"PENICILLIN IN ACUTE GONORRHOEA".

A Thesis submitted for the Degree of
Doctor of Medicine of Edinburgh University
by
E. M. Donaldson,
M.B., Ch.B., D.P.H.

Edinburgh
September 1946.
ACKNOWLEDGMENTS.

To Surgeon Captain T. R. Lloyd Jones, Royal Navy, I owe the opportunity of treating the cases described. Without his generous provision of clinical and laboratory facilities this thesis could not have been written; for his unstinted advice and encouragement I am deeply grateful.

Sick Berth Chief Petty Officer T. Jones, Royal Navy, was unfailing with his assistance in the laboratory and in the onerous task of checking case records and other data; his cheerful and willing co-operation are gratefully acknowledged.
I. INTRODUCTION.

The application of penicillin to the treatment of disease ranks with the improved control of malaria as one of the greatest advances in medicine consolidated during the war years.

Gonorrhoea is but one of many infections amenable to the new antibiotics. Therapy of this disease is of special interest not only on account of its present wide prevalence but because of all human afflictions it is perhaps that most responsive to penicillin treatment.

With the wider aspects of epidemiological control I am not here concerned; fascinating though current polemics regarding the complete eradication of the disease from civilised communities may be, such a possibility has yet to enter the realm of practical politics.

This thesis is limited to a consideration of the results reported by others and obtained by myself in male cases with the sodium salt of penicillin. For the sake of clarity in exposition it is divided into four main parts. In the first a brief account is given of the properties and mode of action of penicillin upon which treatment is based; the second describes the results obtained by others. The third part is an account of my own experiences, clinical and laboratory, of treatment with single aqueous injections. Finally a discussion and summary are presented.
II.

The elucidation of the chemical structures of the various penicillins now achieved will render further evaluation necessary as purer preparations become available. Nevertheless it is submitted that such a survey as is here attempted is of interest at the present time.
"The clinical exploitation of the drug now being so actively pursued, and the experimental findings of the laboratory, are so intimately linked together that it is no picturesque overstatement, but a matter of fact and experience, to say that success in the one is dependent on a lively appreciation of the facts revealed by the other." Thus wrote Florey and Jennings in 1944; their words are no less true today.

The development of Penicillin following Fleming's original discovery of its properties in 1929 is a scientific and medical romance of which all concerned may well be proud. That it should emerge as a practical therapeutic agent in the time of global war is a sad reflection of our time. It is perhaps not too much to say that but for the timely co-operation born of necessity - of men of science, of industry and of war, the inestimable benefits of the drug would have been available only to the few for many years to come.

The series of observations, experiments, and early clinical trials on which modern penicillin therapy is founded have now been frequently described. I do not intend to recapitulate the work done by individuals and by teams. As an introduction to the penicillin treatment of gonorrhoea, it is sufficient to state briefly what is known of those properties of
2. the drug relevant to this disease. For the sake of clarity the sodium salt alone will be considered.

Definition:– The British Pharmacopoeia defines Penicillin as the anti-infective acid produced when Penicillium Notatum or related organisms are grown under appropriate conditions on or in a suitable culture medium, converted into the sodium or calcium salt.

Standards:– Penicillin (B.P.) is available as the sodium or calcium salt. Tests for toxicity, pyrogens and sterility are required. Manufacturers must declare the total number of units in the container and the minimum number of units per milligram of penicillin.

Potency must be assayed by biological methods based on tests which measure the degree of bacteriostasis produced by the sample under assay.

The "Oxford Unit" was defined by its originators as that amount of penicillin which, when dissolved in 1 c.c. of water, gives the same inhibition as the original standard. This implies the same inhibition of growth against a known inoculum of the test organism. Later pure Penicillin was obtained and an international conference established the Oxford Unit as an International Unit containing 0.0006 milligram of pure crystalline sodium salt of Penicillin II, which is maintained as a standard at the National Institute of Medical Research. Thus 5,000 units of Penicillin II weighs 3 milligrams.
The Therapeutic Substances Act forbids the use of preparations containing less than 300 units per mg; The Pharmacopoeia requires preparations for Parenteral injections to contain not less than 900 units per mg.

As sold by manufacturers today, the best samples of sodium penicillin have a potency up to 1,400 units per mg. It is apparent that potency is an expression of the degree of purity of a sample.

**Description:** Pure sodium penicillin is available as a white powder having a potency of 1,666 units per mg.

The sodium salt is extremely hygroscopic and must be stored in sealed containers at a temperature not above 15°C. Reports on the stability of the dry powder vary according to the degree of purity of the sample. Thus the pure sodium salt remains in the dry condition if heated to 100°C for 2 hours; samples of the salt as supplied commercially lose considerable potency at 56°C. (Randall, Welch and Hunter 1945).

**Chemistry:** British and American workers have collaborated during the war in intensive research on what are now recognised to be the penicillins. The results of this research were released for publication a year ago. The chemical structures of the penicillins were then completely elucidated.
The general structural formula is the B-lactam formula

\[
\begin{align*}
\text{CH}_3 & \quad \text{---} \quad \text{CH. COOH} \\
\text{CH}_3 & \quad \text{S} \\
\text{CH} & \quad \text{N} \\
\text{CH} & \quad \text{CO} \\
\text{CH} & \quad \text{NH. CO. R}
\end{align*}
\]

R varies in the different penicillins, which have been designated I., II., III., and IV. in England; F, G, X, and K in the U.S.A.

R is as follows in the 4 penicillins.

I. (F) -- (2-pentenyl)CH\(_3\) CH\(_2\) CH = CH. CH\(_2\)
II. (G) (benzyl) C\(_6\) H\(_5\) CH\(_2\).
III. (X) (p-hydroxybenzyl) CH. C\(_6\) H\(_4\). CH\(_2\).
IV. (K) (n-heptyl) CH\(_3\) CH\(_2\) CH\(_2\) CH\(_2\) CH\(_2\) CH\(_2\) CH\(_2\)

Commercial penicillin is a mixture of penicillin I., II., and III. (F, G, X). The most widely-used production method is the growing of P. Notatum in submerged cultures, which produces Penicillin II. (G) in largest amounts.

Penicillin K (IV) is produced by a different strain of P. Notatum from that currently employed in large-scale manufacture.
PROPERTIES:- A knowledge of these is essential to the proper handling and administration of the drug. They may be summarised:-

Stability. Its stability in the dry state has already been discussed. In solution it loses potency at room temperature; solutions should therefore be prepared just before injection, or kept in the refrigerator for not more than 24 hours.

Destruction occurs rapidly in the presence of acids or alkalis, heavy metals and their salts, alcohols, oxidising agents and penicillinase - an enzyme produced by many common bacteria.

The above properties indicate the precautions essential in preparing and administering the drug, which in essence are strict asepsis at all stages to protect from penicillinase - producing contaminants, and the avoidance of antiseptics containing heavy metals or their salts, or oxidising agents.

Selective Antibacterial Power. The two properties which distinguish penicillin from all other chemotherapeutic agents are its lack of toxicity to leucocytes and human tissues generally, and its remarkable antibacterial power. The latter are highly selective, acting only against certain organisms, and are apparent in extremely low dilutions of the drug. This selective action of penicillin was stressed by Fleming in his original paper; in fact it was in virtue of this property that he suggested its use for the isolation of non-sensitive from sensitive bacteria.
The division of organisms into two categories - sensitive and non-sensitive - is by no means absolute, as different strains of the same species may show wide variation in their degree of sensitivity to the drug. This must always be taken into account even when treatment of an infection due to a known sensitive species of organism is under consideration; much higher concentrations of penicillin may be required to secure adequate antibacterial action against a particular strain than those sufficient to deal with the vast majority of strains in a given species.

Administration: Choice of method is limited by two factors. (1) Its rapid destruction by acids and by penicillinase places in the way of external administration a number of obstacles all of which have yet to be satisfactorily overcome. (2) Following intramuscular injection in aqueous solution it is rapidly absorbed, reaching a maximum concentration in the bloodstream within a few minutes, thereafter rapidly excreted in the urine with rapid disappearance from the blood. Thus the maintenance of an adequate concentration in the body requires either repeated injections at short intervals, or continuous administration by a drip method.

The problems of administration will later be considered at greater length.
THE MODE OF ACTION OF PENICILLIN. Fleming described his first observation in 1929. "It was noticed that around a large colony of a contaminating mould the staphylococcus colonies became transparent and were obviously undergoing lysis." In the same paper he reported an experiment demonstrating its bactericidal action on staphylococci in nutrient broth at 37°C. The staphylococci were completely killed only after an interval of 4½ hours, even in a concentration 30 to 40 times stronger than that necessary to inhibit completely the culture in broth. From this he concluded that penicillin belongs to the group of slow-acting antisepsics.

In 1941 Florey and colleagues noted that the oxygen uptake of suspensions of staphylococci in the resting phase was not affected by penicillin even in high concentrations; they therefore concluded that its action was predominantly bacteriostatic and not bactericidal, at least in the concentrations likely to be used in therapeutics.

Largely as a result of this pronouncement, the impression became general that it was similar in action to the sulphonamides which, in the concentrations attained in the blood after oral administration, are solely bacteriostatic. This impression was enhanced by Garrod (1944) who wrote "Penicillin is in a true sense an antiseptic rather than a germicide; it does not kill bacteria quickly." Later (1945), he amplified
this statement by experiments in which penicillin was examined to see how far it conformed to the general laws governing the action of disinfectants; his results were in conformity with Fleming's original view that penicillin belonged to the group of slow-acting antiseptics. In addition he observed that concentrations of 10 to 1000 units per c.c. were less actively bactericidal than a concentration of 1 unit per c.c., a finding that may be related to impurities in the samples examined as this result has not since been reproduced.

This work resulted in continued acceptance of the view that the keystone of successful therapy was the maintenance in the bloodstream of a sufficient concentration of penicillin to prevent the multiplication of the organisms, leaving the host's defence mechanisms responsible for the coup de grâce.

Meanwhile Hobby, Meyer and Chaffee (1942) demonstrated a powerful bactericidal action on cocci; 99% of the organisms were destroyed under conditions favourable to growth of the organism, while no bactericidal action was observed under conditions unfavourable to growth (e.g. low temperature, exhausted culture medium).

The work of Hobby and Dawson (1944 A and B) supported these observations by showing that the bactericidal action was enhanced by substances increasing growth, diminished by substances (e.g. sulphadiazine) interfering with growth.
Rantz and Kirby (1944) confirmed the bactericidal effect on the staphylococcus in nutrient media and also Fleming's original observation on the lytic effect on staphylococcal suspensions.

Bigger (1944 a and b), reached the same conclusions as Hobby et al. He also found that 99.96% of staphylococci were killed by penicillin in low concentrations after 24 hours incubation in a nutrient medium. The small number of surviving organisms he termed "persisters" and outlined a method of intermittent penicillin therapy designed to exploit to the full the bactericidal powers of the drug, which he had demonstrated with concentrations as low as 1/24th unit per c.c.

Chain and Duthie (1945), confirmed and extended the observations of previous workers. They concluded that penicillin interferes with a metabolic function involved in the early stages of bacterial development, thus destroying the bacteria in the early "lag" phase before the actual cell division has taken place. By contrast the sulphonamides exert their bactericidal action only after a number of cell divisions have occurred in their presence.

In dismissing Bigger's (1944 b) proposals for "intermittent penicillin therapy", they state -- "There is as yet no convincing evidence that Penicillin ever prevents staphylococci entering the growth phase, and consequently there is as yet no reason for abandoning the usual therapeutic procedure of giving penicillin
continuously until the infection is sterilised. The factors responsible for the survival of a small % of organisms apparently resistant to the bactericidal action of Penicillin are not yet understood."

Chain and Duthie further point out that in its mode of action penicillin differs fundamentally from the common antiseptics and still occupies an unique position among known antibacterial agents; the degree of its activity is so great that as small an amount as 0.04 units per c.c. (the equivalent of 0.02 u g of the pure substance) is sufficient to kill and dissolve 200 million organisms. This is an activity of the same order as that of highly active enzymes and suggests that penicillin is either a part of an enzyme or acts by setting in motion an enzymatic mechanism; there is as yet no evidence that it ever exerts a bacteriostatic effect.

Todd (1945) expresses the opinion that the most probable explanation of bacteriolysis is that penicillin first kills the organisms, which are then destroyed by autolysis.

Recently Mackie (1946), reported that the experience of Edinburgh laboratory workers was in agreement with the work of Chain and Duthie. The Edinburgh experiments however suggest that a very high concentration of bacteria may annul the effect of penicillin; this experience is at variance with that of other workers.
11.

