twelve hours. Ambulatory patients spent one night in hospital and returned to work next morning, injections being given at 5 p.m., 8 p.m., 11 p.m., 2 a.m., and 5 a.m.

The results of treatment with four doses, at four-hour intervals, of 25,000 units were less satisfactory. In a series of 200 cases the rate of cure was 92%.

Gonococcal Ophthalmia.—One case of ophthalmia was observed in which the patient had infected his eye, and as the organ was completely sulphonamide-resistant it was feared that the eye infection might be intractable. Treatment was given by 100,000 units of penicillin, administered as ten doses of 10,000 units at three-hour intervals. In addition drops of penicillin solution in a strength of 1,000 units per ml. were instilled into the conjunctiva after preliminary washing with

sterile normal saline. The patient made a very rapid and complete recovery.

Gonococcal Prostatitis and Epididymitis.—Many cases of subacute prostatitis and of acute epididymitis were treated according to the dosage scheme of 100,000 units in ten injections. The results were very satisfactory; resolution of the inflamed organ took place rapidly, and was usually complete within ten days without additional treatment.

Observation and Test of Cure.—Cases were followed for three months. Urethral and prostatic smears were taken frequently during the first two weeks, but thereafter observation was, of necessity, at longer intervals and irregular. Before acceptance of cure the patient had anterior urethroscopy, and often a large curved sound was passed in addition. Reinfection was probable in several cases, but every case that had a return of gonococci has been classified as a failure. Cultural methods could not be employed as a test of cure.

Summary

A series of 1,737 cases of sulphonamide-resistant gonorrhoea were treated with penicillin and 93.9% were cured.

The highest percentage of cures in this series was obtained with 100,000 units given as ten intramuscular injections of 10,000 units at intervals of three hours.

Equally good results were obtained in a small additional series of 204 cases with 100,000 units given as five injections of 20,000 units at three-hour intervals.

Less satisfactory results were obtained in a third series of 100 cases treated with four injections of 25,000 units at intervals of four hours.

The lower limit of effective dosage (94.3% cure) was obtained with 60,000 units given as six doses of 10,000 units at three-hour intervals.

Treatment with 50,000 units and 30,000 units produced poor results.

Treatment with sulphathiazole followed by 30,000 units of penicillin did not give satisfactory results in a small series of cases, and the experiment was not pursued.

Seventy-five cases which had failed with primary treatment with penicillin were re-treated with higher dosage of penicillin, and 74 were cured. Subsequent results with cases not in this series suggest that this observation is unduly optimistic. Cases have been observed of persistence of gonococci after 240,000 units given as 15,000 units at three-hour intervals.

Genito-urinary complications of gonorrhoea such as epididymitis responded rapidly to and were completely cured by 100,000 units of penicillin.

This research was made possible only by team work, and a large number of V.D. specialists in C.M.F. co-operated—too many to mention by name. These officers were enthusiastic workers and spared no pains to ensure that the work was done well and records were kept. Lieut.-Col. J. Jeffries and Lieut.-Col. S. H. Bentley and Major Scott Thomson of No. 1 Penicillin Control Team gave invaluable advice and assistance, and organized distribution of the drug. Much of the work was done in tented hospitals with very insufficient assistance, and the R.A.M.C. orderlies who gave the injections deserve the highest praise, for no mishap occurred. I am also indebted to Major-Gen. W. C. Hartgill for his support and for permission to publish these observations.

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Lord Samuel, president of the British Institute of Philosophy, the Provost of Oriel (chairman), and the Master of Balliol (deputy chairman) have issued an appeal for support for the Institute, which came of age on April 6. Founded under the late Lord Balfour, its council has been throughout composed of leading representatives not only of philosophy but also of science, of politics, and of industry and commerce. For twenty-one years the Institute has been active in promoting the purposes for which it was founded—to serve as a link between philosophers and the everyday world, and to spread such general understanding as can be reached of the universe and of man's place in it. There have been continuous courses of lectures and popular addresses, and a journal—*Philosophy*—is issued once a quarter. The annual subscription is one guinea, which includes receipt of the journal, and there is no entrance fee. Further information and forms of membership may be had from the Director of Studies, British Institute of Philosophy, University Hall, 14, Gordon Square, London, W.C.1.