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A WHO STUDY OF TREATMENT SCHEDULES FOR EARLY SYPHILIS IN USE THROUGHOUT THE WORLD

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SYNOPSIS

Ten years have elapsed since penicillin was introduced in the treatment of syphilis. In order to appraise recent trends in syphilotherapy in the world, WHO carried out a detailed study of treatment practices in early syphilis. A questionnaire was circulated to leading venereologists and clinics in the world, and 277 replies were received from 55 countries giving particulars of 294 schedules.

A total of 65.3% of the participants used penicillin alone and 28.9% used it in combination with other drugs. In North America all clinics relied solely on penicillin as against 52.2% in Europe; and procaine penicillin G in oil with aluminium monostearate (PAM) was used in 91% of clinics in the Americas and Asia and in 60.6% of European clinics. The most common dosage of penicillin in all stages of early syphilis was 4.8-6.0 million units; but appreciably larger doses were used in Europe than elsewhere, some 39.4% of schedules using 10.8 million units or more. There were single instances of 36 million units being given. Consolidation treatment was given in none of the North American clinics; seldom in Asia; by about one-third of the participants in Central and South America; and, for secondary syphilis, in 59% of European schedules.

This study shows that with intensive treatment with PAM the saving in drug cost to clinics over the classical courses of arsenic and bismuth may be as much as £4 per case, but the overhead expenses are, of course, not reduced.

First used 10 years ago in the treatment of syphilis, penicillin is now established as the therapeutic agent of choice in this treponematosis. The use of penicillin involves a new principle of syphilotherapy whereby curative doses can often be given before the immunological processes of the host have become fully developed. Previously, when subcurative doses of arsenic and bismuth were given over long periods of time, the immunological background was very different. Physicians accustomed to the latter drugs, therefore, were imbued with the doctrine of consolidation whereby regular treatment had to be given for many months even after seronegativity had

been attained. When penicillin became available, many physicians were, quite understandably, not prepared to abandon their old processes of thought, and in some parts of the world, even today, arsenic, bismuth, mercury, and sometimes penicillin itself are added to the initial use of penicillin as consolidation of the treatment. A few clinics still rely solely on arsenical and bismuth drugs.

The situation is thus not dissimilar to that obtaining immediately after the first World War, when the new arsphenamines had shown themselves to be markedly superior in their treponemacidal powers to the mercury preparations previously in use. The medical literature of the period shows that clinicians were unprepared to abandon the familiar mercury although the curative powers of the arsphenamines were acknowledged to be superior.

Thus Hazen [6] and Harrison [4] recommended neoarsphenamine and mercury for the treatment of early syphilis, and the latter drug was still commended as an alternative to bismuth in 1926 (Harrison).[5] Mercury was used with neoarsphenamine by Baketel [1] and, in his textbook devoted almost entirely to the administration of the then " wonder drug ", room was still found for a quotation from one authority : " In all cases mercury should be regarded as still our sheet anchor in syphilis ".

Doubts concerning the ultimate results were evident, and at that time most authors considered that reversion to seronegativity did not indicate a " cure " unless subsequent observation was prolonged. Thus Hazen [6] wrote : " One of the most difficult things to know about syphilis is to know when the patient is cured, that is permanently cured. Certain it is that when he is Wassermann-negative he is not necessarily well forever ". And Baketel : [1] " We believe that eternal vigilance is necessary in the consideration of a ' cure ' and, as elsewhere expressed, we should for a period of years follow up these cases and watch them carefully through the eyes of the Wassermann reaction ". Harrison [4] likewise wrote : " ... if continuation treatment is necessary after the Wassermann reaction has been converted to negative (and I believe strongly that it is necessary) I think the only reasonable course is not to employ mercury only, but the much more powerful arsenobenzol compounds as well ".

On the other hand, somewhat different views were expressed by Parnell & Fildes [8] in an investigation concerning the treatment of syphilis with arsenical compounds in the British Navy sponsored by the Medical Research Committee. It is refreshing to note that the use of adjuvant mercury was discouraged in these trials. The statement " There is no evidence whatever that syphilis can remain dormant for years, if we are to understand by this that its presence can remain totally undemonstrable... the prolonged period of observation formerly thought to be necessary before cure might be assumed, is not *on the whole* necessary if a case is treated on the lines here adopted " might have been written 30 years later and doubtless was not considered unprovocative at the time.

However, the dose of arsenobenzol compounds used in these trials was a little in excess of one half of one of the three to four courses of arsphenamine and bismuth drugs which later came to be standard treatment for the disease in many parts of the world. Thus this commendable ready acceptance of a new principle of treatment came ultimately to be considered premature. It is of interest to note that the course employed by these workers, whose views were clearly stated with such conviction, was semi-intensive in nature (six injections of 0.45 g of neoarsphenamine being given at intervals of three days). The course used therefore bears some resemblance to that of present-day penicillin therapy, and this may account for the apparently modern approach of the report.

The verdict of history was given in favour of those who displayed caution. Mercury was in due course replaced by bismuth, but until the second World War leading syphilographers (Moore,[7] for instance) still recommended continuous treatment employing arsenic and bismuth drugs for a full year after the serum and cerebrospinal fluid tests had become negative. At this time, in order to try to reduce the military dislocation occasioned by the prolonged courses of treatment given to syphilitic soldiers, the more toxic intensive and semi-intensive schedules were again introduced, but the use of both arsenical and bismuth drugs was found to be necessary. The opportunity which the discovery in 1943 of the efficacy of penicillin in syphilis gave of substituting for these a safe intensive treatment was gratefully accepted by the armed forces.

Today we have a considerable body of evidence by which to judge the effectiveness of penicillin therapy. The world-wide acceptance of the two-year observation period following clinical and serological normality after long-term treatment of early syphilis with arsenic and bismuth has also become general for penicillin therapy, as has the regular use of the diagnostic lumbar puncture as a test of cure. We are thus able to compare the results of short courses of penicillin with those formerly obtained, and are left in no doubt concerning the comparative adequacy of the new treatment.

We now know that a positive serum test for syphilis will revert to negative sometimes months after intensive penicillin treatment has been given for early syphilis, and that a positive serum test does not therefore necessarily indicate activity of the disease. These aspects are covered fully elsewhere in this journal by Idsoe et al. (see page 507); and we are left wondering how far a lack of appreciation of these facts was responsible for the more protracted treatments of former days, which are still perpetuated, albeit in a truncated form, in some clinics today. It is felt that this historical background will to some extent explain the apparent greater reluctance of European clinics in particular, compared with clinics in other parts of the world, to realize the full potentialities of penicillin—a point which emerges repeatedly in the material under study.