To be considered in conjunction with all the above investigations are the changes in the morphology of organisms occurring in the presence of low concentrations of penicillin in vitro.

Gardner (1940) was the first to describe such changes, which he noted in concentrations as low as 1/10th, and in some cases 1/30th, of that required for complete inhibition of the organism. The principal changes appeared to be due to incomplete division, giving rise to swollen and grotesque giant forms; staphylococci showed gross spherical enlargement with imperfect fission. Gardner's observations have since been confirmed by many other workers, and in a recent (1946) paper the same author, working with spores concluded that: "The action of penicillin is on feeding bacteria and begins directly they begin to feed".

Similar changes to these described by Gardner had been noted previously by many workers with substances other than penicillin. Thus Walker and Murray (1904) observed the same phenomena while studying the effects of dyes on the Typhoid group of organisms; Tunnicliff (1939) reported similar changes in streptococcus viridans in the presence of sulphanilamide.

The same phenomenon occurs with organisms insensitive to penicillin, and known sensitive organisms do not always show it. It has been observed in vivo in patients undergoing treatment (Herrell, Heilman and Williams 1942; Miller, Scott and Moeller 1944; Fleming 1946).
Comment:

From the reports considered above it is apparent that there is now general agreement that penicillin is bactericidal and bacteriolytic and that such effects are dependent on and proportional to the vital activity of the organism. In other words the more active the growth, the more susceptible the organism.

In exactly what manner penicillin interferes with the vital chemical activity of bacteria leading to their death and disintegration is not yet known; the morphological changes and final lysis are clearly no more than secondary phenomena, following the primary action of penicillin on the bacterial cell.

Discussion of the mode of action of the drug is of more than academic interest. The clinician is exercised to find that method of administration which will give the best results and be least burdensome to the patient; economy of penicillin is daily becoming of less importance. If penicillin is no more than a bacteriostatic agent, continuous administration is logically the method of choice; the demonstration that it is bactericidal should lead to a careful reconsideration of the hitherto accepted principle, first enunciated by the Oxford workers, of endeavouring to maintain a relatively constant "bacteriostatic" level in the blood.

The conflicting views of Bigger and of Chain and Duthie regarding treatment already indicated leave the clinician in a position whereby he is forced
to study further the optimum dosage and mode of administration for each group of infections. If Bigger's view is accepted it appears logical to aim at the more rapid bactericidal action to be expected in the presence of relatively high concentrations of penicillin.

The matter is further complicated by the fact that lysis and other phenomena observed in vitro may be due not to penicillin but to some impurity in the preparation used. Furthermore, commercial penicillin as now supplied is a mixture of penicillins in undefined proportions; until the activity of each fraction is accurately known, comparison of clinical results with the commercial product is subject to an obvious error.

THE BASIS OF PENICILLIN TREATMENT: This rests on an intelligent appreciation of the properties already considered. Successful treatment of any given infection demands the fulfilment of the following conditions:

1. The causative organism must be sensitive to penicillin.
2. The organism must be accessible to penicillin carried in the bloodstream.
3. Penicillin must reach the organism in sufficient concentration to destroy it.
4. Such a concentration must be maintained for a sufficient time to overcome the infection.

The above basic principles of penicillin treatment will now be examined as they relate to the treatment of gonorrhoea.
(I) **Sensitivity of the organism:**

Species Sensitivity: It has been amply demonstrated by many workers that the gonococcus is among the most susceptible of all organisms. In his original paper Fleming included it in the group of sensitive organisms, and the Oxford workers found that 6 of the seven strains they encountered were completely inhibited in dilutions as high as 1: 2,000,000, the 7th in a dilution of 1: 32,000. It must be remembered that the purest preparations available at this time contained but 5% of the pure substance; nevertheless the data in this paper remain significant as a comparison of the degree of sensitivity shown by various species and showed that the gonococcus was by far the most sensitive of the wide variety of organisms examined.

Recently Frazier and Frieden (1946), working with the purest available preparations, demonstrated inhibition of gonococci in dilutions up to 1: 50,000,000.

Strain sensitivity: In the case of some organisms, strain sensitivity assumes considerable importance, many strains in a given species exhibiting relative insensitivity to penicillin. Wide variations in sensitivity of strains was demonstrated by the Oxford workers in 1941, subsequent reports such as that of Heilman and Herrell (1942) indicating that this variation was most marked in the Streptococcus Viridans group. Previously Bornstein (1940), using crude broth filtrates containing penicillin, had suggested the use of
penicillin as an aid in the identification of related bacterial strains, so wide were the limits of sensitivity he observed within a given species.

Hill, Petroskas and Huffer (1944) point out that there is still time to determine the base-line of natural resistance, so that later accurate measurements of any increase of resistance can be made if necessary; they recall that marked variations of resistance were found to exist in gonococci genealogically free from any exposure to these drugs.

Aside from the possibility of acquired absolute or relative insensitivity consequent on previous contact with the drug, natural variations in sensitivity are of obvious importance in determining the response to treatment of individuals infected with different strains.

A number of reports on this subject are now available. Cohn and Seijo (1944) examined 82 freshly-isolated strains; all were killed in a 1:19,000 dilution of penicillin, equivalent to approximately 0.176 units per c.c., but "the susceptibility of different strains to penicillin varied strikingly in different dilutions".

Frisch (1944) studied 181 freshly-isolated strains; all were sensitive to penicillin in low concentrations. He also cultivated the same strains on media containing increasing concentrations of penicillin in an endeavour to render the organism resistant to the action of the drug, but failed to render a single strain penicillin-resistant.
Lankford (1945) tested 203 freshly-isolated strains for resistance to penicillin and found the extremes of tolerance were 0.0025 to 0.02 units per Ml.; the median falling between 0.0075 and 0.01 units per Ml. This is a relatively narrow range compared to the very wide range observed in the results of simultaneous tests with sulphathiazole.

Meads, Ory, Wilcox and Finland (1945), summarising the results obtained with 240 strains of gonococci examined at the same time as pneumococci, streptococci, meningococci and staphylococci, concluded that the strains of gonococci and group A haemolytic streptococci were the most sensitive to penicillin and showed the greatest uniformity in this respect.

(2) Accessibility to Penicillin in the Blood:

It is now well established that gonorrhoea, by the time symptoms are apparent, is more than a mere acute inflammation of the urethral mucosa. Finger, Ghon and Schlagenhafer (1894) showed by post-mortem examination of condemned prisoners inoculated at varying periods before execution that gonococci had reached the submucosal connective-tissue interspaces within 36 hours of inoculation. In this situation they are of course readily accessible to medicaments carried in the bloodstream, and this holds good for the majority of acute local extensions and complications of the disease in the male. Only in situations with a poor blood supply - Tyson's glands and ducts, paraurethral sinuses
or in longer-standing infections with abscess formation or much protective fibrosis, are the organisms in any sense inaccessible.

It may thus be accepted that in recent acute infections, the organism is eminently accessible to penicillin carried in the blood; in many complications it can be rendered accessible by appropriate local measures such as the establishment of adequate drainage.

(3) Concentration of Penicillin:

The order of penicillin concentration required to kill the gonococcus in vitro has been considered in connection with the sensitivity of the organism; all strains so far examined have been killed by a concentration of 0.176 units per c.c. Blood levels in patients under treatment will be considered more fully later, but it may be stated here that a concentration of 0.25 units per c.c. is present in the serum for over half an hour following an intramuscular injection of 15,000 units (Fleming, Young, Suchet and Rowe (1944), smaller amounts being detectable for several hours.

(4) Length of time required to overcome the infection:

A number of reports are available which show that the action of penicillin is extremely rapid - a matter of hours rather than days. Herrell, Cook and Thompson (1943) in experiments in vitro, found that gonococci became non-viable between the 3rd and 4th hours of contact with penicillin. Using 3 strains
freshly-isolated from sulphonamide-resistant cases they obtained the results shown in the Table, which is reproduced from their article.

The Antibacterial effect of Penicillin on Neisseria Gonorrhoea.

<table>
<thead>
<tr>
<th>Strain</th>
<th>Dilution</th>
<th>1 hour</th>
<th>2 hours</th>
<th>3 hours</th>
<th>4 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:000,000</td>
<td>++ +</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1:200,000</td>
<td>+ + +</td>
<td>+ +</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>+ + +</td>
<td>+ +</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td>2</td>
<td>1:100,000</td>
<td>+ + +</td>
<td>+ +</td>
<td>+ +</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1:200,000</td>
<td>+ + +</td>
<td>+ +</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>+ + +</td>
<td>+ +</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td>3</td>
<td>1:100,000</td>
<td>+ + +</td>
<td>+ +</td>
<td>+ +</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1:200,000</td>
<td>+ + +</td>
<td>+ +</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>+ + +</td>
<td>+ +</td>
<td>+ +</td>
<td>+ +</td>
</tr>
</tbody>
</table>

+++ = heavy growth
+++ = moderate growth
+ = slight growth
0 = no growth.

Observations of the time taken for organisms to disappear or become non-viable in patients under treatment are in accord with the above in vitro results.

In 1944 Miller, Scott and Moeller carried out a careful study of the response of gonorrhoea to penicillin by means of frequent urethral smears and cultures taken from male patients under treatment, and they reported striking changes in the urethral discharge within two or three hours of the commencement of treatment, the first negative smear being obtained in an average time of 3 to 4 hours. The same
observations had been made in previous reports, but the authors considered that the remarkable rapidity of action had not been sufficiently emphasised by the earlier writers.

The rapidity with which gonococci disappear from the discharge constitutes one of the most striking features of penicillin therapy, and has been confirmed by workers in all parts of the world. Lees (1946B) points out that this speed of action is of some importance in deciding the precautions, such as isolation of patients and sterilisation of fomites, indicated in dealing with patients.

Unfortunately failure to demonstrate the organism shortly after treatment is not a reliable indication that the infection has been overcome. Disappearance of the organism may be only temporary, to be followed in days, weeks or months by a recrudescence of symptoms and signs, with reappearance of the organism in the discharges. It is for this reason that in gonorrhoea an estimate of the length of time required for penicillin to overcome the infection should rest not on the initial response to treatment of the individual, but on full consideration of the results of conscientious, prolonged, and repeated tests to establish cure in a large number of cases. Only in this way can a dosage scheme be evolved which, by covering individual variations of host and of organismal strains, may be expected to show reasonably uniform results when applied to individual sufferers.
It will be seen later that in fact a number of different dosage schemes give comparable clinical results; few attempts have been made to relate height and duration of penicillin blood concentrations in patients under treatment to the results achieved. However Lloyd-Jones, Maitland and Allen (1945) found that a level of 0.25 units per c.c. maintained for 9½ hours was essential to attain a cure-rate of over 95%. Romansky, quoted by Gillick and Chinn (1945) considers a concentration of 0.19 to 0.25 units per c.c. for 8 hours is associated with cure in the majority of cases.

**SUMMARY:**

1. The gonococcus is highly sensitive to penicillin; a concentration of 0.176 units per c.c. is sufficient to inhibit the growth of all strains so far examined.

2. In uncomplicated gonorrhoea the organism is readily accessible to penicillin carried in the bloodstream.

3. In vitro and in vivo studies suggest that gonococci become non-viable after about 4 hours contact with penicillin.

4. In practice a longer period of contact is required to attain consistent clinical results.

**COMMENT:**

If we leave out of account the natural powers of the host to overcome infection, therapy resolves itself into maintaining an inhibitory concentration of penicillin in the serum for a number of hours, the exact time to be defined by a process of trial and error on clinical cases. There is good evidence, however, that the 'host' factor is of considerable importance;
the fact that many cases are cured by doses inadequate to overcome all infections suggests that natural or acquired resistance on the part of the host plays a not inconsiderable part in determining final cure.
PART II.

PENICILLIN IN GONORRHOEA.

"Cure" in Gonorrhoea.

It is convenient to consider the question of "cure" in gonorrhoea at this point, before describing the clinical results achieved with penicillin.

Prior to the introduction of the sulphonamides, the sheet-anchor of treatment was local lavage of the urethra and bladder pending the development by the host of sufficient immunity to the organism to eliminate the infection. A representative standard of cure at this time was that of David Lees (1931), which called for repeated bacteriological tests over a six-month period following suspension of treatment.

