Bull. Org. mond. Santé }
Bull. Wld Hlth Org. } 1961, **24**, 297-306

Failure to Control Gonorrhoea

T. GUTHE [1]

There is increasing evidence of emerging resistance of the gonococcus to antibiotics, particularly penicillin, but apparent resistance may sometimes be due to concomitant infection with micro-organisms other than the gonococcus, which are not susceptible to this antibiotic. There is also evidence that clinical complications, particularly in the female, are much more frequent than was previously believed to be the case. The incidence of gonorrhoea has increased significantly in many countries in spite of the availability of the "ideal" drug, penicillin. The reasons for the failure to control gonorrhoea in the individual and in the mass of patients are discussed, taking into account a number of factors relating to emerging drug resistance of the gonococcus, insufficient criteria for diagnosis, the possibility of persistence of infection and increased frequency of reinfection.

INCIDENCE PATTERNS

In countries where venereal infections are notified there are recognized limitations to the value of the statistics on their incidence. It is, however, generally acknowledged that the data obtained are *minimum* figures, and that the long-term trends that they show do illustrate a true variation in the reservoir of these infections. Special surveys in the USA have shown that five to ten times more cases of gonorrhoea probably occur than are reported annually in that country. But even without taking this factor into account, gonorrhoea was the third and syphilis the fourth most frequent infection among communicable diseases reported in the USA in 1959. Only measles and scarlet fever and streptococcal sore throats had a higher reported annual incidence. Poliomyelitis came ninth on the list.

The reported incidence of gonorrhoea in different countries in different regions of the world, since 1945, is shown in Fig. 1, 2, 3 and 4, which, for comparative purposes, also show data on early infectious syphilis.

It will be seen that there is a difference between the pattern of gonorrhoea and that of syphilis in the countries where an effort to control them has been made (e.g., the Scandinavian area and the USA). While a steady decline in reported cases of syphilis has taken place in the Americas, in Asia and in Europe, until recently in most countries the initial decline in gonorrhoea had not been maintained, and the incidence of gonorrhoea remained high. (In the African region, the pattern is somewhat different. There is no indication of a downward trend in syphilis, while the long-term component for gonorrhoea shows a decided upward tendency.)

The difference in the syphilis and gonorrhoea patterns in non-African countries is of considerable interest in view of the unique situation that in two major communicable diseases with the same mode of transmission, the same drug—penicillin—has been shown, over 10-15 years, to have been highly effective clinically in individual cases, but has apparently failed, when applied on a large scale, to control one of the diseases—gonorrhoea. Thus gonorrhoea as a health problem of the public was never reduced to the same level as syphilis following the introduction of antibiotics fifteen years ago. The epidemiological and other reasons for this have been discussed elsewhere (Guthe, 1958) and are probably mainly related to the very short incubation period of gonorrhoea as compared with syphilis. Furthermore, a recrudescence of gonorrhoea is currently becoming evident in some areas. The WHO Expert Committee on Venereal Infections and Treponematoses (1960) has pointed to the increase in reported incidence in 15 of 22 countries in the world on the basis of a survey carried out by the World Health Organization.

Age and sex

Another trend which has become evident in recent years in several countries is related to the age and sex distribution of new cases of gonorrhoea: the