The Present Study

Believing that a study of the methods of treatment in force for early syphilis in January 1953 would provide helpful information for the technical discussions on syphilis at the Sixth Health Assembly,[3] WHO circulated a detailed questionnaire to 403 leading venereologists and venereal disease clinics of the world. Replies were received from 277 venereologists and clinics (68.6%) from 55 countries, giving particulars of 294 schedules of treatment (see Annex 1).

TABLE I. PARTICIPANTS IN STUDY AND SCHEDULES RETURNED ARRANGED BY REGION

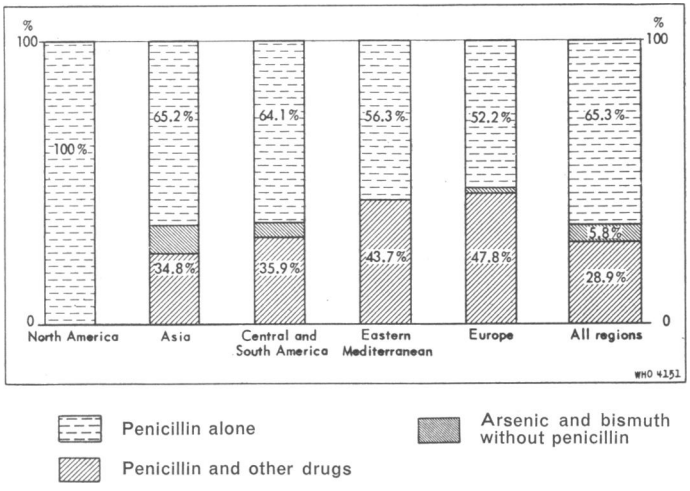
Region	Number of countries	Number of participants	Number of schedules per WHO region	Number of schedules per study region	Number of schedules on which detailed information available
WHO grouping					
Americas	26	57	70	—	—
South-East Asia	7	139	139	—	—
Western Pacific	1	2	2	—	—
Eastern Mediterranean	6	13	16	—	—
Europe	15	66	67	—	—
Total . . .	55	277	294	—	—
Study grouping					
North America	2	26	—	31	31
Central and South America	24	31	—	39	37
Asia	8	141	—	141	88
Eastern Mediterranean	6	13	—	16	16
Europe	15	66	—	67	67
Total . . .	55	277	—	294	239

The grouping of the participating clinics and the number of schedules covered in this study are shown in table I by region and country. For convenience, there has been some geographical readjustment. Europe and the Eastern Mediterranean have retained their WHO regional basis, but Asia in this study includes the South-East Asia Region of WHO with the addition of Malaya. The Americas have been split into a North American area, covering Canada and the USA, and Central and South America, which includes the Caribbean islands.

Use of Penicillin Alone

Faith in penicillin as the sole curative agent for early syphilis was 100% in the North American clinics, and in this area no participant in the study used drugs other than penicillin. Taking the world as a whole, 192, or 65.3%, of the clinics used penicillin alone; 85, or 28.9%, used penicillin in conjunction with other drugs; and 17, or 5.8%, employed metal chemotherapy without penicillin (fig. 1).

FIG. 1. PERCENTAGE OF CLINICS SURVEYED USING PENICILLIN IN THE TREATMENT OF EARLY SYPHILIS (294 SCHEDULES)



It was found that only one clinic (in Europe) used arsenic and bismuth without penicillin as a matter of choice, preferring the older drugs to what was considered still to be an unproved preparation. Sixteen other clinics in Asia and Central and South America also used metal chemotherapy without penicillin, but only because penicillin was not readily available and with the indication that had it been available it would have been used instead. The remaining 277 clinics, or 94.2%, employed penicillin either alone or in combination with other drugs.

Europe appeared to be least confident in the powers of penicillin, for only 52.2% of the 67 European schedules studied employed this antibiotic without other drugs in addition. Table II shows the countries returning four or more schedules, and it will be noted that, as far as Europe is concerned, this lack of faith in penicillin alone was not shared by the northern countries, for no less than 15 of the 17 schedules in this area (88.2%) used penicillin without other assistance.

TABLE II. TOTAL NUMBER OF TREATMENT SCHEDULES AND SCHEDULES CONSISTING OF PENICILLIN ALONE*

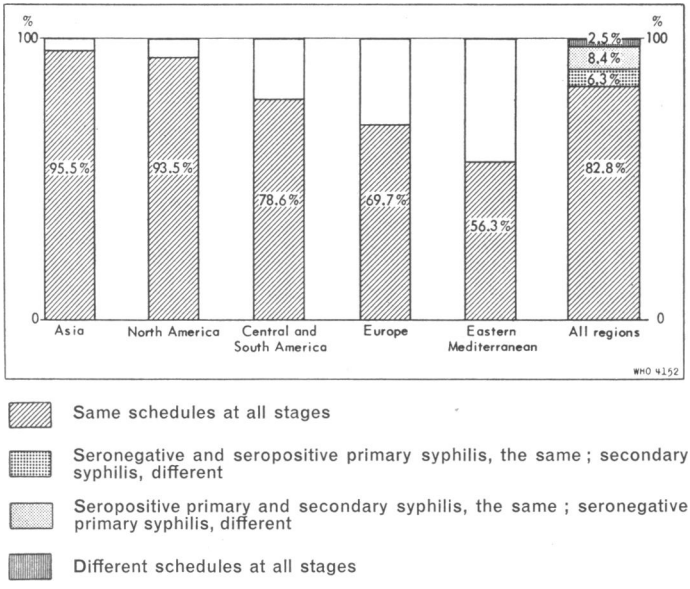
Area and country	Number of schedules returned	Schedules using penicillin alone	
		number	percentage of all schedules
North America			
USA	29	29	100
Other	2	2	100
Total	31	31	100
Central and South America			
Venezuela	5	5	100
Others	34	20	58.8
Total	39	25	64.1
Asia			
Ceylon	45	45	100
Burma	9	9	100
Thailand	17	10	58.8
India	63	22	35.1
Others	7	6	85.7
Total	141	92	65.2
Eastern Mediterranean			
Iraq	6	6	100
Israel	5	1	20.0
Others	5	2	40.0
Total	16	9	56.2
Europe			
Denmark	4	4	100
Finland	4	4	100
Norway	4	4	100
Sweden	5	3	60.0
Belgium	8	4	50.0
Yugoslavia	4	2	50.0
Great Britain	12	5	41.7
Switzerland	5	2	40.0
France	7	2	28.6
Italy	4	1	25.0
Others	10	4	40.0
Total	67	35	52.2
Sum total	294	192	65.3