The rapid cessation of clinical signs in cases treated with sulphonamides soon led to a great increase in the number of patients who ceased to attend for the performance of such tests, an attitude encouraged by those practitioners who considered that a prescription for a few tablets constituted adequate management of a case of gonorrhoea. Responsible clinicians continued to stress the need for adequate tests over a period of 3 months, as relapse was encountered not infrequently after apparently successful sulphonamide therapy. (Batchelor et al 1938; Cokkinis and McElligott, 1938, 1939).

The value of such provocative measures as the passage of urethral sounds, and the injection of gonococcal vaccine before obtaining material for
bacteriological tests was, however, questioned. Thus Jefferiss and McElligott (1943), reporting a series of 567 cases treated with sulphathiazole, concluded that "relapses almost invariably declare themselves within four days of the cessation of chemotherapy". They further state "... it has been our experience that these classical methods of provocation are singularly ineffective ... the relapses do not seem to be in any way connected with them".

A year later Koch, Mathis and Geiger (1944), in a meticulous study of 926 cases treated with the same drug, demonstrated conclusively that this view was too sanguine. In accordance with current American practice, they eschewed provocative measures, demanding only consistently negative clinical and laboratory findings over a period of at least 3 months; these to include a minimum of 3 consecutive negative cultures taken not less than one week apart. Of 640 cases which became symptom-free after a single course of sulphathiazole, 205 (32%) yielded positive cultures up to 3 months and longer after cessation of treatment, although remaining free from symptoms. At the end of a further 3 months, no less than 4.9% of these patients were still harbouring gonococci. The authors rightly conclude that "great care should be taken to avoid referring to asymptomatic cases as 'cured' unless laboratory tests have really shown the absence of infection".

The standards of cure adopted by clinicians in penicillin-treated cases have similarly varied within
wide limits. At one extreme are the criteria recommended by the Surgeon-General U.S. Army, quoted by Raines, Barrett and Galt (1945), which may be summarised:

1. If no urethral discharge is present 48 hours after treatment, the patient is considered cured and returns to duty.

2. If discharge is present at 48 hours and is negative for gonococci, the patient is considered cured.

3. Three weekly inspections; smears and cultures taken only if urethral discharge is present.

The majority of independent American workers, however, insist on a maximum of 3 negative cultures at weekly intervals. Many reduce the length of observation by increasing the number of cultures to 1 daily for 7 days; they claim that by this means relapses are diagnosed before the recurrence of clinical signs.

British workers lay more stress on the length of the observation period, and criteria widely adopted are on the lines of those recommended by Lees (1946 A), which call for repeated clinical and bacteriological tests for 3 months after treatment, a final serum test for syphilis being carried out after a further 3 months.

It is evident that until a large number of penicillin-treated cases have been examined by accurate cultural methods over a period of at least 3 months, no valid conclusions are possible regarding minimum standards of cure. There is urgent need for a repetition of the work of Koch and associates on penicillin-treated cases. That this is recognised in responsible quarters is evident from a recent editorial (V.D.I 1945).
"There has as yet been no conclusive report concerning the possible development of asymptomatic carrier states".

**TREATMENT BY MULTIPLE INJECTIONS:**

The findings of Fleming (1929) and the Oxford workers (1941) that the gonococcus was extremely sensitive to penicillin in vitro were the pointers to trial of the drug in clinical cases whenever supplies became available.

At this time the view was current that penicillin was a bacteriostatic agent; it was assumed that a low level of penicillin maintained for an as yet undetermined time could be expected to cure a high proportion of cases. This assumption was justified by the first clinical reports, which were uniformly enthusiastic.

Herrell Cook and Thompson (1943) treated 5 males whose infections had failed to respond to sulphonamides; all were cured. Mahoney and colleagues (1943) cured 74 of 75 male cases with 160,000 units given in divided intramuscular doses over a period of 45 hours. In the same year British Army experience was equally striking; 10 cases of gonorrhoea were treated with an arbitrary dose of 180,000 units given in 12 intramuscular injections over 48 hours; dramatic cessation of urethral discharge "like turning off a tap" was noted in all cases, and no relapse was seen during an
observation period of 2 to 4 weeks. (Florey & Cairns 1943).

Responses such as these eclipsed the best results obtainable with the sulphonamides; most important of all, it appeared that the ever-increasing number of cases in which sulphonamides failed to effect cure were readily amenable to penicillin treatment. Clinicians everywhere waited impatiently for an opportunity to see for themselves the remarkable responses described.

The years 1944 and 1945 saw the steadily increasing production of penicillin on a commercial scale, and the literature of this period abounds with reports endorsing the enthusiastic claims of the earlier workers.

During the war the bulk of the penicillin produced was earmarked for the use of the armed forces; it is not surprising therefore that the only reports on a considerable number of cases relate to the treatment of service personnel. Leaving aside the large number of publications dealing with small series of cases, the results reported by British, Canadian and American workers are summarised in Table I.:--
### Table I. Results of Treatment in Gonorrhoea obtained by various authors.

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of cases treated</th>
<th>Percentage cured</th>
<th>Dose of Penicillin (Units)</th>
<th>Duration of Treatment (Hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hannsen</td>
<td>865</td>
<td>100</td>
<td>75,000 *</td>
<td>12</td>
</tr>
<tr>
<td>Robinson</td>
<td>1000</td>
<td>94.7</td>
<td>100,000</td>
<td>12</td>
</tr>
<tr>
<td>Schwartz &amp; Edge</td>
<td>4,439</td>
<td>95.9</td>
<td>100,000 *</td>
<td>12</td>
</tr>
<tr>
<td>Sternberg &amp; Turner</td>
<td>1,686</td>
<td>92.5</td>
<td>50,000 to 100,000</td>
<td>12</td>
</tr>
<tr>
<td>Farquharson</td>
<td>1,000</td>
<td>95</td>
<td>90,000 to 120,000</td>
<td>12</td>
</tr>
<tr>
<td>Lees</td>
<td>1,737</td>
<td>93.9</td>
<td>30,000 to 100,000</td>
<td>27</td>
</tr>
</tbody>
</table>

* = "average dose."
The results are remarkably uniform, bearing in mind the inevitable variations in potency of the drug, and the varying standards of cure and length of follow-up after treatment already considered.

A recent analysis of 29 reports revealed that 94.2% of 12,403 complicated and uncomplicated male cases were cured following one course of penicillin injections. (Bulletin of Communicable Diseases 1945). Of the failures, three-quarters responded to a second course of injections, giving a total of 98.2% cured with two courses.

Without considering each paper in detail, it may be stated that there is general agreement on the following :-

1. The total dose of penicillin should be at least 100,000 units.
2. The size of individual dose is not important; it should be such that the treatment is completed within 12 hours.
3. The treatment recommended by the majority of these authors is 20,000 units given as an intramuscular injection three-hourly for 5 doses.
4. Sulphonamide-resistant and chronic cases respond in the same manner as acute cases of recent origin. Complicated cases, on the other hand, may require larger doses of penicillin and several courses of treatment; prostatitis is more amenable to treatment than other complications.
5. Treatment failures and relapses can be cured by repetition of the treatment.

Individual response to treatment:— It is agreed that dramatic relief from such symptoms as dysuria is apparent within a few hours of commencing treatment; that gonococci disappear from the discharges as a rule within 24 hours. Miller Scott and Moeller (1944), in a paper
already cited, emphasised that negative smears were obtained within 3 or 4 hours. Dunfield and Mandel (1945) report similar findings in 154 cases examined by smear and culture, of which 50% became bacteriologically negative in 3 hours and more than 80% in 6 hours. They advocate a cautious attitude towards cases showing a persistence of gonococci beyond these times. Reversion of smears to positive during treatment or in the three weeks following treatment were noted in 7 cases.

Observers differ in their estimates of the time taken for the urethral discharge to disappear. The majority state that it disappears in from 24 to 48 hours. Sternberg and Turner (1944) found that in about 20% of cases a thin mucoid discharge persisted for one to three weeks; as this did not contain gonococci and eventually ceased spontaneously they regarded it as "a normal finding incidental to the healing process."

The birds-eye view of results in a large number of cases treated by different clinicians presented above leaves no doubt as to the efficacy of penicillin in the treatment of gonorrhoea in the services. The treatment-schedules so far considered have in common a time-spread of at least 12 hours, involving the admission of cases to hospital. It seems from the work of Sternberg and Turner (1944) that no advantage accrued from prolonging administration beyond 12 hours; thus 96.6% of 261 male cases were cured by 100,000 units given in 12 hours but results were no better if the same dose was spread over 27 hours.
In America several "accelerated" schedules in which the time-spread was further reduced were suggested with a view to making out-patient treatment of civilians possible. Van Slyke and Steinberg (1944 and 1945) investigated various combinations of time-dose relationships designed to meet the requirements of merchant seamen; they claimed a cure-rate of 94% in 66 patients with 2 injections of 100,000 units given 4 hours apart.

In this country Lloyd-Jones Maitland and Allen (1945) studied the effects of a total dosage of penicillin ranging from 100,000 to 150,000 units, with varying individual doses and time-spread. Their best results were obtained with 5 injections of 30,000 units at 2-hourly intervals, a total of 150,000 units curing all but one of 265 consecutive cases. This scheme reduced the time required for treatment to 8 hours, and was introduced as the routine treatment for gonorrhoea in the Royal Navy. It gave good results in other hands and was recommended for use in the Army a few months later (A.M.D. Bull. June 1945). McLachlan (1945) reported it curative in "nearly all" cases, and this view was echoed by Harrison (1945).

Schedules in which the time required for treatment is still further reduced have not yet been tested on a large scale. Examples are that of Cohn and Kornblith (1945) who adduced a cure rate of 85.2% in 102 male cases receiving 100,000 units in 4 hours, and of Fidler (1945) who cured 95% of 42 cases with 3
injections of 33,333 units at 2-hour intervals.

Of greater significance are the results obtained by Batchelor, Donald, and Murrell (1946) following 2 injections of 200,000 units at intervals of six to eight hours: These workers cured 182 of 190 male cases (95.8%) by this method which, though it does not reduce the total time-spread, is eminently suitable for the treatment of outpatients.

**COMMENT:** In comparing the results reported by different workers it is important to remember the conflicting views as to what constitutes cure of gonorrhoea. Generally speaking American workers are of the opinion that repeated negative cultural investigation over a period up to 3 weeks is adequate criterion of cure; in the case of the papers considered here this requirement is seldom met as many workers report cure after a few days post-treatment observation. Responsible British clinicians lay more stress on the length of observation required, negative tests over a period of 3 months being the usual requirement.

As comparatively few of the reported cases have been observed for this length of time "cure" in this section should be regarded as "early" or "apparent" cure.

It appears reasonable to conclude from the data presented that :-
1. Penicillin is highly effective in the treatment of gonorrhoea in the male.

2. The dose should be at least 100,000 units if treatment extends over 12 hours: 150,000 units if the time-spread is reduced to 8 hours.

3. To offset a reduction in the time-spread below 8 hours, or in the number of injections, increased dosage is required.

TREATMENT BY A SINGLE INJECTION:-

Once accepted that amounts of penicillin of the order of 100,000 to 150,000 units were effective in curing the vast majority of sufferers, it was a natural step to define the shortest period in which administration of this dose could be completed. The results already quoted had shown a time-spread of at least 8 hours to be essential if a cure rate of around 95% was to be attained.

Injecting the whole dose in a single injection gives poor clinical results. In support of this statement a number of reports may be cited. Thus Marshall (1945) treated 50 cases with a single injection of 100,000 units and cured only 18 (36%), of whom 3 required adjuvant treatment with irrigations to clear up residual urethritis. Cohen and Grover (1945) cured 25 (41.4%) of 58 cases with a similar injection. The experience of Batchelor, Donald and Murrell (1946)
indicated that a single injection of 200,000 units cured only 77% of 135 cases. Similar experiences have been reported by a number of other workers.

Few attempts had been made to relate levels of penicillin attained in the blood to clinical results. However, Lloyd-Jones, Maitland and Allen (1945) suggested that "... unless 'serum inhibition' was present in a serum dilution of not less than 1 in 8 (approximately 0.25 units per c.c.), and was maintained for 92 hours, ... high rate of cure ... was not obtained". Such blood levels were regularly obtained in cases treated with their dosage scheme of 150,000 units spread over 8 hours.

Endeavours to attain comparable levels in the blood by other methods were conditioned by the over-riding necessity for economy in the use of penicillin. This consideration applied with unusual force to the treatment of a non-fatal disease such as gonorrhoea, in which satisfactory results were obtainable within the range 100,000 to 150,000 units.

Consequently further attempts to reduce the time required for treatment were based on attempts to prolong penicillin effect following a single injection.

