ARMY EXPERIENCE OF SYPHILIS THERAPY

BY

C. C. M. JAMES, DONALD G. MACKAY, and J. T. WRIGHT

1. INTRODUCTION

The prevention of syphilis is a major problem of social medicine; and its prevention is closely interlocked with the efficacy of treatments available. For this reason it is surely appropriate in this context to examine new sources of information with respect to its therapeutic control as a pre-requisite to consideration of other methods of eliminating the disease. Experience of syphilis therapy in the Army during the late war provides unique materials for assessing therapies in current use, and it is the aim of this communication to assess their value.

During the first phase of the war, Army medicine relied exclusively on long-term arsenotherapy with bismuth. Later a certain number of cases was treated by means of short-term mapharside with bismuth. In the last phase penicillin treatment replaced or supplemented the use of arsenicals for a trial period pending the outcome of experience. In all, we are in a position to examine the results of eight procedures which we specify more fully below (part 5):

1. 2.4 mega units of penicillin.
2. 4.0 mega units of penicillin.
3. 2.4 mega units of penicillin + 0.6 g. mapharside.
4. 2.4 mega units of penicillin + 0.4 g. mapharside + 1.0 g. bismuth.
5. Long-term arsenic therapy, high aggregate dosage.
6. Long-term arsenic therapy, low aggregate dosage.
7. Long-term arsenic therapy + 2.4 mega units of penicillin.
8. Short-term arsenic therapy.

2. SOURCES OF MATERIAL

Long-term arsenic cases were traced through the War Office Central Card Index which supplied a nominal roll of all syphilis cases admitted to hospital for treatment during the twelve months 1943-4. The same nominal roll also served for a survey of post-arsphenamine jaundice (Truelove and Hogben, 1947). Nominal rolls obtained from the Adviser in Venereology made it possible to trace cases undergoing initial treatment (by methods later specified) at Army Special Treatment

Centres in Britain during the period September, 1944, to June, 1946. During this period each Special Treatment Centre (S.T.C.) was treating all cases of *early* syphilis with a standard schedule of therapy notwithstanding the duration or severity of the disease. Hence such nominal rolls should provide an unbiased sample of the total Army early syphilitic population at home. By recourse to the serial numbers supplied by them, it was possible to extract hospital record cards (A.Fs. I.1220) from the Central File of Medical Documents at the War Office and from the Central Syphilis Register (C.S.R.). The former furnished detailed information with reference to *initial* syphilitic infection and treatment. The latter supplied surveillance notes relating to each case.

Many cases on the nominal rolls from S.T.Cs. were unserviceable for the following reasons:

- (1) patients from other Services, initially treated in military units were subsequently transferred from Army supervision;
- (2) some patients had had previous treatment for the disease;
- (3) some cases were congenital, tertiary, neuro-syphilitic, or latent syphilitic;
- (4) relevant documents of a small group were incomplete:

All cases under consideration are *early*. They had neither suffered previously from the disease nor undergone previous treatment, but otherwise include any diagnosed as sero-negative primary syphilis, sero-positive primary syphilis, and early secondary syphilis. The diagnostic criterion of *primary* cases was presence of a primary chancre confirmed by detection of *Treponema pallidum* by dark-ground examination, with or without positive serological test (Wassermann or Kahn). That of secondary syphilis was a positive Wassermann or Kahn test together with such clinical manifestations as a rash, mucous patches, or condylomata (confirmed as such by dark-ground examination).

3. CRITERIA OF EFFICACIOUS TREATMENT

Inter alia we may judge the therapeutic efficacy of a drug in terms of the risk of relapse, or the frequency of beneficial response whether temporary or otherwise. Accordingly, we here distinguish two categories of cases as *relapses* and *failures*, the former among whom the benefit of treatment is only temporary, the latter because they fail to derive any manifest benefit at all. Any index which combines figures referable to both criteria is necessarily arbitrary, because we have no reason to

suppose that a treatment which is accredited by a lower *relapse* rate will be accredited by a lower *failure* rate; and if the two methods of assessment point to different conclusions, no formula applicable to all diseases prescribes which should have priority. Since we cannot compute relapse rates without excluding cases which at no time responded to treatment, we have thus to apply to our data two independent criteria of efficacy: (a) what proportion of all cases treated *fail* to respond at any time; (b) among cases which do respond at some time, what proportion subsequently relapse.