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FIG. 1

ANNUAL INCIDENCE OF GONORRHOEA AND EARLY SYPHILIS IN EUROPE PER 100 000 INHABITANTS AGED 15-49 YEARS, 1946-59

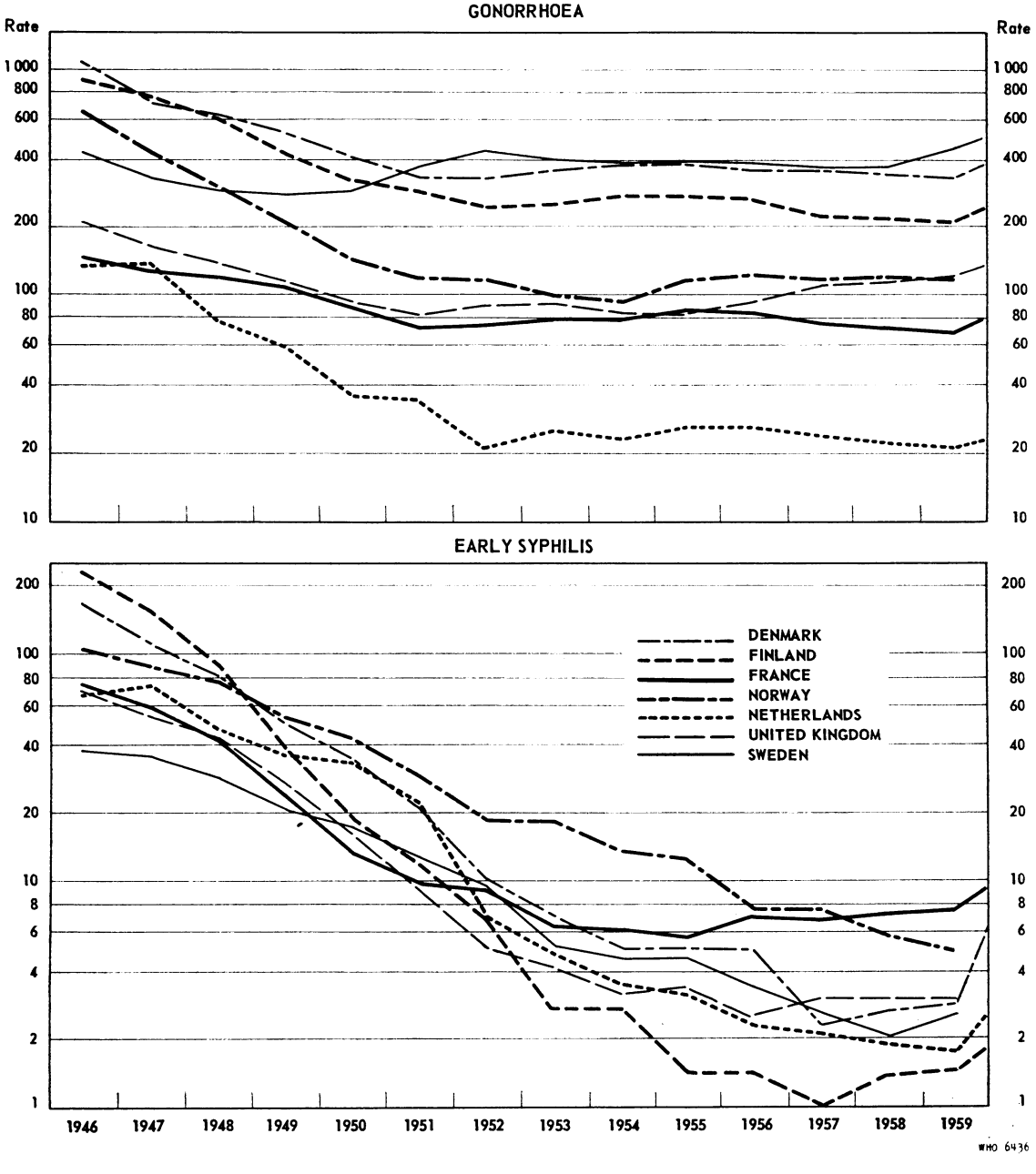