As this is a subject of some interest, it is considered systematically below.

**Prolongation of Penicillin effect:**

The rapid excretion of penicillin following injection was mentioned in connection with the general
properties of the drug. Florey has likened the attempt to maintain a constant level of penicillin in the blood to that of keeping a bath full with the plug removed; this remains the central problem of systemic penicillin therapy today.

At first the crude solution of continuous infusion or frequently-repeated injections was adopted. By such means penicillin is supplied to the body in amounts sufficient to counterbalance its rapid excretion.

With the object of avoiding the necessity for frequent injections, and of economising in penicillin, several principles have been invoked in attempts to maintain adequate blood concentrations with a smaller number of injections. These may be outlined as follows:

1. **Delay of Excretion:**

   The kidney unfortunately does not recognise penicillin as a friend, and excretes it rapidly by way of the tubules. It has been demonstrated that in nephritis and other lesions impairing renal function, excretion of penicillin is markedly delayed. (Rammelkamp and Keefer (1943); Fleming and colleagues 1944).

   Other substances which are excreted by the tubules compete with penicillin for priority of excretion, and this may delay the elimination of the drug. Rammelkamp and Bradley (1943) suggested the use of diodone (diodrast) for this purpose; more recently para-aminohippuric acid has proved effective in dogs and
man. (Beyer and co-workers 1944 and 1945; Loewe and co-workers 1945). Benzoic acid has been used for the same purpose by Bronfenbrenner and Favour 1945).

Safe and effective though these drugs are, they themselves require continuous administration and so have no application to the single injection treatment of gonorrhoea.

II. Delay of absorption from the injection site:

(1) By cooling.

Trumper and Hutter (1944) introduced this ingenious method for the treatment of gonorrhoea in U.S. Navy personnel. By means of an icebag applied to the site of injection, they so slowed the circulation that effective concentrations were maintained in the blood for at least 5 hours after an intramuscular injection of 100,000 units; control cases maintained effective levels for 2 hours only.

Recently Trumper and Thompson (1946) reported results in 100 cases of gonorrhoea treated by this method; of 43 cases receiving 100,000 units as a single injection 39 (91%) were cured.

Though this technique is feasible under Service conditions at sea, it necessitates the wearing of an icebag for 2 hours before and 12 hours after injection, which renders it impracticable for the use of civilian outpatients.

(2) By the use of vasoconstrictors:

The use of vasoconstrictors to prolong the
Action of local anaesthetics has long been familiar. As the result of experiments on animals and human subjects, Fisk, Foord and Alles (1945) suggested the addition of adrenaline to solutions of penicillin for injection.

This method has been used in Scotland by Batchelor and his associates (1946), who mixed 2 minims of 1:1000 adrenaline with a saline solution of penicillin in the syringe. The addition of adrenaline had no significant effect on their results in the treatment of gonorrhoea cases.

(3) By the use of special vehicles:

A large number of vehicles, pectin, gelatin etc., have been recommended. Recently Armstrong and colleagues (1945) advocated the substitution of 5% glucose in place of saline for solution of penicillin. As no adequate clinical trials have yet been reported, such vehicles will not be considered further.

Of all the vehicles proposed for use, that most fully investigated is the peanut-oil and beeswax mixture - hereafter referred to as P.O.B. - devised by Romansky and Rittman (1944 A & B) for the treatment of gonorrhoea in the U.S. Army. The originators emphasise that calcium Penicillin is essential to the preparation of satisfactory mixtures; minutiae of preparing the mixtures were modified in the light of experience, and in their most recent paper (1945) the authors recommend the use of a "unit dose" consisting of:-
37.

a. 300,000 units of calcium penicillin of approximately 1000 units per Mg.

b. 1 millilitre of peanut-oil containing 4.8% by volume of purified beeswax U.S.P.

Clinical results are reported by Romansky, Murphy and Rittman (1945); they cured 93 of 100 patients with 100,000 units of P.O.B., and all of 75 patients with 150,000 units P.O.B.

Leifer, Martin and Kirby (1945), report the following results in 92 cases treated with a single injection of P.O.B.

<table>
<thead>
<tr>
<th>Dose of Penicillin (Units)</th>
<th>Cases Treated</th>
<th>Cases cured</th>
</tr>
</thead>
<tbody>
<tr>
<td>100,000</td>
<td>88</td>
<td>74 (84%)</td>
</tr>
<tr>
<td>200,000</td>
<td>13</td>
<td>11 (85%)</td>
</tr>
<tr>
<td>300,000</td>
<td>91</td>
<td>83 (91%)</td>
</tr>
</tbody>
</table>

In discussing their results the authors emphasise that they are not strictly comparable with those reported by Romansky and colleagues; the mixtures used were not identical, and their cases were followed for 21 days against the 7 days of the other workers.

There is a further discrepancy between the two groups of workers in regard to penicillin blood levels following P.O.B. injections. Thus Romansky et al (1945) state that "assayable levels are maintained for 7½ to 10 hours following a dose of 100,000 to 150,000 units."

Leifer Martin and Kirby (1945) found "assayable levels" following a dose of 100,000 for 0 to 16 hours, the majority for 4 to 8 hours; they point out that in many cases penicillin is detectable for less
than 4 hours - that is for approximately the same period as that following the same dose given in saline.

"Assayable levels" by the methods of assay used are approximately 0.04 units per c.c.

In a later paper Kirby and colleagues (1945) present a full report on blood levels attained at varying dosage levels of P.O.B.; they suggest that equally good results are obtained with sodium and calcium penicillin, and that subcutaneous injections are as effective as intramuscular.

In 54 cases of gonorrhoea treated with 300,000 units P.O.B. intramuscularly, penicillin was detectable in the blood for 12 hours in 37 and for 16 to 38 hours in 17; small amounts were present in the urine for periods up to 72 hours. In 9 of these cases there were 1 or more occasions on which no penicillin was demonstrable in the blood. The authors conclude that there is "striking variability of absorption and excretion with all the mixtures employed", and that a dose of 300,000 with P.O.B. gives results comparable with 100,000 units in divided doses in aqueous solution.

The only large-scale trial of P.O.B. preparations so far reported is that of Van Slyke and Heller (1945) who analyse results in 1060 cases, of whom 38% were males, treated with 200,000 units in 2 c.c. of the vehicle. They adduce an overall cure-rate of 92.2% in the series.
In Scotland Batchelor and associates (1946), using a preparation containing 50,000 units calcium penicillin and 2.5% beeswax in 1 ml. of peanut oil treated 41 males with 200,000 units with 4 failures.

P.O.B. preparations suffer the grave disadvantage of being extremely inconvenient in use.

"The mixtures are extremely viscid, even after being heated in an incubator or water-bath at 37°C for 30 minutes". (Leifer Martin and Kirby (1945).

Syringes and needles used for injections must be warmed.

In an attempt to overcome these disadvantages Lloyd-Jones, Donaldson and Allen (1946) evolved a vehicle consisting of magnesium sulphate monohydrate in peanut oil. 1 c.c. of this preparation, containing 250,000 units sodium penicillin cured 108 (95.6%) of 113 outpatients; penicillin was demonstrated in the sera of 8 out of 11 patients 24 hours after treatment.

They found that the best clinical results followed subcutaneous injection, and pointed out that such mixtures were fluid at room temperature in contrast to the highly viscous mixtures of P.O.B. Large-scale clinical trials with such preparations have not yet been reported.

**COMMENT:** The most successful "one-shot" treatment presently available appears to be 300,000 units of penicillin in a vehicle of beeswax and peanut-oil. This has the grave disadvantage of requiring elaborate preparation for injection. The B.P. preparation
containing 150,000 units per c.c. has not yet been evaluated; it may prove less efficacious than the more viscid preparation containing 300,000 units per c.c.

The manner in which P.O.B. delays absorption remains a matter for speculation; the rationale of its use is an attempt to maintain a constant low level of penicillin in the serum of the order attainable with multiple aqueous injections.

In all the work quoted above, the basis of successful treatment is considered to be the maintenance of a bacteriostatic level of penicillin until the infection is overcome, namely, to reproduce the effect produced by multiple aqueous injections. This of course is in accord with the views propounded by the Oxford workers in 1941.

Another method of approaching the problem is to discard these hitherto generally accepted views and observe the effect in terms of blood levels and clinical results of increasing the dosage of penicillin.

Aqueous solutions have the obvious advantage of being generally available and simply administered, and considerations of economy now carry less weight than formerly. At the time of writing, August 1946, I am unable to trace any reference in the literature to a detailed report on a series of cases of gonorrhoea treated with single aqueous injections of penicillin in a dosage higher than 200,000 units. For this reason I believe the work reported in Part III. of this thesis may give some indication of the
results to be anticipated if this approach is carried to its logical conclusion - the definition of that dose which, given as a single injection, is productive of results comparable to those attainable by multiple injection methods.

Apart from the expense of such treatment in terms of penicillin, the danger of interfering with the diagnosis of syphilis acquired at the same time as gonorrhoea has been advanced as an argument against the use of doses above 300,000 units.

This danger will now be considered.

The "MACKING"OF SYPHILIS:-

For the first time in the history of the venereal diseases a single drug is available which is effective against both the spirochaete of syphilis and the gonococcus.

In their original report on the penicillin treatment of early syphilis, Mahoney Arnold and Harris (1943) showed that doses of penicillin of the order of 100,000 to 200,000 units were amply sufficient to cause disappearance of spirochaetes from the surface lesions of syphilis. Later Moore and his associates (1944) proved that such doses were insufficient to cure established human syphilis. These facts were later confirmed in a multitude of reports from all over the world.

Among cases of gonorrhoea are a number who
have been exposed to the risk of infection with syphilis at the same time as they acquired their gonorrhoea. The incubation period of syphilis varies from 10 to 90 days compared with that of gonorrhoea which lies as a rule between 2 and 21 days. It follows that an individual who acquires both diseases simultaneously is likely to seek advice for gonorrhoea before his syphilis is manifest clinically or serologically, that is during the incubation period of the latter disease. A further possibility is that a case of syphilis in the incubation period may acquire gonorrhoea at a later exposure, urethral discharge appearing weeks or months before the chancre or other manifestation of syphilis. Thus at the time they receive penicillin treatment for gonorrhoea, a number of cases are likely to be incubating syphilis.

From the above basic facts it follows that in such cases penicillin treatment of gonorrhoea may have one of the following effects on syphilis:—

(1) It may prolong the incubation period.
(2) It may suppress the symptoms - clinical or serological - and lead to an asymptomatic infection.
(3) It may abort the disease.

At the time of writing, clinical evidence is available only in respect of the first possibility, to which attention was drawn by several authors in the early days of penicillin treatment. (Sternberg and Turner 1944; Van Slyke and Steinberg (1944).
The literature abounds with innumerable isolated clinical anecdotes relating to the healing of primary lesions unnoticed until after penicillin had been administered; as the opportunity for diagnosis by demonstrating spirochaetes had been missed, final diagnosis had to await the development of a positive serum test for syphilis. Such observations prove only that 100,000 or 200,000 units of penicillin constitute inadequate treatment for early syphilis - a fact already well attested.

It is of obvious importance to determine whether the incubation period of concomitantly-acquired syphilis is likely to be prolonged by treatment of gonorrhoea; if it is, the usual 3-month surveillance period will require to be extended.

Cronin (1945) in a succinct discussion, emphasises that essential data in case-reports are firstly a reliable history of absence of a re-exposure to infection in the period between penicillin treatment and the appearance of the syphilitic lesion; secondly - "a primary exposure sufficiently remote in time from any previous exposure so as to render it the probable source of the double infection". He cites 10 cases in which chancres were diagnosed within two months of penicillin treatment and suggests that surveillance for 3 months is adequate.

A search of the literature reveals few reports in which sufficient data are given for any
conclusions to be permissible. These are summarised in Table II.

**TABLE II.**
The Effect of Penicillin on the Incubation Period of Syphilis.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Number of Cases</th>
<th>Days from exposure to diagnosis of syphilis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1944</td>
<td>Carpenter</td>
<td>1</td>
<td>54</td>
</tr>
<tr>
<td>1944</td>
<td>Van Horn &amp; Dakin</td>
<td>1</td>
<td>52</td>
</tr>
<tr>
<td>1944</td>
<td>Boyd Wagner &amp; Hewson</td>
<td>1</td>
<td>56</td>
</tr>
<tr>
<td>1945</td>
<td>Atcheson</td>
<td>1</td>
<td>32</td>
</tr>
<tr>
<td>1945</td>
<td>Cronin</td>
<td>10</td>
<td>47.2 (Average)</td>
</tr>
<tr>
<td>1946</td>
<td>Derzavis &amp; Bond</td>
<td>1</td>
<td>54</td>
</tr>
<tr>
<td>1946</td>
<td>Batchelor Donald &amp; Murrell</td>
<td>7</td>
<td>82 (Average) (39 to 184).</td>
</tr>
</tbody>
</table>

With the exception of Batchelor and associates, all the above authors maintain that 3 months surveillance is adequate for penicillin-treated cases of gonorrhoea.