*** Only countries for which four or more schedules were returned are listed separately.**

Use of Different Schedules in Different Stages of Early Syphilis

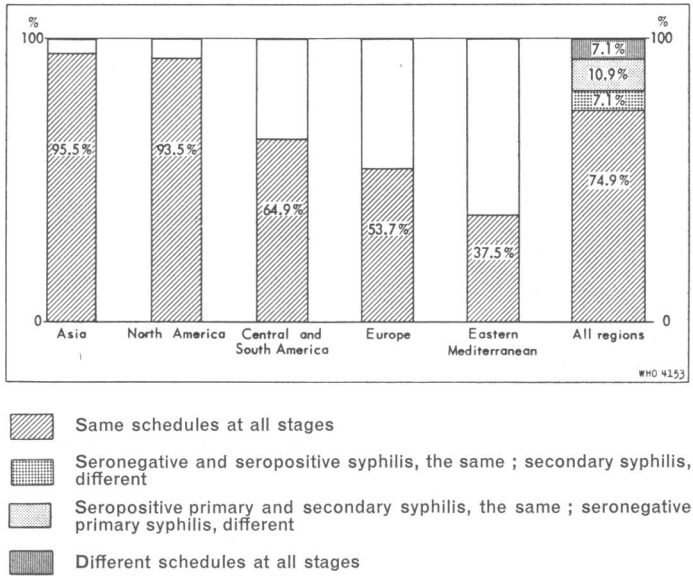
Experience has shown that, for a given dose of penicillin, the treatment-failure rate is highest in secondary syphilis and lowest in seronegative primary syphilis. This observation was also made in the arsenic and bismuth era, and cases of secondary syphilis then received appreciably more treatment than cases of seronegative primary syphilis. Today a number of clinics give a graded dosage of penicillin and/or a graded schedule of consolidation with arsenic and bismuth—when used—for the different stages of early syphilis. The world status in this matter, in respect of both 238 penicillin schedules and 239 schedules of treatment with all drugs used, concerning which detailed information is available, is shown in fig. 2 and 3.

FIG. 2. PENICILLIN SCHEDULES USING SAME TREATMENT FOR ALL STAGES OF EARLY SYPHILIS (238 SCHEDULES)



In areas where penicillin is plentiful it is administratively easier to prescribe the same course of penicillin for all stages of the disease and such, it will be noted, is the practice in North America. Even when penicillin is in relatively short supply, and the dosage used is a " calculated risk " to ensure the greatest good for the greatest number, it is also often administratively more convenient to have one schedule for all forms of early syphilis in areas where diagnostic and treatment facilities are in the process of development; this is apparent in Asia.

FIG. 3. SCHEDULES WITH ALL DRUGS USING SAME TREATMENT FOR ALL STAGES OF EARLY SYPHILIS (239 SCHEDULES)



In general, the same schedules were used in all three stages of early syphilis in nearly all the clinics of North America and Asia and the least often in Europe and the Eastern Mediterranean.

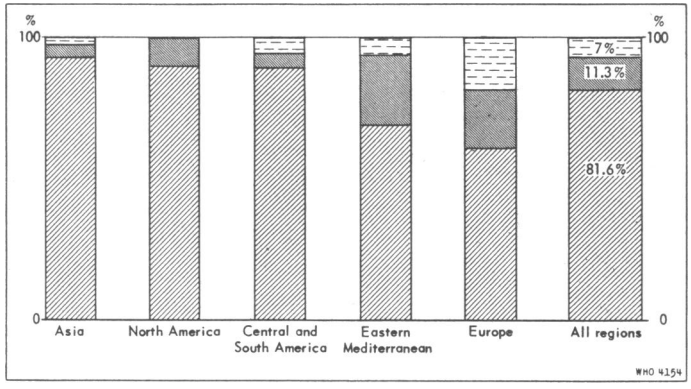
It should be noted in this connexion that the WHO Expert Committee on Venereal Infections and Treponematoses,[9] prompted by considerations of economy for areas where penicillin is for financial reasons scarce, recommended different penicillin schedules for seronegative and seropositive primary syphilis and for secondary syphilis. Most of the clinics participating in the present study, however, did not make this distinction or tended to draw the line at a different level. Some were in the practice of giving less treatment for seronegative primary syphilis than for seropositive primary syphilis and secondary syphilis, and others employed different schedules in all three stages. Only in 6.3% of the penicillin schedules and in 7.1% of the schedules involving all drugs was the distinction made between all forms of primary syphilis and secondary syphilis.

Type of Penicillin Preparation

One of the early advances in the penicillin treatment of syphilis was the evolution of repository preparations which enabled treponemacidal serum levels to be maintained for 24 hours or more following a single injection.

This finally led to the discovery by Buckwalter & Dickison [2] of procaine penicillin G with aluminium monostearate (PAM), which is the penicillin preparation of choice recommended by the WHO Expert Committee on Venereal Infections and Treponematoses.

FIG. 4. PENICILLIN SCHEDULES USED IN DIFFERENT REGIONS (294 SCHEDULES)



Repository penicillin—PAM—(including 9 schedules using procaine penicillin in oil)

Procaine penicillin in water (including 2 schedules using "fortified" penicillin)

Aqueous penicillin (including 5 schedules which may have been either aqueous penicillin G or procaine penicillin in water)

It will be noted in fig. 4 that Europe has apparently been the slowest to utilize this therapeutic development, and nearly 40% of the participating European clinics preferred procaine penicillin in water or aqueous crystalline penicillin. On the other hand, PAM was the penicillin preparation in routine use in approximately nine-tenths of the clinics of Asia, North America, and Central and South America.

It should be stated that, although procaine penicillin in water has notably less effect in prolonging the penicillinaemia than PAM, it will still, in the doses prescribed, give an adequate serum level for 24 hours following each injection, and will be quite effective in syphilis treatment provided the patient completes the schedules recommended. Even so, a greater percentage of clinics in Europe than in the other areas studied were using aqueous crystalline penicillin G, requiring multiple daily injections, which must today be considered an impractical regime.

In Europe, PAM was used more frequently in the northern and southern countries than it was in Great Britain and the western and central countries (table III).