FIG. 2

ANNUAL INCIDENCE OF GONORRHOEA AND EARLY SYPHILIS IN ASIA PER 100 000 INHABITANTS AGED 15-49 YEARS, 1946-59

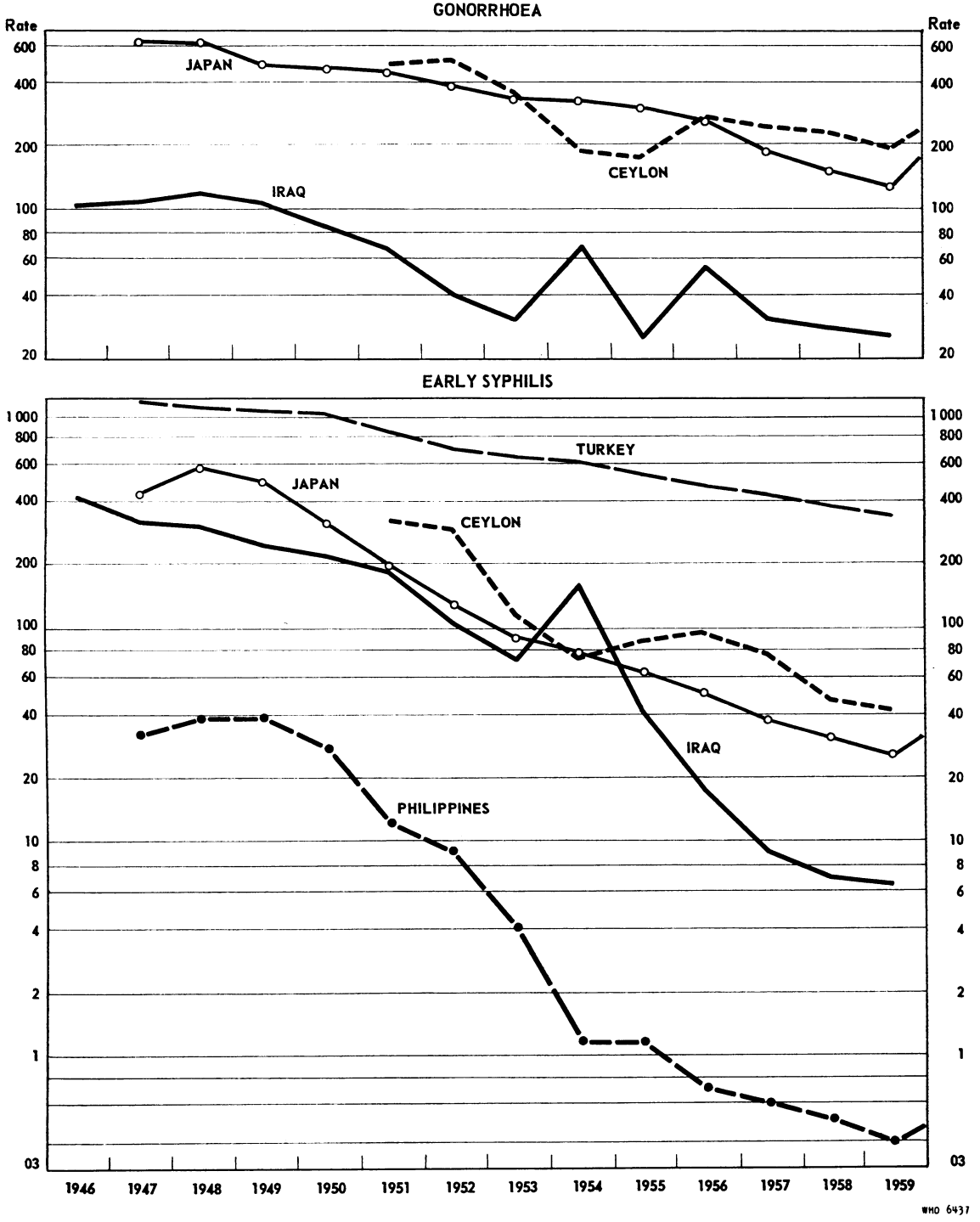
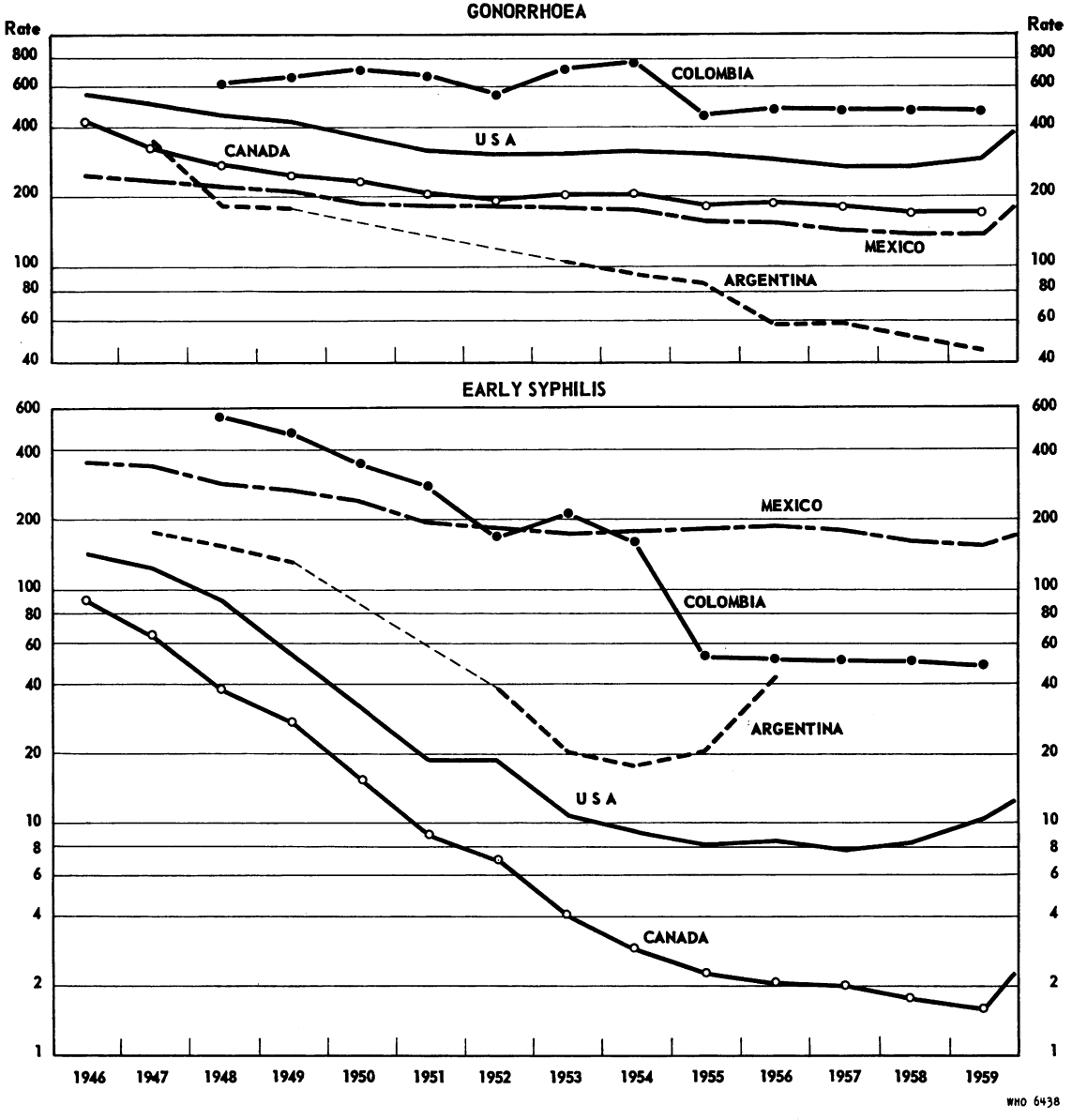