The Edinburgh workers rightly conclude that on the basis of their results such cases should be observed for at least six months, and possibly longer.

It is of interest to observe that only 1 case of those shown in the Table had received more than 200,000
units of penicillin; this is the 4th case reported by Batchelor and was given a total of 560,000 units - the incubation period was 60 days.

Approaching the problem from another angle, Magnuson and Eagle (1945) observed the effects on rabbits infected with syphilis of small doses of penicillin comparable to those used in the treatment of human gonorrhoea. They found that the evolution of early rabbit syphilis was significantly modified by such doses, the incubation period being prolonged.

Most important of all, they showed that if penicillin was given early in the incubation period, complete abortion of the disease frequently resulted; in none of the animals was asymptomatic infection produced.

Conclusions drawn from work on rabbit syphilis are not to be accepted unconditionally as applying to the human disease. Nevertheless, this work may be cited in support of suggestions that a single large dose of penicillin, given early in the incubation period, may prevent the appearance of syphilis acquired at the same time as gonorrhoea. (Romansky Murphy and Rittman 1945; Lloyd-Jones, Donaldson and Allen 1946).

Comment:-

From the work cited above it would appear that the incubation period of syphilis can undoubtedly be prolonged by penicillin treatment of gonorrhoea. The number of such cases reported is an infinitesimal proportion of the total number treated. According to
McElligott (1946), 3% of all cases of acute gonorrhea are likely to be incubating syphilis.

May this discrepancy not be explained on the assumption that a considerable number of syphilitic infections are aborted? If this is so there would appear to be an actual advantage in giving larger doses of penicillin.
PART III.

Personal experience of treatment with single injections

During the year 1945 it was my good fortune to be associated with Surgeon-Captain T.R. Lloyd-Jones, R.N., in experimenting with several single injection techniques for the treatment of gonorrhoea in the Navy.

It seemed apparent from this work that a single injection of penicillin in a vehicle of magnesium sulphate monohydrate in peanut oil, constituted the most efficient of the methods investigated. (Lloyd-Jones, Donaldson, and Allen, 1946).

As the need for economy in the use of penicillin became less important, it occurred to me that the results to be expected following single injections in aqueous solution would be of some interest.

Accordingly I selected from among these cases of gonorrhoea personally observed during 1945, a number treated with such injections. The results presented are in no sense those of a planned investigation; I believe, however, that they permit of some estimate of the efficacy of single aqueous injections of penicillin in the treatment of male gonorrhoea.

It is necessary to consider the clinical material and its management in some detail.
CLINICAL MATERIAL:

This consists of 205 cases selected as follows:

Treatment: Throughout the period during which these cases were treated, a variety of methods was in use. Some of these involved the use of relatively large amounts of penicillin, others required special vehicles. The treatment received by individual patients on a given day depended on a number of factors - supplies of penicillin, availability of vehicles, etc.etc.

The exact method of treatment to be employed was decided in advance; not infrequently a number of different methods were used in rotation. Thus a decision as to the form of treatment had been taken in every case prior to the examination of the patient.

The 205 cases receiving single aqueous injections may fairly be regarded as a random sample of cases passing through the clinic.

Post-Treatment observation: Only cases examined personally over a minimum period of eight weeks are included; many of these have been observed for considerably longer periods. A uniform standard of reporting and assessment can thus be claimed. I believe such a standard to be of sufficient importance to justify exclusion of the considerable number who were examined in ships and at other centres with entirely satisfactory results.

Management:

The following standards were adhered to in all
cases reported.

1. **Diagnosis:**
   Gonococci were demonstrated in smears of the urethral discharge in every case before treatment was instituted.

   The anatomical extent of the disease was determined by the two-glass urine test; gentle examination of the prostate and seminal vesicles was made only in the presence of a hazy urine in the second glass, or if the symptoms indicated probable involvement of these structures.

   A thorough search was made of the skin and mucous membranes for surface lesions of syphilis; a sample of blood was withdrawn for examination by Wassermann Reaction.

2. **Treatment:**

   The majority - 130 - were treated as outpatients, but 75 were admitted to the ward for purposes of investigation, for administrative reasons, or on account of complications. Uncomplicated cases were invariably discharged to duty on the second morning after treatment.

   **Penicillin:** This was supplied as dry powder of sodium penicillin; the brands used were:

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Units per Milligram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wyeth Inc. U.S.A.</td>
<td>420</td>
</tr>
<tr>
<td>Heyden</td>
<td>440</td>
</tr>
<tr>
<td>Pfizer</td>
<td>540</td>
</tr>
</tbody>
</table>

   Samples from each batch were assayed in the clinic laboratory on receipt; if any failed to attain
the potency claimed on the label, the whole batch was rejected for use in the treatment of venereal disease. In practice it was found that all three manufacturers allowed a considerable margin for deterioration, and the majority of samples assayed were 10 to 20% more potent than indicated on the container.

Technique of injection:-

The requisite amount of penicillin was dissolved in 1 to 4 c.c. of sterile normal saline under rigid standard precautions against contamination, or inactivation by heat or chemicals.

Injections were made intramuscularly into the upper and outer quadrant of the buttock.

No other treatment was prescribed in uncomplicated cases.

3. Instructions to patients:-

Place in chain of spread: The patient was informed of the diagnosis immediately it was made, and the importance of identifying the probable source of infection and any subsequent sexual contacts was carefully explained to him. In the majority of cases identification of contacts was impossible, infections being contracted in areas remote from the clinic either during leave or while calling at a distant port. With the best intentions few patients could communicate with or identify the source of their infection; however such contacts as were identified in the main readily attended for examination at a civilian clinic. The war-
time sailor had little use for the services of professional prostitutes, and the vast majority of the sexual intercourse which took place was on a friendly and non-commercial basis. At this time penicillin was not in wide-spread use in civilian clinics; there is thus good reason to believe that few strains of gonococci responsible for the infections now under consideration had been in previous contact with penicillin.

Hygiene:— Apart from the injection of penicillin, no other treatment was prescribed. The patient was told to keep his genitalia clean, to consume his customary amount of fluids and to eschew self-examination and in particular "squeezing-up" to look for a urethral discharge.

Full diet was permitted but each patient was told to forego the consumption of alcohol until permitted by the medical officer; outpatients continued full duty.

All patients returned for examination 7 days after treatment.

4. **Surveillance and Tests of cure:**

These may be summarised:

<table>
<thead>
<tr>
<th>Weeks after Treatment</th>
<th>Examinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1. Clinical</td>
</tr>
<tr>
<td></td>
<td>2. Vesiculo-prostatic smear</td>
</tr>
<tr>
<td></td>
<td>3. &quot; culture</td>
</tr>
</tbody>
</table>

Alcohol permitted if above negative and no symptoms or signs.
Clinical examination included examination of urethral smears if available, two-glass urine test, and careful search for surface lesions of syphilis.

Completion of at least eight weeks surveillance is essential for inclusion in the series reported.

Cultures:

After urination, material obtained by massage and "stripping" of the prostate and vesicles was inoculated directly on a plate of medium at 37°C which was returned immediately to the incubator.

Incubation Plates were incubated overnight (18 to 24 hours) at 36.5°C in an atmosphere of 5% carbon dioxide.

If no growth was visible at the end of this time, further incubation in ordinary atmosphere was allowed, final readings being made after a total of 48 hours incubation. Macleod's oxydase Reaction - flooding the plate with a freshly-prepared solution
of 1% tetramethyl-paraphenylendiamine - was employed at the final reading, to aid in identification of gonococcal colonies.

A gram-negative diplococcus giving a positive oxydase reaction was accepted as a gonococcus; no attempt was made by sugar fermentations or other tests, further to identify the organism.

Medium: - This was a modification of the Egg Albumin Agar recommended by Price (1935).

King (1942 and 1948) has discussed the difficulties encountered in obtaining suitable materials for this medium in wartime. It was found that frozen bullock's heart could be substituted for the fresh material without impairing the results, and such a modification permitted S.B.P.C. T. Jones to prepare a medium which has proved highly satisfactory in the clinic over a period of 3 years. A further modification introduced by Jones is adsorption of the broth with animal charcoal, which removes bacterial inhibitors from the medium; the latter is standardised to a pH of 7.4 to 7.5 as in Price's original method.

Summary:— A sample of 205 cases has been selected for analysis. The basis for selection was :-

1. Treatment by single aqueous injections of penicillin.
2. Personal observation during a period of at least 8 weeks after treatment.

Minutiae of treatment and tests of cure are given in detail to emphasise the uniform standards to which every case conformed.
ANALYSIS OF CLINICAL MATERIAL:

In the series of 205 cases now under consideration, all were otherwise healthy young naval ratings of ages 17 to 38 years.

The average duration of urethral discharge was 5 days; extremes 1 to 22 days.

Table III shows the condition on first attendance.

The term "sulphonamide-resistant" is used as a matter of convenience to designate the 25 cases which had been treated unsuccessfully with sulphonamides before examination. All such cases had received a minimum of 25 gms. Sulphathiazole or Sulphadiazine over a period of 5 days or longer.

The majority of cases - 180 - had received no treatment before being referred.

The separation into "anterior" and "posterior" urethritis is an arbitrary one based on the result of the two-glass urine test.

RESULTS OF TREATMENT:

Treatment consisted of a single intramuscular injection of penicillin given in the manner already described. Dosage ranged from 300,000 to 1,000,000 (1 Mega) units. No toxic effects were noted.

In Table IV are summarised the results obtained with each dose of penicillin. The number of cases receiving the higher doses is so small that those
**TABLE III.**

**SHOWING CONDITION BEFORE TREATMENT.**

<table>
<thead>
<tr>
<th>Condition on first examination</th>
<th>Number of cases.</th>
<th>Number of Sulpha-resistant Cases.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A.</strong> Uncomplicated Urethritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior Urethritis</td>
<td>129</td>
<td>6</td>
</tr>
<tr>
<td>Posterior Urethritis</td>
<td>54</td>
<td>16</td>
</tr>
<tr>
<td>Total Uncomplicated Cases</td>
<td>183</td>
<td>22</td>
</tr>
<tr>
<td><strong>B.</strong> Complicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostatitis</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Epididymitis</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Tysonitis</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total Complicated Cases</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Total Cases Examined</td>
<td>205</td>
<td>25</td>
</tr>
</tbody>
</table>
**TABLE IV.**

**SHOWING RESULTS OF TREATMENT.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose of Penicillin (Units)</th>
<th>Number of Cases Treated</th>
<th>Number Relapsing</th>
<th>Number Cured</th>
<th>Cure Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>300,000</td>
<td>49</td>
<td>11</td>
<td>38</td>
<td>77.5</td>
</tr>
<tr>
<td>B</td>
<td>500,000</td>
<td>67</td>
<td>8</td>
<td>59</td>
<td>88.2</td>
</tr>
<tr>
<td>C</td>
<td>600,000</td>
<td>55</td>
<td>4</td>
<td>51</td>
<td>92.7</td>
</tr>
<tr>
<td>D</td>
<td>700,000</td>
<td>9)</td>
<td>1)</td>
<td>8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>800,000</td>
<td>8)</td>
<td>2)</td>
<td>6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>900,000</td>
<td>34)</td>
<td>5)</td>
<td>29)</td>
<td>85.3</td>
</tr>
<tr>
<td></td>
<td>1,000,000</td>
<td>8)</td>
<td>2)</td>
<td>6)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>205</td>
<td>28</td>
<td>177</td>
<td>86.4</td>
</tr>
</tbody>
</table>
receiving 700,000, 800,000, 900,000 and 1,000,000 units are shown as 1 group — group D in the Table — comprising 34 cases.

It appears from these results that a dose of 600,000 units was the most effective, curing 51 of 55 cases treated. (Group C).

The small number of cases treated at the higher dosage levels do not permit of any conclusion as to the upper limit of effective dosage. On the other hand the results in Group A (300,000 units) show that this amount is insufficient to produce consistent results.