New repository benzyl amine salts—diamine penicillin—were reported to be under trial in five North American clinics and one South American

TABLE III. DISTRIBUTION IN EUROPE OF TREATMENT SCHEDULES FOR EARLY SYPHILIS USING PAM

Region and country	Schedules			
	number per country	number using penicillin	number using PAM.*	percentage using PAM
Northern Europe				
Sweden	5	17	13	76.5
Denmark	4			
Finland	4			
Norway	4			
Southern Europe				
Italy	5	11	8	72.7
Yugoslavia	3			
Greece	2			
Spain	1			
British Isles				
Great Britain	12	15	9	60.0
Ireland	3			
Western and Central Europe				
Belgium	8	23	10	43.5
France	7			
Switzerland	5			
Netherlands	3			
Austria	1			
Total	67	66	40	60.6

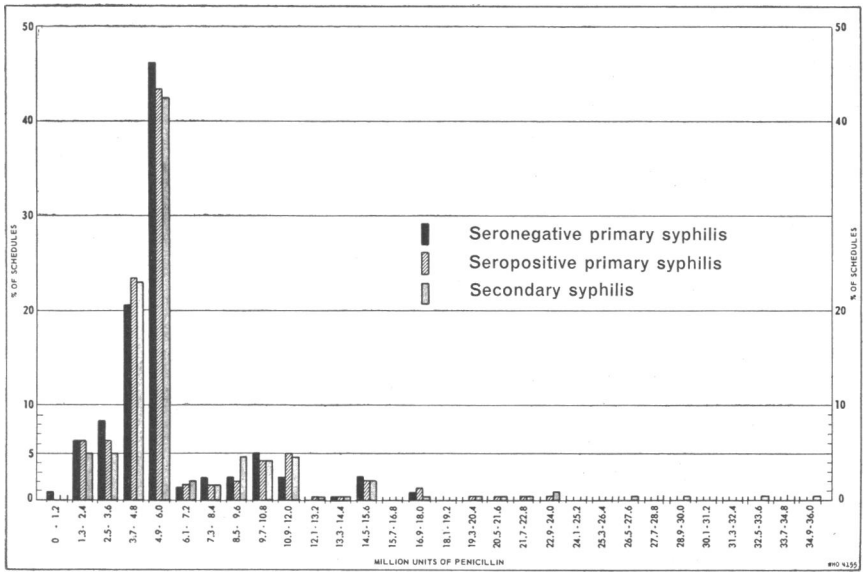
* Including one schedule using procaine penicillin in oil

clinic. Panbiotic was being used in one North American clinic. These all represented experimental treatment schedules and have not been included in this study.

Dose of Penicillin

For the world as a whole the mean dose of penicillin given in all stages of early syphilis fell between 4.8 million and 6.0 million units (fig. 5). The tendency to increase the dose by stage of disease was slight in all areas except Europe, where it was considerable. In the European clinics, not only were much higher doses of penicillin being given than elsewhere, but appreciably more penicillin was also being given for secondary syphilis than for seropositive primary syphilis, and more for seropositive primary syphilis than for sero-

FIG. 5. DISTRIBUTION OF 238 SCHEDULES BY TOTAL AMOUNT OF PENICILLIN



negative primary syphilis (fig. 6). This tendency was also apparent in other areas but was nowhere so marked as in Europe.

The total dose of penicillin was generally given during an initial course in all areas except Europe, where some use was made of the drug for " consolidation ". Of the 238 schedules under review using penicillin, only 31 provided for doses of more than 10 million units for secondary syphilis and 26 were from Europe : 15 of the latter were in excess of 13 million units and 8 were for 20 million units or more, the highest being no less than 36 million units ! There was thus a considerable difference in the penicillin-dose distribution for Europe as compared with the rest of the world. This was most marked in respect of secondary syphilis but was also apparent in seropositive and seronegative primary syphilis.

Duration of Initial Penicillin Course

The mean duration in days of the initial penicillin course for 233 of the 238 penicillin schedules is shown in fig. 7. This was shortest in the Eastern Mediterranean (10.4-11.1 days) and in Central and South America (10.4-12.7 days) and longest in Europe (14.1-14.9 days). In all areas except Asia and North America the duration of therapy was to some extent related to the stage of the disease, and was longer for secondary than for seronegative primary syphilis. On the other hand, the mean duration of treat-

ment in Asia (13.1-13.2 days) and in North America (13.3-13.6 days) was not far behind the European figures.

As has previously been stated, the clinics of Asia and North America used PAM predominantly. As will be noted when the PAM schedules are considered in greater detail, greater use was being made in these areas of the marked repository powers of PAM (as judged by the duration of penicillinaemia obtainable), and relatively longer treatment times were

FIG. 6. MEAN DOSE OF PENICILLIN IN MILLION UNITS BY STAGE OF DISEASE (238 SCHEDULES)

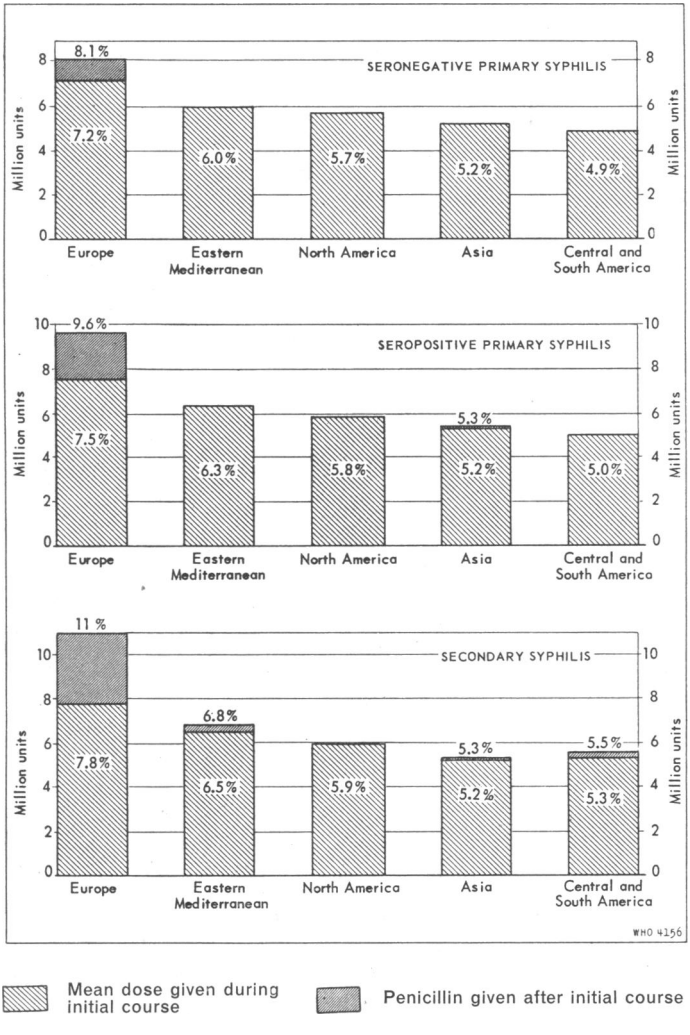
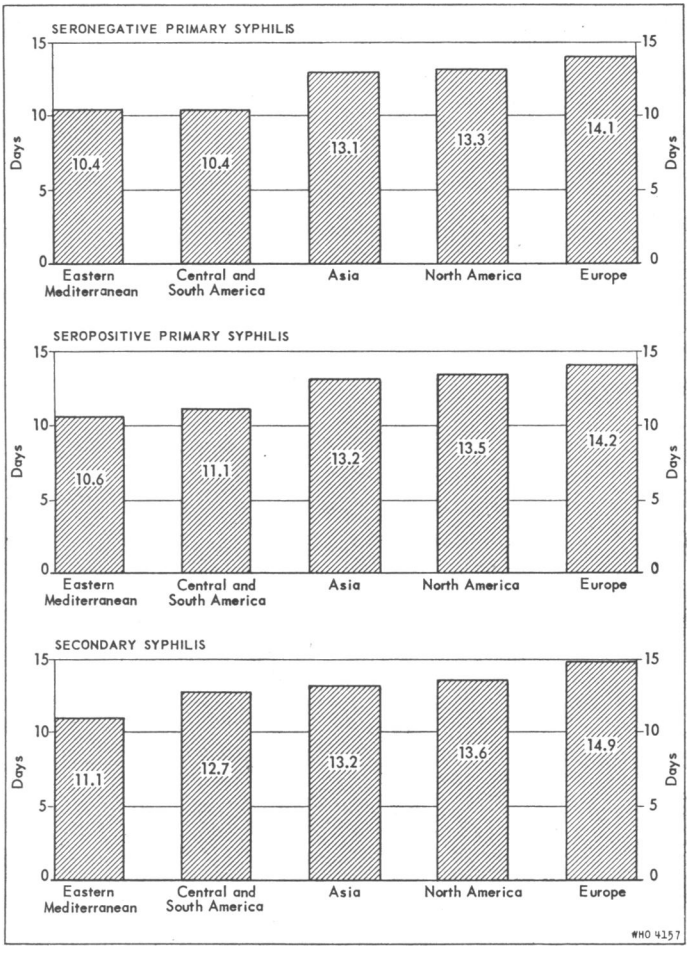