FIG. 3

ANNUAL INCIDENCE OF GONORRHOEA AND EARLY SYPHILIS IN THE AMERICAS PER 100 000 INHABITANTS AGED 15-49 YEARS, 1946-59

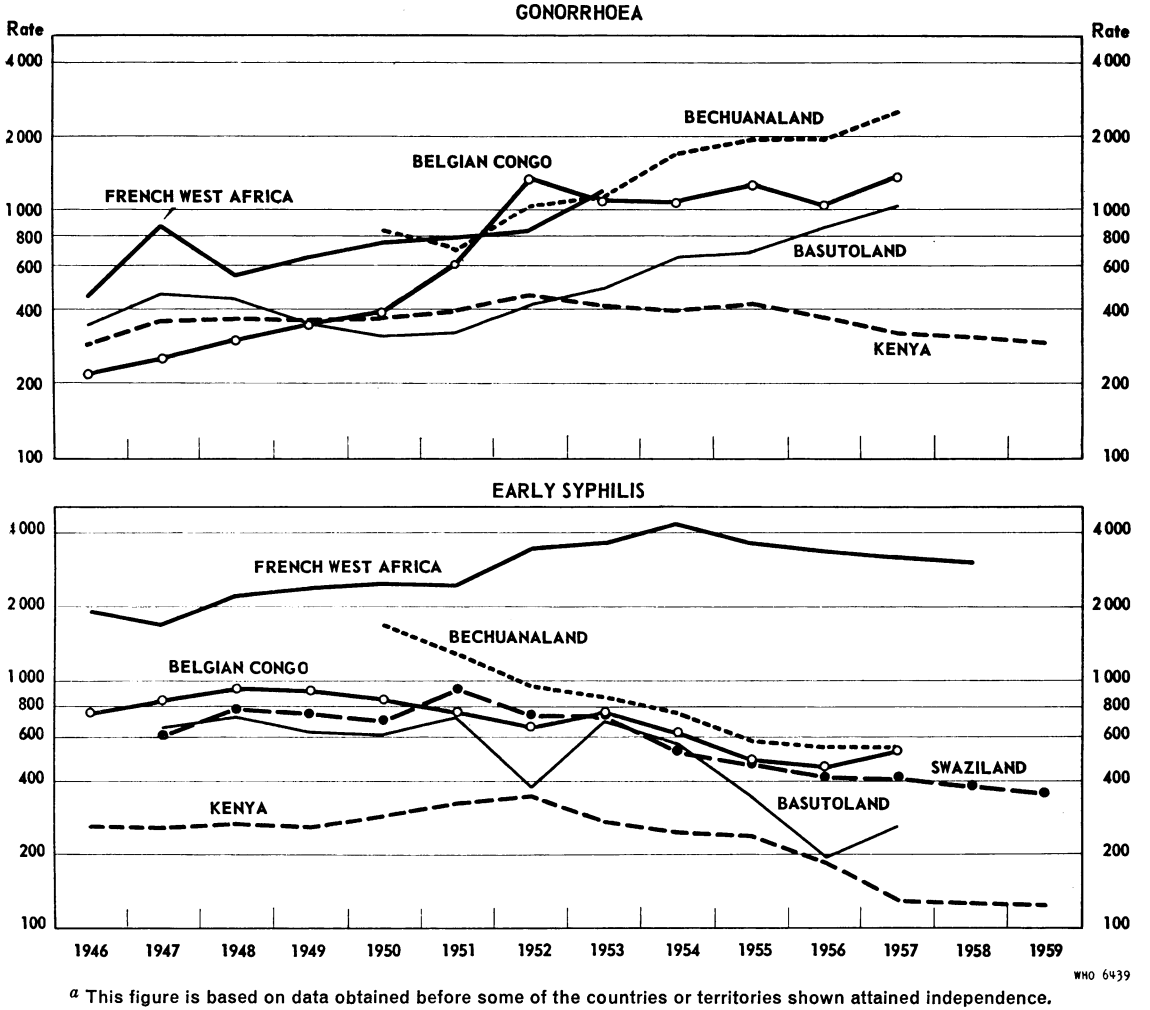


ratio between males and females has varied from 2 : 1 to 4 : 1 in many countries, suggesting the existence of large latent female reservoirs of infection. In addition the incidence of new cases of gonorrhoea is increasing in the lower age-groups, so that this infection is becoming a social problem in the "teenagers"—and even below the 15-19-year age-group. This has been demonstrated in careful studies by several investigators, for instance, in Sweden [1]

[1] See the article by Gisslén, Hellgren & Starck on page 367 of this issue.