INDIVIDUAL RESPONSE TO TREATMENT:—

Disappearance of gonococci from smears was the subject of much attention in the early days of penicillin therapy. It has been my experience that the actual time of disappearance is fairly constant at 4-6 hours from the commencement of treatment whatever method is employed. There appears to be no relation between the time of the first negative smear and the outcome as to cure or failure. Gonococci may disappear by the fourth hour, discharge may cease soon afterwards, only to be followed in a few days by relapse. Conversely the organism may be demonstrable for 3-4 days, the discharge subsiding gradually, and complete and lasting cure may result. In serial smears it is possible to observe a variety of morphological changes in the organism — swelling,
disintegration, "ghost-forms" inside pus cells - before final disappearance.

As I attached little importance to the time taken to attain a negative smear, I was not surprised on consulting the case-records of the present series to find that few detailed observations had been recorded.

Of the 130 outpatients, none had smears taken before the seventh post-treatment day unless they returned prior to this on account of failure of the treatment.

72 cases treated as in-patients had negative smears 24 hours after treatment; the remaining 3 cases showed negative smears at 12 hours, with temporary reversion to positive at 24 and 36 hours. At 48 hours all were negative and remained so during the follow-up period.

Serial smears were examined at hourly intervals in 30 cases; of these, 25 became negative at the 5th and 6th hours. Such results are in close agreement with those obtained with multiple-injection techniques.

Clinical improvement denoted by abatement of the discharge and relief from such subjective symptoms as dysuria and frequency, commenced about 3 hours after injection. Discharges originally purulent had become less profuse and mucopurulent or mucoid by the 4th or 5th hour in all cases observed.
PERSISTENCE OF SYMPTOMS IN CURED CASES:

Table V. shows that by no means all cases subsequently passing the tests of cure became symptom-free immediately after treatment. In the Table 'symptoms' indicate either a mucoid to mucopurulent discharge, or threads or haze in 1 or both glasses in the two-glass test. Urethral smears showed pus cells; a few contained gram-positive organisms in addition; none showed gonococci.

As already explained, the majority of the cases were re-examined for the first time on the seventh day after treatment. Thus no estimate can be made of the proportion becoming symptom-free on any given day in the first week. For this reason the 151 cases clinically clear on the seventh day are shown in Table V. as having symptoms for 0.6 days.

The Table shows that no less than 26 of the 177 cured cases (14.7%) had symptoms and signs of urethritis during surveillance. In 2 cases such urethritis persisted for over 3 weeks.

Sternberg and Turner (1944) previously cited, reported similar findings in 20% of their cases.
TABLE V.

Showing Persistence of Symptoms in 177 cured cases.

<table>
<thead>
<tr>
<th>Days</th>
<th>0 - 6</th>
<th>7 - 13</th>
<th>14 - 20</th>
<th>over 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>showing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptoms.</td>
<td>(151)</td>
<td>26</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

"Symptoms" = (1) Discharge Negative for Gonococci and/or (2) Shreds or haze in urine.
It is impossible to dogmatise on the reason for the persistence of symptoms in these cases. For purposes of treatment I regarded all those showing symptoms on the 7th day as suffering from a residual urethritis following elimination of the gonococcus.

They were instructed to drink 5 pints of water daily, avoid alcohol, and, most important of all, to avoid "squeezing up" to look for urethral discharge. The latter practice I found to be a common one among naval ratings, and one which died hard. Resulting as it does in much needless trauma, it may of itself be sufficient to institute a mild non-specific urethritis with mucoid discharge in a previously healthy urethra. It is not surprising therefore that it should perpetuate symptoms in a urethra not yet fully recovered from an acute inflammatory process.

Only if the patient complained of subjective symptoms such as dysuria did I prescribe a simple alkaline mixture in conjunction with the above régime.

On re-examination a week later 21 of those showing symptoms on the 7th day had become symptom-free. The remaining 5 were instructed to continue as before and report for re-examination in another week.

On the 21st post-treatment day, the two cases having a persistent mucoid discharge were prescribed urethral irrigations with a lotion of
1:10,000 potassium permanganate twice daily. One became clinically clear after 7 days of such treatment, the other required irrigations for 14 days.

The explanation of such occurrences, which have been noted by other observers, is not clear.

I see no reason why an infection of non-specific urethritis acquired at the same time as gonorrhoea may not be the cause of persistent symptoms in a proportion of cases of gonorrhoea successfully treated with penicillin.

Jefferiss and McElligott (1943) are among the many writers who have noted a similar persistent urethritis after treatment of gonorrhoea with the sulphonamides; they suggest that such an occurrence may frequently be the result of a concomitantly-acquired non-specific infection.

It is pertinent to recall that the consensus of expert opinion indicates that in the treatment of non-specific urethritis, penicillin is of much less value than sulphonamides; one would therefore expect to find a larger proportion of "residual urethritis" among gonorrhoea cases receiving penicillin than in those treated with sulphonamides.

The important lesson to be learnt is that persistence of symptoms per se is not an indication for further penicillin therapy; the majority of cases require no more than simple advice regarding hygiene, and increased fluid intake.
Table IV. shows that a total of 28 cases relapsed after treatment; these will now be considered in more detail.

It has already been stated that of the 75 inpatients, 72 had negative smears at 24 hours, 3 at 48 hours after treatment. Similar information is not available regarding the 130 cases treated as outpatients, but all cases relapsing after treatment were emphatic that their discharge had disappeared or at least markedly abated during the first few days after treatment. Thus it is reasonable to assume that no case failed to derive some benefit, if only temporary, from the treatment. In other words no case could be classed as a "non-response" to penicillin.

Diagnosis of relapse:- Only one case failed to show clinical signs; he successfully passed all tests up to 8 weeks after treatment, and was instructed to report for final examination at the 12th week. He returned on the 10th week, when he was found to have a prostatic smear and culture showing gonococci. As his case is of some interest it is recorded in detail at the end of this section.

The remaining 27 cases showed unequivocal clinical signs of infection, gonococci being readily demonstrated in smears of the urethral discharge. Several admitted sexual intercourse after treatment and so may have become reinfected; all are shown in the Tables as relapses.
Time at which relapse occurred:

Table VI. shows the number of days after treatment on which relapses were diagnosed.

Some cases were unable to report for examination until several days after noticing a recurrence of symptoms; the longest interval between re-appearance of symptoms and diagnosis was 4 days in 2 cases. All others reported within 48 hours of the reappearance of symptoms.

It is apparent from the Table that dosage exerts no influence on the time taken to relapse; 1 case receiving 600,000 units relapsed on the 70th day while all 5 cases relapsing after larger doses did so by the 10th day.

The Table also shows that the bulk of relapses had occurred by the end of the second week after treatment. This point is clearly demonstrated in Table VII.

Conditions associated with relapse:

In Table VIII. are summarised the findings in the 28 cases relapsing after treatment. As examination comprised inspection of the external genitalia and rectal palpation only, no opinion can be expressed regarding the incidence of such conditions as Littritis. In the majority of relapses no complications are found, I am of the opinion that the passage of instruments into an inflamed urethra is a procedure as harmful as it is unnecessary at this time.
**TABLE VI.**

Showing time (in days) after Treatment at which Relapses were diagnosed.

<table>
<thead>
<tr>
<th>Dose of Penicillin (Units)</th>
<th>Time in Days.</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>13</th>
<th>14</th>
<th>16</th>
<th>21</th>
<th>70</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>300,000</td>
<td></td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>500,000</td>
<td></td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>600,000</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>700,000 to 1,000,000</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Number of Cases Relapsing</td>
<td></td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>28</td>
</tr>
</tbody>
</table>

* Detailed Case History on page .70.

---

**TABLE VII.**

Summary of Table VI.

<table>
<thead>
<tr>
<th>Days after Treatment</th>
<th>Number of Cases relapsing</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to 7</td>
<td>18</td>
</tr>
<tr>
<td>8 to 14</td>
<td>7</td>
</tr>
<tr>
<td>15 to 21</td>
<td>2</td>
</tr>
<tr>
<td>Over 21</td>
<td>1</td>
</tr>
<tr>
<td>Total number of Relapses</td>
<td>28</td>
</tr>
</tbody>
</table>
The Table requires no further comment beyond a statement that "Prostatitis" implies a palpably enlarged and tender gland with or without constitutional symptoms. It is apparent that the presence of complications is not the only factor in determining relapse.

Response of relapses to further treatment:

The 28 cases relapsing after initial treatment were given a second injection of penicillin in the same dose, immediately on diagnosis.

21 returned to duty forthwith, with instructions to return in a week, or immediately their symptoms recurred; 5 cases with complications were admitted to the ward for observation.

Table IX shows the effect of further treatment on cases relapsing after the initial injection. The three cases failing to respond to the 2nd injection all had poorly-draining foci of infection, viz., 1 Tysonitis, 1 meatal stenosis; 1 infected parameatal sinus. All received a third injection of 600,000 units penicillin in addition to local treatment appropriate to the condition.

Such conditions as abscess of Tyson’s gland and infection of parameatal sinuses are notoriously liable to relapse. In several such cases treated with penicillin I had seen rapid and permanent cure without the necessity for recourse to drainage or local treatment of any kind. For this reason local measures were not employed in the present cases until they had failed
TABLE VIII.
Clinical Findings in Relapse.

<table>
<thead>
<tr>
<th>Conditions associated with Relapse</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostatitis</td>
<td>4</td>
</tr>
<tr>
<td>Tyson's Gland Abscess</td>
<td>1</td>
</tr>
<tr>
<td>Meatal Stenosis</td>
<td>1</td>
</tr>
<tr>
<td>Infected Parameatal Sinus</td>
<td>1</td>
</tr>
<tr>
<td>Urethritis alone</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
</tr>
</tbody>
</table>

TABLE IX.
Response of Relapses to Further Treatment.

<table>
<thead>
<tr>
<th>Cases Treated</th>
<th>1st Injection</th>
<th>2nd Injection</th>
<th>3rd Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>205</td>
<td>28</td>
<td>3*</td>
</tr>
<tr>
<td>Cases Relapsing</td>
<td>28</td>
<td>3</td>
<td>Nil</td>
</tr>
</tbody>
</table>

* Appropriate local Treatment in addition.
to respond to 2 injections of penicillin.

Failures of this kind do not constitute relapse in the strict sense; rather are they the result of reinfection of the urethra from a focus of infection inaccessible to the drug carried in the bloodstream.

It is to be clearly understood that I do not advocate the neglect of local treatment aimed at securing free drainage in all cases showing readily-accessible foci. On the contrary such conditions should be dealt with radically when first seen; the cases here described were treated at a time when it was intended to demonstrate exactly what single injections of penicillin could and could not do in such conditions. As a matter of interest 3 of 4 cases in this series with infected Tyson's gland ducts responded promptly to a single injection of penicillin, and have remained clinically and bacteriologically cured over a period of 12 weeks.
ILLUSTRATIVE CASES.

(1) Case of Late Asymptomatic Relapse:-

Case 156. Naval rating aged 30.

Previous History:- Acute gonorrhoea at age 19 treated at a civil clinic with irrigations and "vaccine injections". He attended the clinic at intervals during a period of 3 months and was told he was cured.

Six months later he attended the same clinic on account of a urethral discharge first noticed after straining at stool; he admitted further exposure to possible infection a week before the appearance of the discharge. He received no treatment for his symptoms, which disappeared a few days after it had been explained to him that they were unlikely to be venereal in origin.

No further symptoms until onset of present condition.

Present Illness:-

He was referred on 11.7.45 on account of a urethral discharge of 3 days duration.

Examination:- Profuse purulent urethral discharge, containing numerous gonococci.

Urine = Slight haze and shreds in 1st glass. 2nd glass clear.

External genitalia appear normal. Prostate and Vesicles not examined.

(His consort was examined and found to have acute gonorrhoea; this responded to treatment with sulphonamides at the local civilian clinic.)
Treatment:— 600,000 units penicillin as a single injection on 11.7.45. Returned to duty.

Progress:— 19.7.45 stated that discharge disappeared the morning after his injection. Clinical and bacteriological examination negative.

26.7.45 — Symptom-free. Normal prostatic smear.


10.9.45 — Above tests repeated; all negative.

20.9.45 — Came to request "final test of cure" as he was being drafted away from the area. Clinical examination negative. Urine clear. Urethroscopy — normal urethra. Curved sounds passed to bladder.

21.9.45 — No urethral discharge. Urine clear. Prostate and Vesicles normal to palpation. Prostatic Smear—Moderate number of pus cells; a few intracellular organisms resembling gonococci.