FIG. 7. MEAN DURATION IN DAYS OF INITIAL TREATMENT FOR EARLY SYPHILIS WITH 238 PENICILLIN SCHEDULES



being obtained from a smaller number of injections in these areas than in Europe.

PAM Schedules

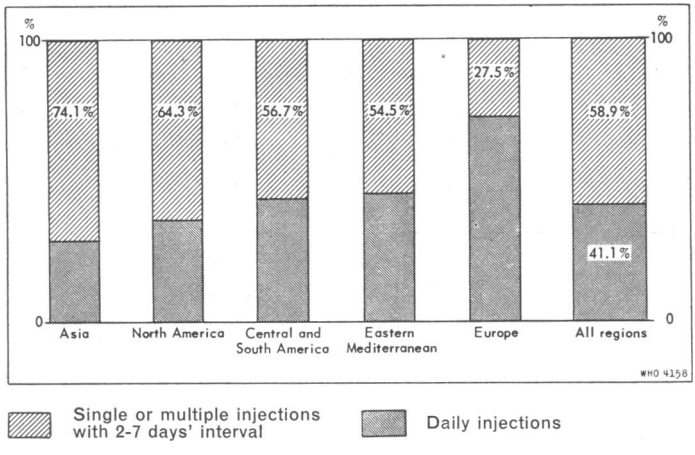
PAM was used in 194 schedules, detailed information being available concerning 190. The average doses of PAM given during the initial course are shown in table IV. The lowest average dose was 4.5 million units for seronegative primary syphilis in Central and South America, and the highest was 7.3 million units for seropositive primary syphilis and secondary syphilis in Europe. Similarly, the average number of injections used in the

TABLE IV. AVERAGE DOSE IN INITIAL PAM COURSE AND AVERAGE NUMBER OF INJECTIONS

Region	Seronegative primary syphilis		Seropositive primary syphilis		Secondary syphilis	
	average dose (million units)	average number of injections	average dose (million units)	average number of injections	average dose (million units)	average number of injections
Europe	6.6	11.9	7.3	12.6	7.3	13.0
North America . .	5.9	7.3	5.9	7.3	6.1	7.4
Asia	5.3	7.7	5.4	8.0	5.4	8.0
Eastern Mediterranean	5.0	6.4	5.4	6.5	5.7	7.0
Central and South America	4.5	6.3	4.6	6.8	4.9	6.9

three stages of early syphilis ranged from 11.9 to 13.0 in Europe and in the rest of the world from 6.3 for seronegative primary syphilis in Central and South America to 8.0 for secondary syphilis in Asia. These striking differences between Europe and the rest of the world again indicate European reluctance to take advantage of the fewer number of injections which are necessary when PAM is used.

FIG. 8. PERCENTAGE OF 190 SCHEDULES UTILIZING REPOSITORY POWERS OF PAM



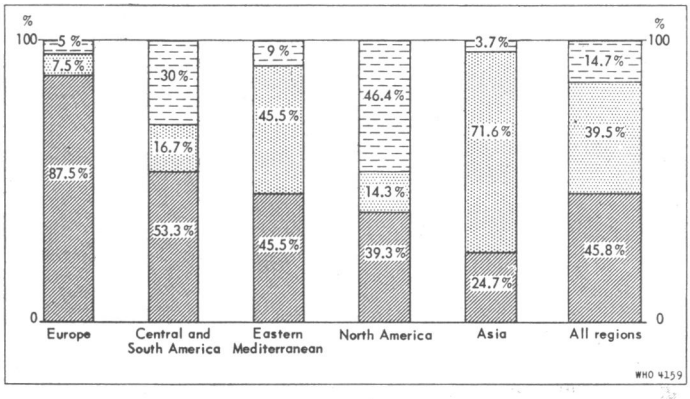
This point is illustrated in fig. 8, which gives the percentages of schedules employing daily injections and the percentages of schedules making fuller use of the repository powers of PAM, by giving either single injections or repeated injections at intervals of two to seven days.

Epidemiological Dose of PAM

In the fourth report of the WHO Expert Committee on Venereal Infections and Treponematoses,[9] the recommendation is made not only that PAM be used for the treatment of syphilis but also that a minimum dose of 2.4 million units should be used in primary syphilis and 4.8 million units in secondary syphilis. A number of schedules are suggested by which these doses may be spread over from one to 17 days. In all stages of early syphilis, however, it is recommended that half the total dose (i.e., 1.2 million units for primary syphilis and 2.4 million units for secondary syphilis) should, for epidemiological reasons, be given at the time the diagnosis is made so that, should the patient then default, he would already have received a minimal curative dose (known as an " insurance " or " epidemiological " dose).