FIG. 4

ANNUAL INCIDENCE OF GONORRHOEA AND EARLY SYPHILIS IN AFRICA PER 100 000 POPULATION, 1946-59 [a]



[a] This figure is based on data obtained before some of the countries or territories shown attained independence.

and in the United Kingdom (Willcox, 1958; King & Wisdom, 1960).

Attitude of the public

Yet another trend—perhaps unmeasurable—is the changed public attitude to gonorrhoea which has resulted from the ease and rapid action of antibiotics in the cure of the disease, and from what is believed to be a reduced frequency of complications. An attitude of indifference to the dangers of the disease has in turn resulted in carelessness and less use of precautionary measures. A large proportion of the cases of gonorrhoea are now " repeaters " in special social or ethnic groups, as brought out by several investigators in 1958 in the report of the First WHO Seminar on Venereal Disease Control in the Western Pacific Region [1] and by King & Nicol [2] and others.

VIRULENCE AND CLINICAL ASPECTS

It was suggested in Germany as early as 1953 (Wesener et al., 1953) that a prolongation of the

[1] Unpublished document WPRO 5—WPR/VDT/48.

[2] See the article on page 373 of this issue.

incubation period of gonorrhoea has taken place with the introduction of antibiotics as compared with the situation prior to 1938; this opinion is also held in Sweden (Lodin, 1956). In Finland (Härö & Pätiälä, 1957) and in the USA [1] it was observed in 1957 and 1959 respectively that the reported incubation period stayed within the normal limits, as determined in human experimental infections by Mahoney et al. (1946). It has generally been believed that clinical complications have become markedly reduced in the last twenty years, and there has been speculation as to the extent to which this might be due to systemic chemotherapy, as contrasted with local " traumatic " treatment previously used, or to a change in virulence of gonococcal strains. These beliefs have had little scientific foundation. Recent very careful investigations by Gisslén et al.[2] have, however, shown that gonococcal salpingitis complications in the female occur in 10% and sterility in 3% of the cases. That these complications are not immediately obvious may be due to the fact that most such cases are seen by the surgeon or the gynaecologist, and not by the venereologist, and special investigations are required to bring out this information. It should be noted, therefore, that gonorrhoea remains a dangerous disease of women, although the true etiology of its complications may often remain unrecognized. In the male most investigators agree that prostatitis and epididymitis now occur only perhaps in 1%-2% of cases of gonorrhoea. On the other hand, there are investigators who emphasize the increased incidence of persistent post-gonorrhoeal catarrh as an important " complication ". Thus Gentele et al. (1961) found this condition to occur in 52% of a series of 640 cases of male gonorrhoea.

When penicillin was first used for treatment of gonorrhoea 15-18 years ago, as little as 0.1 to 0.3 mega-unit sufficed to cure acute anterior urethritis in the male. The use of 0.3 mega-unit of long-acting aqueous procaine or benzathine penicillin became standard treatment in many lands in subsequent years. But a WHO clinic survey (Willcox & Guthe, 1957) in 171 ports and major cities of the world in 1955 showed that no less than 84.4% of the participants used 0.6 mega-unit, while 35.6% in Europe, 50% in South Africa and New Zealand, and 21.4% in the USA used 1.2 mega-units or more. Since 1957 cases of gonorrhoea have been reported to fail to respond to penicillin in Australia (1958), Austria (1957), Cambodia (1958), Hong Kong (1958), Japan (1958), Korea (1959), Laos (1958), Philippines (1958), the United Kingdom (1957) and some other countries. In some countries we have the impression that failures or " clinical drug resistance " have started to occur only recently, for instance, in Sweden and Norway.

As regards streptomycin, it has been the drug of choice in the treatment of gonorrhoea for many years in France in preference to penicillin, but only few data are available. On the other hand, in Italy (Chiarenza, 1954) 97% of 421 cases were cured with 1 g of streptomycin in 1951, while the same dosage in 1954 gave a failure rate of 27%. The failure rates increased in the United Kingdom from 1954 to 1956 from 2.5% to 7% with 0.5 g in acute anterior male urethritis.[3] Cases are also reported in the literature resistant to as much as 15 g of streptomycin (Martres, Bonjean & Phillip, 1959). From a world standpoint, it should be noted that streptomycin has been used to a relatively small extent in the therapy of gonorrhoea as compared with penicillin.