Prostatic Culture:— Characteristic colonies present at 24 hours; These consisted of typical gram-negative diplococci.

24.9.45 — Slight mucopurulent urethral discharge.

Urine (1) Slight haze with threads.
(2) Very slight haze.

Urethral smear — Numerous pus cells and intracellular gonococci.

Denies any exposure since July.

Penicillin 600,000 units intramuscular.

Further Progress:—

1.10.45 — No discharge. Urine clear.
Prostatic smear and culture negative.
8.10.45 - Remains clear.  
Prostatic smear negative.  
Left the area; no information available as to final outcome.

**COMMENT:** Is this a case of genuine relapse or a reinfection following re-exposure to infection? I believe it is a relapse. The patient had no reason to deny re-exposure, and I gained the impression that he was telling the truth. Moreover he had no symptoms or signs whatever until 72 hours after the prostatic massage which yielded a fluid containing gonococci.

The subsequent urethritis is to be explained as a local reinfection of the urethra arising from a focus of infection in the prostate.

The fact that he remained symptom-free and showed negative results to repeated tests over a period of 10 weeks is of the first importance; the conclusion that he was an "asymptomatic carrier" seems inescapable.

What relation the passage of urethral sounds bears to the subsequent demonstration of gonococci it is impossible to say.

The occurrence of even one such case in a series of 205 is a matter for concern; the role of asymptomatic carriers in the dissemination of gonorrhoea has not yet been defined, but it cannot be dismissed as of minor importance until a thorough follow-up of a large number of treated cases has been reported.
(2) Concomitantly - Acquired Syphilis.

Of the cases treated in this series only 1 was later diagnosed as having syphilis.

Case 38: Naval rating aged 22. Single.

This rating exposed himself to infection with an unknown "amateur" on 9.4.45. He denied having had any sexual intercourse during the 6 months preceding this date. On 11.4.45 while at sea he reported sick complaining of burning dysuria and a urethral discharge; he was allowed to rest in his hammock, given copious fluids and a mixture containing gr. xxx each of Sodium Citrate and Sodium Bicarbonate.

On arrival in port he was referred to the clinic where I examined him on 14.4.45. He then had a profuse purulent urethral discharge in which numerous gonococci were demonstrated; both glasses showed haze in 2-glass test; external genitalia, prostate and vesicles showed no abnormality. No lesions of syphilis on skin or mucous membranes. W.R. negative.

Treatment:– 800,000 units penicillin as a single intramuscular injection on 14.4.45.

Admitted to the ward as his ship had proceeded to sea.

Response:– Gonococci absent from smears at 6, 12 and 25 hours. At 48 hours no urethral discharge, urine clear, symptom-free.

Progress:– Clinical and bacteriological findings negative on 23.4.45 and 7.5.45.
14.5.45 - No discharge. Urine clear. Prostatic smear negative. A superficial erosion \( \frac{3}{4} \) cm. in diameter is present in the coronal sulcus. No inguinal adenitis; no other lesion on skin or mucous membranes. Patient denies exposure since 9/4/45.


Further Treatment - 10 daily injections 300,000 units penicillin; total 3 Mega units.

Response: Blood W.R. remained negative.

Lesion healed in 10 days.

Has remained clinically and serologically negative for 6 months.

Summary: Exposure 9.4.45.
Penicillin 14.4.45.
Chancre 14.5.45.

Incubation period of syphilis = 35 days.

In this case the administration of 890,000 units of penicillin 5 days after exposure in no sense "masked" the chancre; neither did it prolong the incubation period, as 5 weeks is well within generally accepted normal limits.

It is of interest to note that the patient was quite unaware that he had a chancre; this case demonstrates the value of a thorough examination for surface lesions of syphilis at regular intervals in every case of gonorrhoea.
SUMMARY.

(1) 205 cases were treated with a single aqueous injection of sodium penicillin; 177 (86.4%) were cured. Of the 28 failures, 25 were cured by a second injection.

(2) The best results were obtained with a dose of 600,000 units (Group C, Table IV.), which cured 51 (92.7%) of 55 cases. The upper limit of effective dosage could not be defined; at the lower level 300,000 units was insufficient to attain a cure rate of 80%.

(3) The majority of relapses occurred within a week of treatment; one case of asymptomatic relapse was diagnosed 10 weeks after treatment.

(4) A closed or poorly-draining focus of infection was demonstrated in 7 of the 28 cases relapsing after treatment.

(5) The response of individual cases to treatment was similar to that reported for multiple-injection techniques. 14.7% of the cured cases showed symptoms of urethritis for 7 days or longer after treatment.

(6) One case of syphilis was diagnosed during the period of surveillance; the incubation period was within normal limits.

(7) No toxic effects were noted.
CONCLUSIONS.

(1) A single injection of penicillin in aqueous solution constitutes a simple and effective treatment for gonorrhoea. In order to attain a cure-rate of over 85% a dose of 500,000 units is necessary.

(2) Failure of such treatment does not prejudice subsequent treatment.

(3) Individual response to treatment is similar to that encountered with multiple-injection techniques.

(4) A period of 8 weeks surveillance is insufficient to detect all late relapses.

(5) An asymptomatic carrier state may follow apparently successful treatment.
OBSERVATIONS ON SERUM PENICILLIN LEVELS FOLLOWING
SINGLE INJECTIONS IN AQUEOUS SOLUTION:

The conditions prevailing in a busy venereal disease clinic under Service conditions do not lend themselves to leisurely laboratory investigations. A systematic study of serum penicillin levels was therefore out of the question; cases were selected at random when time was available for carrying out the necessary estimations.

Material: In 35 cases under treatment estimations of penicillin in the serum were made at half-hourly intervals from the time of injection until no penicillin was detectable by the method used. (See below).

Not all of these cases are included in the series reported above. Many of them did not fulfil the criteria for inclusion in the clinical assessment.

Selection of Cases: Serial estimations required as many as 28 blood samples from a single case in the course of 14 hours. Accordingly only ratings volunteering to participate were available; nevertheless no difficulty was encountered in finding a sufficiency of suitable subjects whose only reward was a few days stay in hospital.

Method of estimating penicillin:

No chemical test for penicillin in blood is available but its concentration in the serum can readily be estimated by titrating its bacteriostatic power.
against a suitable (susceptible) test organism. Ideally this would be the gonococcus, but technical difficulties in handling the organism make this impossible.

The micro-method described by Fleming (1944) was used for all the estimations; this is simple and requires but a superficial knowledge of bacteriological technique. I preferred the capillary tube method and adhered rigidly to the technique described by Fleming. The haemolytic streptococcus used was obtained from his laboratory at St Mary's Hospital.

In accordance with Fleming's practice I have expressed all results in terms of the dilutions of the patient's serum completely inhibiting the growth of the Haemolytic streptococcus (Milne). In addition, and to afford a basis of comparison with results obtained by other workers, such serum dilutions are converted to units per c.c. of penicillin.

Such conversion can of course be only approximate; the equivalents are as follows:

<table>
<thead>
<tr>
<th>Serum Dilution</th>
<th>Units per c.c.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/1</td>
<td>0.03</td>
</tr>
<tr>
<td>1/2</td>
<td>0.06</td>
</tr>
<tr>
<td>1/4</td>
<td>0.125</td>
</tr>
<tr>
<td>1/8</td>
<td>0.25</td>
</tr>
<tr>
<td>1/16</td>
<td>0.5</td>
</tr>
<tr>
<td>1/32</td>
<td>1.0</td>
</tr>
<tr>
<td>1/64</td>
<td>2.0</td>
</tr>
<tr>
<td>1/128</td>
<td>4.0</td>
</tr>
<tr>
<td>1/256</td>
<td>8.0</td>
</tr>
<tr>
<td>1/512</td>
<td>16.0</td>
</tr>
<tr>
<td>1/1024</td>
<td>32.0</td>
</tr>
<tr>
<td>1/2048</td>
<td>64.0</td>
</tr>
</tbody>
</table>
RESULTS. The actual readings obtained are shown in the Tables and Graphs on the following pages.

<table>
<thead>
<tr>
<th>Units</th>
<th>Cases</th>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>300,000</td>
<td>11</td>
<td>X</td>
<td>81.</td>
</tr>
<tr>
<td>500,000</td>
<td>8</td>
<td>XI</td>
<td>82.</td>
</tr>
<tr>
<td>600,000</td>
<td>5</td>
<td>XII</td>
<td>83.</td>
</tr>
<tr>
<td>700,000</td>
<td>4</td>
<td>XIII</td>
<td>84.</td>
</tr>
<tr>
<td>800,000</td>
<td>4</td>
<td>XIV</td>
<td>85.</td>
</tr>
<tr>
<td>1,000,000</td>
<td>3</td>
<td>XV</td>
<td>86.</td>
</tr>
</tbody>
</table>

Graphs I to VI. on page 87.

In Table XVI., the results are summarised to show:

I. The average time for which a serum inhibition level of 1/8 (= approx. 0.25 units / c.c.) was maintained at each dosage level.

II. The average time for which penicillin remained detectable in the serum. (= approx. 0.03 units / c.c.).

It is apparent that a concentration of 0.25 units per c.c. was maintained for an average of 5.8 hours following a dose of 300,000 units, this time being extended to 7.5 hours with a dose of 1,000,000 units. Concentrations of 0.03 units per c.c. were observed for 9.6 and 13.16 hours with 300,000 and 1,000,000 units respectively.

I am not aware of any detailed report on serum levels following single doses of this order; there are therefore no figures with which the above may be compared.

They may, however, be considered in conjunction with the work of Lloyd-Jones, Maitland and Allen (1945), and of Kirby, Leifer and Martin (1945) to which reference has already been made. It is apparent from
these reports that cure-rates of 90 to 95% are associated with either of two types of serum penicillin levels. These are a level of 0.25 units per c.c. maintained for 9½ hours, or a level of 0.04 units per c.c. maintained for 12 hours.

Table XVI. shows that no case conformed to the first type; however 3 cases receiving 1,000,000 units showed levels of 0.03 units per c.c. for over 12 hours, thereby conforming to the second type. All 35 cases responded satisfactorily to treatment.

The serum levels observed for each dosage vary narrow within limits; they may thus be considered representative of the 205 cases assessed clinically, of whom the majority received a dose of 600,000 units or less. It appears reasonable to assume that few of the treated cases attained either of the types of serum level associated with a high cure-rate. Nevertheless a cure-rate of over 85% was observed, this figure rising to over 90% with a dose of 600,000 units.

COMMENT:— There is no demonstrable relationship between serum levels and clinical results in patients under treatment. The reason for the discrepancies alluded to above is not clear. It appears possible that high serum levels present for a short time may, as Bigger suggests, be as efficacious as lower levels maintained over a longer period; concentrations as high as 64 units per c.c. were estimated in the cases referred to above.
# Table X.

Serum Penicillin Levels in Eleven Cases

Dose = 300,000 Units.

<table>
<thead>
<tr>
<th>Case</th>
<th>Hours after administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

Dilutions of Serum Inhibiting Growth of Test Organism.
**TABLE XI.**

Serum Penicillin Levels in Eight Cases.

Dose = 500,000 Units.

| Case | ½ | 1 | 1½ | 2 | 2½ | 3 | 3½ | 4 | 5 | 5½ | 6 | 6½ | 7 | 7½ | 8 | 8½ | 9 | 9½ | 10 | 10½ |
|------|---|---|----|---|----|---|----|---|---|----|---|----|---|----|---|----|---|----|---|
| 1    |   |   |     |   |     |   |     |   |   |     |   |     |   |     |   |     |   |     |   |
| 2    |   |   |     |   |     |   |     |   |   |     |   |     |   |     |   |     |   |     |   |
| 3    |   |   |     |   |     |   |     |   |   |     |   |     |   |     |   |     |   |     |   |
| 4    |   |   |     |   |     |   |     |   |   |     |   |     |   |     |   |     |   |     |   |
| 5    |   |   |     |   |     |   |     |   |   |     |   |     |   |     |   |     |   |     |   |
| 6    |   |   |     |   |     |   |     |   |   |     |   |     |   |     |   |     |   |     |   |
| 7    |   |   |     |   |     |   |     |   |   |     |   |     |   |     |   |     |   |     |   |
| 8    |   |   |     |   |     |   |     |   |   |     |   |     |   |     |   |     |   |     |   |
TABLE XII.

Serum Penicillin Levels in Five Cases.

Dose = 600,000 Units.