For secondary syphilis this principle was to some extent accepted in more than half the schedules studied, in that a total dose of 1.2 million units of penicillin or over was given at once in 103 schedules out of 190 (54.2%). However, doses of 2.4 million units or more (as recommended by the WHO Expert Committee on Venereal Infections and Treponematoses for secondary syphilis) were used in only 28 (14.7%) of the 190 schedules. The principle of the initial epidemiological dose was most generally accepted in Asia, while there was a noticeable unwillingness in this regard in Europe (fig. 9). The fact that it is apparently more easy to gain acceptance of new ideas in less-highly developed areas gives some grounds for hope that it may be possible to hasten the normal rate of medical and other progress in these areas—an achievement which is a requisite for the success of the many WHO-assisted health programmes in all fields.

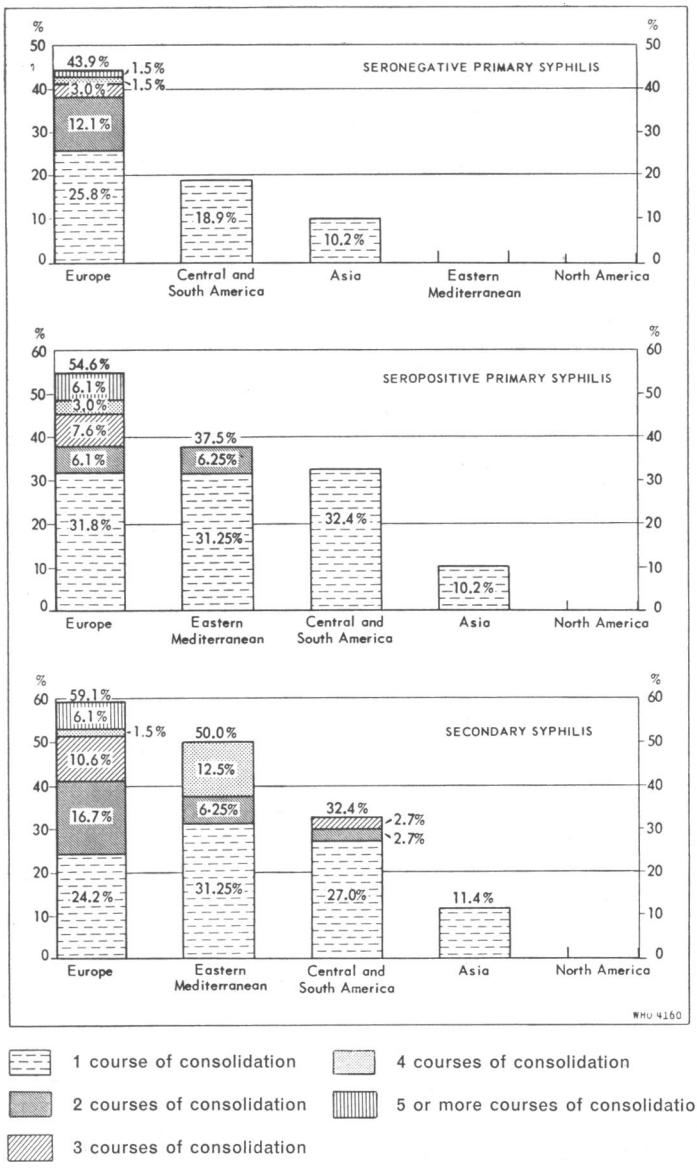
FIG. 9. PERCENTAGE OF 190 PAM SCHEDULES GIVING " EPIDEMIOLOGICAL " DOSE IN TREATMENT OF EARLY SYPHILIS



Consolidation

The concept of " attack treatment " followed by " consolidation treatment ", common among many European syphilologists, became outmoded

FIG. 10. PERCENTAGE OF 238 PENICILLIN SCHEDULES REQUIRING CONSOLIDATION TREATMENT



with the introduction of penicillin, which made a new method of "blitzkrieg" against the disease possible. In this study it was noted that the clinics in North America had entirely abandoned all methods of consolidation and that it was practised by only a few in Asia (fig. 10). Consolidation was employed by less than one third of the participating clinics in Central and South America, and slightly more often in the Eastern Mediterranean area. In Europe a significantly greater tendency to employ multiple courses of consolidation was apparent.

In all areas except North America there was a tendency to give consolidation treatment with a frequency and intensity which varied according to the stage of the disease. This tendency was especially marked in Europe, where 59.1% of the schedules included some form of consolidation for secondary syphilis and 34.9% gave more than one extra treatment course. In other areas studied, one course was usually deemed sufficient if consolidation was given.

Bismuth and then arsenic, often in combination, were the drugs most frequently used for consolidation, followed by penicillin and then mercury in that order (table V). Of each drug, Europe used more than any other region. The use of mercury was very limited. When penicillin was introduced, it was the practice of many European clinics to combine intensive penicillin treatment with one or more classical courses of arsenic and bismuth. The continued toxic effects arising from the arsenic caused many clinicians to pause and consider whether these could be justified by the therapeutic results, and in recent years European clinics have one by one been discarding the arsenic. Many, however, retained the bismuth for a longer period. Many clinicians have since come to the same conclusion as regards bismuth, but without abandoning the principle of consolidation. Some clinicians have felt that if consolidation is to be employed, then penicillin is the safest and most effective drug to employ today. The use of penicillin for consolidation, it will be noted, was practically confined to Europe, where it was used in no less than 25.7% of the schedules for secondary syphilis. As shown in table VI, this practice was most common in the British Isles and least common in the northern countries.

Cost of Treatment

In countries where supplies of antisyphilitic drugs are plentiful, the expense of the treatment of early syphilis has not influenced the choice of schedule, with the result that few comparisons have been made in the past of the relative costs of the older and newer treatments.

Today the costs of antisyphilitic drugs are such that intensive treatment employing penicillin is actually considerably cheaper than the older arsenic and bismuth schedules. At current British prices 3 million units

TABLE V. PERCENTAGE DISTRIBUTION OF 238 CONSOLIDATION-TREATMENT SCHEDULES BY DRUG USED

Basic drug used for consolidation schedule	Area	Stage of syphilis for which consolidation treatment given	Frequency with which schedule used		
			drug or combination of drugs used	percentage of schedules in which applied	
Mercury	Central and South America	1, 2, 3	Mercury alone	2.7	
	Europe	1, 2, 3	Mercury alone	1.5	3.0
			Mercury, arsenic, and bismuth	1.5	
Penicillin	Central and South America	3	Penicillin and bismuth	2.7	
	Asia	2, 3	Penicillin alone	1.1	
	Eastern Mediterranean	2	Penicillin and bismuth	6.2	
		3	Penicillin and bismuth	6.2	12.4
			Penicillin alone	6.2	
	Europe	1	Penicillin alone	6.1	15.1
			Penicillin and bismuth	7.5	
			Penicillin, arsenic, and bismuth	1.5	
		2, 3	Penicillin alone	12.1	25.7
			Penicillin and bismuth	9.1	
			Penicillin, arsenic, and bismuth	3.0	
			Penicillin and arsenic	1.5	
Arsenic	Asia	1, 2, 3	Arsenic alone	2.3	5.7
			Arsenic and bismuth	3.4	
	Eastern Mediterranean	2, 3	Arsenic and bismuth	18.8	
	Central and South America	1	Arsenic and bismuth	8.1	
		2	Arsenic alone	2.7	18.9
			Arsenic and bismuth	16.2	
		3	Arsenic and bismuth	18.9	
	Europe	1	Arsenic and bismuth	13.7	16.7
			Mercury, arsenic, and bismuth	1.5	
			Penicillin, arsenic, and bismuth	1.5	
		2	Arsenic and bismuth	12.1	19.6
			Mercury, arsenic, and bismuth	1.5	
			Penicillin, arsenic, and bismuth	4.5	
			Penicillin and arsenic	1.5	
		3	Arsenic and bismuth	16.7	22.7
			Mercury, arsenic, and bismuth	1.5	
			Penicillin, arsenic, and bismuth	3.0	
			Penicillin and arsenic	1.5	