The reasons for " clinical resistance " or the failures with penicillin treatment must be appraised in the light of a number of difficulties,[3, 4] particularly those related to incomplete criteria for diagnosis, the possibility of persistence of infection and the increased frequency of reinfection.

In a very thorough study (Hughes & Carpenter, 1948) in the USA of 216 so-called penicillin-resistant male cases of gonorrhoea, only 9.3% were found to be actually infected with the gonococcus, the remainder being cases of non-gonococcal urethritis.

Persistence of infection is another reason for observed failures, and this may be due to failure of penicillin to reach the focus in adequate amounts because of deterioration of the preparation, too short a blood duration level (such as may be obtained with aqueous crystalline penicillin G), or too low a blood concentration (such as is sometimes obtained with benzathine penicillin). It is noticeable that no adequate scientific study has so far been published correlating the *in vitro* susceptibility of the gonococcus with the level and duration of the penicillinaemia and the clinical findings in the same series of patients. Failures may also be due to a low renal elimination threshold, abnormal penicillin metabolism, presence of penicillinase-producing micro-organisms in nor-

[1] See the article by Carpenter on page 321 of this issue.
[2] See the article on page 367 of this issue.
[3] See the article by Willcox on page 307 of this issue.
[4] See the article by Carpenter on page 321 of this issue.

mal or abnormal flora of the host, and other factors. Limitations, in the female, of present diagnostic techniques will also favour the persistence and perpetuation of the infection in the individual and in the community. It remains to be seen what practical advantages can be obtained in gonorrhoea control with the introduction of the fluorescent antibody technique for the diagnosis of the gonococcus (Deacon et al., 1960).

Reinfection has been suggested to be more common than before, and recurrences are considered more likely to be reinfections than relapses in the male, in view of the ease of modern therapy. There is also some indication that symptomless male " carriers " of gonococci, as well as symptomless, infected females, may actually be more frequent than was previously believed. The fact that there are no objective means by which to distinguish relapse or persistence of infection from reinfection or superinfection increases the difficulties in establishing criteria for study.

The laboratory findings in the case of lowered streptomycin susceptibility of the gonococcus correlate fairly well with the clinical resistance picture and the dosages required to cure the disease; but the evidence is not so convincing as far as penicillin is concerned, and it is perhaps only since 1957—and to begin with only in some countries and cities—that there has been evidence in the laboratory of the emergence of relatively penicillin-resistant strains of gonococci. The penicillin dosage of 0.6 mega-unit corresponds approximately to a blood concentration which should kill strains of gonococci sensitive below 0.2 u/ml. While strains with this low susceptibility have been demonstrated only recently, clinical failures have been observed for some years. An important question which therefore arises is to what extent non-gonococcal urethral or vaginal infection may actually represent a continuation of a gonococcal infection treated and cured with penicillin. Alpha and gamma streptococci, coliform organisms, *Chlamydozoon oculogenitale* and possibly viruses, pleuropneumonic organisms, *Proteus*, *Pseudomonas*, staphylococci and *Trichomonas vaginalis*, have all been mentioned by Carpenter [1] as causing urogenital infections at an increasing rate in some countries. It has been shown that non-gonococcal urethritis may occur as a primary or secondary infection with concurrent gonorrhoea, and in England in the last decade the number of annually reported cases of non-gonococcal urethritis at dispensaries throughout the country has increased considerably and exceeds the number of cases of confirmed gonorrhoea. It should be recognized that our knowledge of the etiological, clinical and other aspects of non-gonococcal urogenital infections is extremely limited, and there is no evidence that their epidemiological cycle may not be interfering increasingly with that of gonorrhoea at the same time as the gonococcus has gradually become less susceptible to penicillin.

[1] See the article on page 321 of this issue.

MICROBIOLOGICAL ASPECTS

Diagnosis

The amelioration of culture media by Stuart (1946), improvement of transport media by Reyn, Korner & Bentzon [2] and the introduction of fluorescent antibody methods for identifying the gonococcus by Deacon [3] have contributed to refining available diagnostic techniques in recent years. Earlier and more certain diagnoses can now be made in the male and perhaps in the female. However, the advances made so far do not include what is most needed as a contribution by the laboratory to more effective gonorrhoea control—namely, a specific, sensitive serological laboratory test for the early diagnosis of the disease. Nevertheless, progress in this direction has been made by the work of Tauber & Russell, Thayer et al. and Deacon,[4] in which new sensitive polysaccharide and other antigenic components of the " endotoxin " of the gonococcus have been isolated, and which may justify a revision of previous immunological concepts.