<table>
<thead>
<tr>
<th>Case</th>
<th>1/2</th>
<th>1</th>
<th>1 1/2</th>
<th>2</th>
<th>2 1/2</th>
<th>3</th>
<th>3 1/2</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>8 1/2</th>
<th>9</th>
<th>9 1/2</th>
<th>10</th>
<th>10 1/2</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1/32</td>
<td>1/16</td>
<td>1/32</td>
<td>1/16</td>
<td>1/32</td>
<td>1/16</td>
<td>1/32</td>
<td>1/16</td>
<td>1/32</td>
<td>1/16</td>
<td>1/32</td>
<td>1/16</td>
<td>1/32</td>
<td>1/16</td>
<td>1/32</td>
<td>1/16</td>
<td>1/32</td>
<td>1/16</td>
</tr>
<tr>
<td>2</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
</tr>
<tr>
<td>3</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
</tr>
<tr>
<td>4</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
</tr>
<tr>
<td>5</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
<td>1/64</td>
<td>1/32</td>
</tr>
</tbody>
</table>
TABLE XIII.

Serum Penicillin Levels in Four Cases.

Dose = 700,000 Units.

<table>
<thead>
<tr>
<th>Case</th>
<th>Hours after administration.</th>
<th>1/2</th>
<th>1 1/2</th>
<th>2</th>
<th>2 1/2</th>
<th>3</th>
<th>3 1/2</th>
<th>4</th>
<th>4 1/2</th>
<th>5</th>
<th>5 1/2</th>
<th>6</th>
<th>6 1/2</th>
<th>7</th>
<th>7 1/2</th>
<th>8</th>
<th>9</th>
<th>9 1/2</th>
<th>10</th>
<th>10 1/2</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>1/32</td>
<td>1/16</td>
<td>1/8</td>
<td>1/4</td>
<td>1/2</td>
<td>2</td>
<td>2 1/2</td>
<td>3 1/2</td>
<td>4 1/2</td>
<td>5</td>
<td>6 1/2</td>
<td>7 1/2</td>
<td>8 1/2</td>
<td>9 1/2</td>
<td>10</td>
<td>10 1/2</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1/32</td>
<td>1/16</td>
<td>1/8</td>
<td>1/4</td>
<td>1/2</td>
<td>2</td>
<td>2 1/2</td>
<td>3 1/2</td>
<td>4 1/2</td>
<td>5</td>
<td>6 1/2</td>
<td>7 1/2</td>
<td>8 1/2</td>
<td>9 1/2</td>
<td>10</td>
<td>10 1/2</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1/32</td>
<td>1/16</td>
<td>1/8</td>
<td>1/4</td>
<td>1/2</td>
<td>2</td>
<td>2 1/2</td>
<td>3 1/2</td>
<td>4 1/2</td>
<td>5</td>
<td>6 1/2</td>
<td>7 1/2</td>
<td>8 1/2</td>
<td>9 1/2</td>
<td>10</td>
<td>10 1/2</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>1/32</td>
<td>1/16</td>
<td>1/8</td>
<td>1/4</td>
<td>1/2</td>
<td>2</td>
<td>2 1/2</td>
<td>3 1/2</td>
<td>4 1/2</td>
<td>5</td>
<td>6 1/2</td>
<td>7 1/2</td>
<td>8 1/2</td>
<td>9 1/2</td>
<td>10</td>
<td>10 1/2</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**TABLE XIV.**

**Serum Penicillin Levels in Four Cases.**

*Dose = 800,000 Units.*

<table>
<thead>
<tr>
<th>Case</th>
<th>Hours after administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/8</td>
</tr>
<tr>
<td>1</td>
<td>1/4</td>
</tr>
<tr>
<td>2</td>
<td>1/4</td>
</tr>
<tr>
<td>3</td>
<td>1/4</td>
</tr>
<tr>
<td>4</td>
<td>1/4</td>
</tr>
</tbody>
</table>
TABLE XV.

Serum Penicillin Levels in Three Cases

Dose = 1,000,000 Units.

<table>
<thead>
<tr>
<th>Case</th>
<th>Hours after administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1/2 1/3 1/4 1/5 1/6 1/7 1/8 1/9 1/10 1/11 1/12 1/13 1/14</td>
</tr>
<tr>
<td>2</td>
<td>1/32 1/64 1/128 1/256 1/512 1/1024 1/2048 1/4096 1/8192 1/16384 1/32768</td>
</tr>
<tr>
<td>3</td>
<td>1/32 1/64 1/128 1/256 1/512 1/1024 1/2048 1/4096 1/8192 1/16384 1/32768</td>
</tr>
</tbody>
</table>

Dilutions of Serum Inhibiting Growth of Test Organism.
BLOOD LEVELS IN REPRESENTATIVE CASES FOLLOWING SINGLE INJECTIONS OF PENICILLIN

DILUTION of PATIENT'S SERUM INHIBITING STREPTOCOCCUS (CAME)
TABLE XVI.
To Show Duration in Hours of Serum Levels with Increasing Doses of Penicillin.

<table>
<thead>
<tr>
<th>Dose of Penicillin (Units)</th>
<th>Case</th>
<th>Duration in Hours of 0.25 units per c.c. Serum Level</th>
<th>Duration in Hours of 0.03 units per c.c. Serum Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>300,000</td>
<td>1</td>
<td>6.5</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>6.5</td>
<td>10.5 Average</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>6.5</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>5.5</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>5.5</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>5.5</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>5</td>
<td>9.5</td>
</tr>
<tr>
<td>500,000</td>
<td>12</td>
<td>6.5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>6.5</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>6.5</td>
<td>8.5 Average</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>6.5</td>
<td>11.5</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>6.5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>600,000</td>
<td>20</td>
<td>6.5</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>5.5 Average</td>
<td>10.5 Average</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>6.5</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>6.5</td>
<td>10.3</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>6</td>
<td>10.5</td>
</tr>
<tr>
<td>700,000</td>
<td>25</td>
<td>6.5 Average</td>
<td>11.5 Average</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>6.5</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>6.5</td>
<td>10.75</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>5.5</td>
<td>10.5</td>
</tr>
<tr>
<td>800,000</td>
<td>29</td>
<td>6</td>
<td>11.5 Average</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>6.5</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>6.5</td>
<td>11.5</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>5.5</td>
<td>11.87</td>
</tr>
<tr>
<td>1,000,000</td>
<td>33</td>
<td>8 Average</td>
<td>13.5 Average</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>7.5</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>7.5</td>
<td>13.16</td>
</tr>
</tbody>
</table>
It has to be remembered that every treatment so far introduced for gonorrhoea has followed a set course of enthusiastic reception, more gradual evaluation, and eventual decline in general favour.

One important reason for this is the fact that, at least in the male, the uncomplicated disease is self-limiting. If not hindered by such fifth columnists as alcohol, overexertion, or sexual excitement, the natural defences of the host overcome the infection and bring about spontaneous cure in a large proportion of cases.

Viewed broadly, the greatest advantage offered by sulphonamide and now penicillin therapy is the speed with which the gonococcus is attacked. The majority of infections are overcome before the onset of complications, and before the host has any considerable opportunity to transmit the disease to others.

The present phase is one of sober evaluation in which the early enthusiastic claims have for the most part been confirmed. However the shadows no less than the highlights merit consideration; important gaps in knowledge concerning the drug have yet to be filled.

Thus the ultimate fate of those patients - the majority - who show a prompt response to treatment and are apparently cured, remains unknown. To distinguish clinical or symptomatic cure from the biological cure
which is the real aim of therapy has been the concern of clinicians since Neisser first demonstrated the causative organism. Such a distinction assumes even greater importance today, when penicillin can banish signs and symptoms overnight. The subject of cure has already been considered; it is sufficient here to recall the work of Koch, Mathis and Geiger. This did much to disturb the general complacency by showing that a substantial proportion of clinically cured cases had failed to attain true biological cure, and remained for long periods asymptomatic carriers. Cases such as that described in this thesis indicated that with penicillin treatment this danger remains; its extent can be defined only by means of careful cultural examination of a large number of treated cases.

The activity of Penicillin against the spirochaete of syphilis poses a new problem in gonorrhoea therapy; there can be no doubt that in certain circumstances the course of concomitantly-acquired syphilis can be significantly modified. Already there are indications that fractions of penicillin differ in their activity against the spirochaete and the gonococcus; the eventual use of that penicillin which is lowest in spirochaeticidal power appears to be the only satisfactory solution to the problem of "masking" syphilis by treatment given for gonorrhoea.

When all this has been said, the fact remains that penicillin is by far the most potent remedy at present available for the therapy of gonorrhoea. The
multiple-injection schedules which proved so successful under service conditions are difficult of application in an outpatient clinic. Much effort has been expended in attempts to reduce the inconvenience suffered by civilians in attending for treatment. Allan (1946) has entered a plea for the trial of a single-injection method. More recently Batchelor and associates concluded that 2 injections are necessary if a cure-rate of around 95% is to be attained.

I have long held the opinion that, armed with such a powerful weapon as penicillin, the clinician should be satisfied with nothing less than the completion of treatment with one injection. The ideal treatment for gonorrhoea, as defined by Lloyd-Jones, Donaldson, and Allen, is required to fulfil the following criteria:--

(1) It should be completed with a single injection.
(2) It should entail no toxic effects, including undesirable local reactions at the site of injection.
(3) It should bring about "early cure" in at least 90% of uncomplicated cases, while avoiding the production of asymptomatic carrier states in an appreciable number of "cured" cases.
(4) It should not be liable to produce penicillin-fastness of the responsible gonococcus or otherwise prejudice subsequent treatment in the event of failure.
(5) It should interfere as little as possible with the diagnosis of syphilis acquired concomitantly with gonorrhoea.
(6) It should be readily available and convenient in use.

Several "one-shot" methods are now available which go far towards meeting these requirements.

Leaving aside the use of special vehicles, the
disadvantages of which have already been considered, there remains the single injection of aqueous solutions. Commendable as attempts to emulate the brilliant results obtainable with multiple injections may be, are they really necessary? The difference between a cure-rate of 85% and 95% does not appear to me to be of sufficient practical importance to warrant the additional inconvenience entailed in requiring each patient to submit to two or more injections.

If the results presented in this thesis can be reproduced in a larger number of cases, it is submitted that the single injection of 500,000 or 600,000 units would closely approach the ideal treatment for civilian cases. Such treatment could be expected to cure at least 85%; cases failing to attain cure would have a further 85% chance of recovery following a second injection - there appears to be little or no danger of acquired penicillin resistance. With the advent of purified fractions of penicillin more highly active against the gonococcus, the percentage of cure with one injection will undoubtedly rise still higher.

It may be objected that such a plan is too costly in penicillin. In the near future supplies will be virtually unlimited. Its cost in terms of money is an insignificant item in the total expenditure of a venereal disease service, and is to be set against the saving in industrial man-hours and in travel expenses which would surely follow its adoption.
Hopes have been expressed that oral preparations of penicillin will soon be made available for the treatment of gonorrhoea. As one who has treated cases labouring under the sequelae of ill-advised or unskilful use of the sulphonamides, I cannot share these hopes; not the least advantage of parenteral therapy is that it leaves treatment entirely in the hands of the doctor.

I have been concerned in this thesis to indicate the great advantages to the individual sufferer of penicillin therapy. In company with the newer techniques of public education and case-finding, effcient treatment of the individual case is of first importance in controlling and reducing the incidence of this disease in the community.

Ehrlich's dream has at last come true; its full realisation may yet be responsible for the final overthrow of man's old and stubborn enemy.
SUMMARY.

(1) Penicillin, its properties, mode of action and application to the treatment of gonorrhoea are described.

(2) The results obtained by others are indicated by reference to the literature.

(3) Personal observations on the results of treatment by a single injection in aqueous solution are presented, together with the results of blood level estimations.

(4) The implications of the foregoing are discussed.
REFERENCES


Chain, E. and Duthie, E.S. 1945 Lancet 1: 652.


" " " " 1939 B.M.J. 2: 1080.


" " and Jennings, M.A. 1944 B.J. Surg. 32: 112.


" " 1945 B.M.J. 1: 107.


1944 B " " " " " " 56: 181.


Lees, D. 1931. "Diagnosis & Treatment of V.D." - Edin. 2nd Ed.


" 1946 B B.M.J. 1: 605.


Trumper, M., and Hutter, A.M. 1944 Science 100: 432.

" " and Thompson, G.J. 1946 J.A.M.A. 130: 627.


" " " and Steinberg, S. 1944 V.D.Inf. 25: 229.

" " " " " 1945 " " 26: 1