1 = Seronegative primary syphilis 2 = Seropositive primary syphilis 3 = Secondary syphilis

TABLE V. PERCENTAGE DISTRIBUTION OF 238 CONSOLIDATION-TREATMENT SCHEDULES BY DRUG USED (continued)

Basic drug used for consolidation schedule	Area	Stage of syphilis for which consolidation treatment given	Frequency with which schedule used		
			drug or combination of drugs used	percentage of schedules in which applied	
Bismuth	Asia	1, 2, 3	Bismuth alone	4.5	7.9
			Arsenic and bismuth	3.4	
	Central and South America	1	Bismuth alone	8.1	16.2
			Arsenic and bismuth	8.1	
		2	Bismuth alone	10.8	27.0
			Arsenic and bismuth	16.2	
		3	Bismuth alone	8.1	29.7
			Arsenic and bismuth	18.9	
			Penicillin and bismuth	2.7	
	Eastern Mediterranean	2	Bismuth alone	12.5	37.5
			Arsenic and bismuth	18.8	
			Penicillin and bismuth	6.2	
		3	Bismuth alone	18.8	43.8
			Arsenic and bismuth	18.8	
			Penicillin and bismuth	6.2	
	Europe	1	Bismuth alone	12.1	36.3
			Arsenic and bismuth	13.7	
			Mercury, arsenic, and bismuth	1.5	
			Penicillin and bismuth	7.5	
			Penicillin, arsenic, and bismuth	1.5	
		2	Bismuth alone	10.6	37.9
			Arsenic and bismuth	13.7	
			Mercury, arsenic, and bismuth	1.5	
			Penicillin and bismuth	9.1	
			Penicillin, arsenic, and bismuth	3.0	
		3	Bismuth alone	13.6	43.9
			Arsenic and bismuth	16.7	
			Mercury, arsenic, and bismuth	1.5	
			Penicillin and bismuth	9.1	
			Penicillin, arsenic, and bismuth	3.0	

1 = Seronegative primary syphilis 2 = Seropositive primary syphilis 3 = Secondary syphilis

TABLE VI. USE OF PENICILLIN FOR CONSOLIDATION TREATMENT OF EARLY SYPHILIS

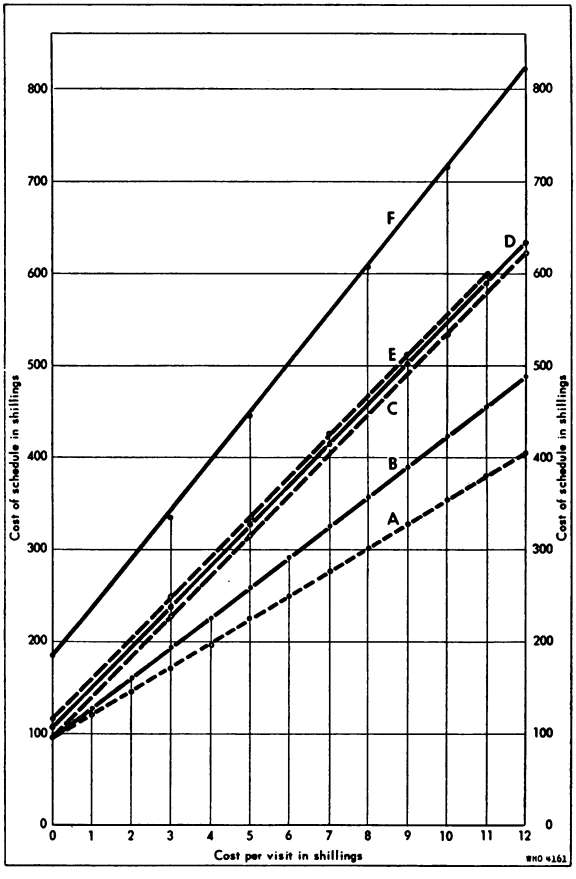
Country	Number of clinics using penicillin consolidation	Number of treatment schedules using penicillin	Number of schedules using penicillin as consolidation			Percentage of schedules for secondary syphilis using consolidation
			in sero-negative primary syphilis	in sero-positive primary syphilis	in secondary syphilis	
India	1	63	—	1	1	1.6
Iraq	1	6	—	—	1	16.7
Israel	1	5	—	1	1	20.0
Northern Europe						
Denmark	1	17	1	2	2	11.8
Sweden	1					
British Isles						
Great Britain	4	15	2	6	6	40.0
Ireland	2					
Central and Western Europe						
Austria	1	23	4	5	5	21.7
Belgium	1					
Netherlands	1					
Switzerland	2					
Southern Europe						
Italy	3	11	3	4	4	36.4
Yugoslavia	1					
Total for Europe	20	66	10	17	17	25.7

of PAM can be obtained by hospitals for only 6/6 or 10/5 for 4.8 million units. An injection of 0.6 g of neoarsphenamine costs 2/3, which comes to 22/6 for a course of ten injections or £4 10s for four such courses. The addition of bismuth makes little difference, as it costs barely one penny for an injection of 0.2 g of bismuth metal.

In the more highly developed countries with established clinics it is difficult, in view of the complexity of the factors involved, to translate the cost per visit into simple terms. Even if the number of visits by patients receiving treatment for early syphilis is drastically curtailed, the overheads of the clinic are not reduced. The clinic still has to serve the needs of the area and to remain open for sufficient hours to serve those needs. The same staff is required to deal with the patients with late syphilis, gonorrhoea, non-specific urethritis, other quasi-venereal complaints, and those requiring routine testing for various reasons. Thus for these clinics the saving brought

about by modern treatment for early syphilis are mainly those resulting from the use of cheaper drugs. Even so, by the substitution of intensive treatment with penicillin for the four classical courses of arsenic and bismuth, the saving is in the neighbourhood of £4 per case !