Resistance

Reference has been made in this article to " clinical resistance " in the treatment of gonorrhoea. It is obvious, however, that such a phenomenon is basically a quantitative microbiological one of drug resistance, which may have clinical, as well as epidemiological and public health consequences. Drug resistance is defined as an increase in the capacity of micro-organisms to survive the drug which affects them—or, perhaps better, as a decrease in the sensitivity to that drug. Such a decrease in sensitivity may gradually take place as a result of strain selection, with the more susceptible strains being gradually " weeded out " over the years. Mutation might also give rise to less susceptible strains.

[2] Unpublished WHO working document INT/VDT/129.

[3] See the article on page 349 of this issue.

[4] See the articles on pages 385, 327 and 349 of this issue.

SUSCEPTIBILITY OF THE GONOCOCCUS TO PENICILLIN

Reference	Year of study	No. of strains	Percentage of inhibition		Range
			0.05 or less	0.10 or more	
Lankford (1945)	1945	100	100	0	0.005-0.025
Love & Finland (1955)	1945	24	100	0	0.002-0.008
Romansky & Robin (1947)	1947	53	100	0	0.002-0.060
Love & Finland (1955)	1947	104	100	0	0.002-0.033
Love & Finland (1955)	1949	52	96	4	0.005-0.333
Marcuse & Hussels (1954)	1950-52	232	99.6	0.4	0.008-0.125
Schümmer & Hubbes (1951)	1951	100	98	2	0.004-0.125
Love & Finland (1955)	1953-54	106	100	0	0.002-0.033
Thayer et al. (1957)	1955-56	31	78	22	0.005-0.200
Röckl (1959)	1956	—	—	—	mean value 0.0058
Thayer [a]	1957	46	70	30	0.005-0.200
Cradock-Watson et al. (1958)	1957	200	81	19	0.008-0.512
Curtis & Wilkinson (1958)	1957	302	80	20	0.004-0.500
Röckl (1959)	1958	—	—	—	mean value 0.015
Thayer et al.[b]	1959	—	—	—	0.1-0.5
Bjornstad (1959)	1959	—	—	—	0.1-0.3
Carpenter [c]	1960	—	—	—	0.5-3.0
Reyn & Bentzon [d]	1944	90	0.01		1-2
Reyn & Bentzon [d]	1957	206	0.225		
Reyn & Bentzon [d]	1958	250	0.3 (atypical strains)		39 % strains with reduced susceptibility

[a] Personal communication.
[b] See the article on page 327 of this issue.
[c] See the article on page 321 of this issue.
[d] See the article on page 333 of this issue.

Very little fundamental work in this field has been carried out with the gonococcus. Only a comparatively low degree of resistance to penicillin has been experimentally produced, although it was shown as early as 1945 (Bahn, Ackerman & Carpenter, 1945) that the resistance of isolated strains of gonococci could *in vitro* be increased 400 times as compared with the initial tolerance. It is therefore of obvious interest to study the reports of laboratories on possible changes in penicillin susceptibility in different countries since that time. Some findings between 1945 and 1960 are shown in the table above.

There are definite limitations to the conclusions that can be drawn from the information in this table, since there is no internationally agreed methodology for determining the penicillin sensitivity of the gonococcus, and the reproducibility of the methods used has only recently begun to be ascertained in different laboratories under the auspices of WHO. Higher values have, however, been generally found in recent years, and a sensitivity from 0.5 u/ml to 8 u/ml has recently been observed in some gonococcal strains. Of particular interest are the findings at the Gonococcus Centre in Copenhagen (Reyn, Korner & Bentzon, 1958; Reyn & Bentzon [1]), where the susceptibility of preserved strains from 1944 was compared with that of strains isolated in 1957 and subsequently with that of more recently isolated ones. In addition to decreased penicillin susceptibility in a higher proportion of the strains, an increased incidence of " atypical " strains with a low growth rate and altered metabolic patterns was demonstrated. In Great Britain the published observations between 1944 and 1955, dealing with a total of 1022 strains

[1] See the article on page 333 of this issue.

of gonococcus, were studied in regard to penicillin susceptibility (Cradock-Watson et al., 1958). A " two-peak " distribution of the minimal inhibitory concentration of penicillin was found in Great Britain as well as in Copenhagen, and the observations are interpreted as a step-wise change in sensitivity of the gonococcus to penicillin, supporting the hypothesis that the penicillin type of resistance may develop by a series of multiple steps. Similar suggestive evidence of developing penicillin resistance in *Neisseria gonorrhoeae* has become available through investigations in the USA (Hirsch & Finland, 1960) of strains from 1949, 1954 and 1959. Further aspects of the problems in the USA are considered by Thayer et al.[1]

Streptomycin resistance was produced *in vitro* in the USA as early as 1946 after four transfers (Miller & Bahnhoff, 1946). *In vivo* findings up to 1000 μg/ml are now said not to be uncommon in France (Durel & Siboulet, 1959).[2] Strains resistant to more than 2000 μg/ml have recently been demonstrated in Denmark.[3] In the Danish investigations, a negative correlation between penicillin and streptomycin resistance was found in the 1944 strains, but a positive correlation was found in the 1957 strains. It is likely that streptomycin resistance can develop in the gonococcus more quickly than penicillin resistance.