FIG. 11. GROSS COST IN SHILLINGS AND PENCE OF DIFFERENT TREATMENT SCHEDULES FOR EARLY SYPHILIS



A = 4.8 million units of PAM in a single injection
B = 4.8 million units of PAM in 8 daily injections
C = 4.8 million units of PAM in 8 daily injections plus 10 injections of bismuth
D = 4.8 million units of PAM in 8 daily injections plus 10 biweekly injections of PAM of 0.6 million units each
E = 4.8 million units of PAM in 8 daily injections plus 10 arsenic and 10 bismuth injections
F = 4 courses of arsenic and bismuth without penicillin

In the underdeveloped areas, on the other hand, where there are no permanent venereal disease clinics, the treatment of early syphilis often has to be undertaken by persons who, if they were not treating syphilis, would

be treating some of the many other diseases present in the area. Here time saved in treating syphilis is time and money saved for the treatment of other important disorders. Thus some comparison of the " cost " of the treatment of early syphilis, taking into account the salaries of the doctors, nurses, almoners, clerks, orderlies, and other staff, and including overheads such as rent and light and laboratory expenses, is of interest even if it has little application in the more developed areas.

The cost per visit of necessity varies considerably from clinic to clinic, depending on the size of the staff, the teaching and research done in the clinic, the number of serum tests performed annually in the laboratory, and other factors—aspects which are difficult to separate in costing. A calculation has therefore been made of the gross expenses of various schedules, based on a sliding scale of cost for the individual patient visit of from 0 to 12 shillings; this is shown in fig. 11. The following schedules are included : 4.8 million units of PAM in a single injection; 4.8 million units of PAM in eight injections; the same plus 10 weekly injections of bismuth; 4.8 million units of PAM in eight injections plus 10 injections each of arsenic and bismuth; the same initial penicillin course plus 10 bi-weekly injections of 0.6 million units of PAM; and, lastly, four courses of arsenic and bismuth only. The number of clinic visits estimated as usually necessary for the six schedules, including follow-up, are 26, 33, 44, 44, 44, and 54, respectively.

Inquiries made at three laboratories in Great Britain indicated that the cost for a routine serum test was approximately 1/6, which sum has been used as a basis for calculation. All the schedules containing penicillin have been allowed 14 such tests, and the arsenic and bismuth schedule has been allowed 12. All patients are assumed to have one complete cerebrospinal fluid examination which has been costed at three guineas, an intentionally high figure to compensate for any possible low costing of the serum tests.

Fig. 11 clearly shows how the expense of any schedule increases markedly with the cost per visit. That all forms of penicillin therapy, whether given alone or in combination with other drugs, are substantially cheaper than the old method of treatment with four courses of arsenic and bismuth is also evident, as it is that schedules involving intensive penicillin alone are considerably cheaper than combined treatments employing consolidation, and which require not only more drugs but more visits. It is also apparent that schedules employing consolidation with bismuth, arsenic and bismuth, and even penicillin itself, show little difference in the total cost.

Conclusion

It is suggested that these findings ten years after the introduction of penicillin in syphilotherapy are of general interest to venereologists and other health workers, since they indicate a situation which is not dissimilar

to that immediately after the first World War, when the new arsphenamines had been introduced. The medical literature of that period shows that many clinicians were not prepared to abandon the familiar practices with mercury although the treponemacidal and curative powers of the arsphenamines were acknowledged to be superior. It is observed that penicillin therapy has apparently taken root more slowly in Europe than in other parts of the world, although it would appear that the acceptance of this antibiotic as the sole curative agent in early syphilis is gradually increasing in this area as well.

Annex I

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RÉSUMÉ

Dix ans après l'introduction de la pénicilline dans le traitement de la syphilis, une enquête a été effectuée par l'OMS dans 55 pays, concernant l'orientation actuelle de la thérapeutique de la syphilis récente.

Pour ce faire, on a examiné 294 schémas de traitement provenant de 277 universités importantes et de dispensaires principaux des Régions des Amériques (57), de l'Asie du Sud-Est, du Pacifique occidental (141), de la Méditerranée orientale (13) et d'Europe (66).

Parmi les institutions participant à l'enquête, 65,3 % utilisent la pénicilline seule, 28,9 % la pénicilline et d'autres médicaments et 5,8 % la métallothérapie sans pénicilline. L'arsenic, le bismuth, la pénicilline et le mercure sont utilisés comme adjuvants ou pour le traitement de consolidation. Tous les dispensaires de l'Amérique du Nord et 52,2 % de ceux d'Europe utilisent la pénicilline seule. On a fait moins souvent la distinction entre syphilis primaire et secondaire qu'entre cas séronégatifs et cas séropositifs. Le PAM est le médicament adopté dans 81,6 % des schémas de traitement passés en revue. Il est utilisé dans 91% des dispensaires des Amériques et de l'Asie du Sud-Est et dans 60,6 % des dispensaires européens (surtout dans les pays nordiques).

Les doses les plus couramment appliquées, dans toutes les Régions, à tous les stades de la syphilis récente, sont de 4,8 à 6 millions d'unités de pénicilline. L'Europe a utilisé des doses plus élevées que les autres Régions : 39,4 % des dispensaires recouraient à 10,8 millions d'unités, parfois davantage (le maximum, exceptionnel, étant de 36 millions). Le nombre moyen d'injections de PAM, pour le traitement initial, a varié de 11 à 13 en Europe et de 6 à 8 dans les autres Régions.

La durée moyenne du traitement initial à la pénicilline a varié de 10 jours (syphilis primaire séronégative) dans la Méditerranée orientale à 15 jours (syphilis secondaire) en Europe. Aucun des dispensaires de l'Amérique du Nord n'administre de traitement de consolidation tandis que 59 % des schémas d'Europe le font, pour la syphilis secondaire, utilisant, par ordre de fréquence — le bismuth, l'arsenic (souvent une combinaison des deux), la pénicilline et le mercure. La consolidation par la pénicilline n'est pratiquée qu'en Europe (dans 25,7 % des schémas de traitement de la syphilis secondaire).

Le remplacement des traitements classiques à l'arsenic et au bismuth par le traitement intensif au moyen du PAM a eu pour conséquence une économie pouvant atteindre 4 livres sterling par cas. Les schémas dans lesquels la pénicilline seule est utilisée sont beaucoup moins coûteux que les traitements combinés suivis de consolidation, qui exigent une plus grande quantité de médicaments et un plus grand nombre de visites. Cependant, les dépenses générales des dispensaires ne sont pas réduites, car le personnel doit s'occuper d'autres formes de la syphilis, de la blennorragie, d'autres affections vénériennes, ainsi que du contrôle post-thérapeutique des malades.

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