No resistance has been shown so far by gonococci to the tetracycline group of drugs or to the dozen other antibiotics subsequently found to be gonococcicidal to a greater or lesser extent, including erythromycin, chloramphenicol, carbomycin, neomycin, bacitracin, polymyxin B, spiramycin, oleandomycin and kanamycin.

Although it may be convenient to treat the individual clinic patient with new effective antibiotics as they become available, this will hardly solve the problem of gonorrhoea control, which is basically an epidemiological one. The main difficulty is that of case-finding, diagnosing, and treating a large part of the infectious reservoir within the very short incubation period of the disease. Adequate machinery for this would be extensive and very costly. In some countries efforts at " speed-zone " epidemiology and cluster testing have been made; however, in many countries such procedures may not be legally possible. Additional intensive research into the antigenic structure of the gonococcus and the immunology of gonorrhoea may possibly be more profitable and may still lead to sensitive diagnostic tests and an immunizing agent useful in the control of the disease where large reservoirs of infection can be localized. Laboratory, clinical and epidemiological research into the non-gonococcal urethritides is also required. And until further fundamental knowledge becomes available on the matter of microbial drug resistance, that question will continue to bedevil antibiotic therapy.

RÉSUMÉ

Pendant les dix dernières années, la fréquence de la blennorragie est restée élevée en bien des pays, et dans 15 sur 22 d'entre eux, d'après l'enquête effectuée par l'OMS en 1959, elle a augmenté. Dans plusieurs de ces pays, le nombre des cas nouveaux chez les moins de 20 ans est plus important qu'auparavant. Enfin, il existe un important réservoir d'infections non diagnostiquées chez la femme.

Contrairement à l'opinion fréquemment exprimée, à savoir que les complications de la blennorragie avaient disparu avec l'antibiothérapie, des recherches récentes ont montré que la salpingite et la stérilité féminine sont encore très fréquemment des conséquences de la maladie.

Il y a dix ans, 100 000 à 300 000 unités de pénicilline suffisaient pour guérir la plupart des urétrites antérieures aiguës chez l'homme, mais actuellement il faut 600 000 à 1 200 000 unités, ou plus, pour obtenir des résultats semblables. Cette « résistance clinique » à la pénicilline a été constatée à plusieurs occasions en différentes régions et de plus en plus souvent. Il en est de même, mais à un moindre degré, pour la streptomycine. Si l'on recherche les causes de ces échecs, il faut tenir compte de plusieurs facteurs, tels que l'apparition d'une résistance du gonocoque aux médicaments, l'insuffisance des critères de diagnostic, la persistance possible de l'infection et la fréquence accrue des réinfections. En outre, il ne faut pas oublier que des urétrites non gonococciques peuvent accompagner la blennorragie comme infections primaires ou secondaires. De plus en plus, leur cycle épidémiologique peut chevaucher celui de la blennorragie.

La résistance « clinique » du gonocoque à la pénicillinothérapie est essentiellement un phénomène microbiologique quantitatif. Une résistance progressive de *N. gonorrhoeae* à la pénicilline et, d'une façon moindre, à la streptomycine, a été observée pendant un certain temps dans

[1] See the article on page 327 of this issue.

[2] See also the article by Durel et al. on page 343 of this issue.

[3] See the article by Reyn & Bentzon on page 333 of this issue.

différents laboratoires, malgré l'imperfection connue des méthodes utilisées et l'impossibilité de comparer directement les résultats. L'apparition d'une résistance de *N. gonorrhoeae* aux antibiotiques ne peut expliquer l'insuccès de la lutte contre l'infection en tant que problème de santé publique.

Il faut reconnaître que la brève période d'incubation de la maladie ne permet pas de dépister les cas de façon satisfaisante, de diagnostiquer et traiter les malades et les contacts dans les 3 ou 4 premiers jours, conditions indispensables à un travail épidémiologique fructueux et à une lutte réellement efficace; il faut entendre par « lutte efficace » une réduction réelle et progressive du réservoir de l'infection et, par suite, de la fréquence des cas nouveaux.

Si les aspects sociaux de la maladie, y compris la nécessité de mesures d'éducation sanitaire, ne doivent pas être méconnus, il est peut-être plus intéressant d'entreprendre des recherches pour mettre au point, non seulement un test sérologique qui permette un diagnostic précoce, surtout chez la femme, mais aussi un agent immunisant. Les récentes recherches sur les fractions antigéniques de l'endotoxine gonococcique n'excluent pas la possibilité de réaliser de tels progrès, en dépit des idées admises jusqu'à présent sur l'immunologie de la blennorragie.

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