Considerations which did in fact guide our classification of cases as failures, relapses, or cures, call for more explicit clarification. Both for diagnosis and for surveillance, treatment centres concerned in the present investigation employed the qualitative Wassermann reaction (W.R.), the qualitative Kahn test (K) and quantitative Kahn test (K.Q.). Owing to exigencies of the Service, the W.R. and Kahn were not always used together in surveillance; but quantitative Kahn tests (K.Q.) performed in the majority of cases give evidence of serological trends. We here consider a serum to be *positive* when the laboratory reported any one of the following: W.R.+, K+, or K.Q. of four or more units. We classify as *doubtful* a result such as K±, W.R.±, or K.Q. readings of less than four units. Blood samples from each case were commonly examined both at beginning and end of treatment. The routine of surveillance entailed clinical and serological examination at 2, 4, 6, 9, 12, 15, 18, and 24 months after completion of treatment. Lumbar puncture was performed at 6, 18, and 24 months.

We here regard a case as *cured*, if it conforms to each of two criteria: (a) all lesions have healed at the conclusion of treatment; (b) the serological test is negative at the end of surveillance. We also regard as a cure, any case ending surveillance prematurely with one sero-negative test (e.g. W.R.) and one doubtful (e.g. Kahn) if it satisfies each of the following criteria: (a) there has been consistent decline from an originally high titre; (b) there are no remaining clinical signs of syphilis. Clinical records (A.Fs. I.1220) provide the information on which we rely for specification of *relapse* in accordance with either of the two criteria on which we base the initial diagnosis, viz. (a) presence of fresh clinical manifestations in which *Treponema pallidum* could be demonstrated; (b) positive serological test, if previous tests had been negative or of lower titre. Reappearance of muco-cutaneous lesions in which *Treponema pallidum* is demonstrable provides clear-cut evidence of relapse; but the serological criterion is not, of itself, unequivocal.

Many cases lost in the follow-up (*defaulters*) were

not sero-negative at the time. They were either sero-positive or serologically doubtful; and their previous serology may have been: (i) positive with a steady or rising titre; (ii) positive with a declining titre; (iii) consistently or at some time negative. Cases we classify as *failures*, in contradistinction to relapses, are cases which did not become sero-negative within four months of the end of treatment but continued with a high titre or an increasing titre until they were lost to surveillance. In this context failure therefore means inefficacy of a treatment to reverse or to reduce the serological titre by the fourth month. There were few among the long-term arsenic series, and only among such as received small aggregate doses of arsenic owing to supervening dermatitis or jaundice. In the penicillin and short-term arsenic series some failures renewed treatment as soon as there was clear evidence of defective response. The rest would almost certainly have been re-treated, had they not defaulted.

Cases defaulting from surveillance with a titre still positive but steadily declining from an initially high level are obviously *doubtful*. Cases with a positive serum after one or more clear-cut negative tests during surveillance are by definition relapses at the month in which they become positive. Others classified as *doubtful* had a doubtful serum reaction at their last surveillance before they defaulted, because further surveillance might have demonstrated a steadily rising titre or fresh muco-cutaneous lesions indicative of relapse. In a very few instances, a weakly positive serum reaction interrupted an otherwise consistently negative surveillance. The subsequent negative clinical and serological trend, confirmed by absence of abnormality in the cerebro-spinal fluid, suggested that such isolated positive

TABLE I

PERCENTAGE OF CASES ENDING WITH AN EQUIVOCAL SEROLOGY REJECTED FROM THE SERIES ON ACCOUNT OF FOLLOW-UP OF LESS THAN FOUR MONTHS

	Primary Sero-positive		Secondary	
	Total cases	% cases rejected	Total cases	% cases rejected
Pen. 2·4	163	0·0	119	0·8
Pen. 4·0	44	6·8	30	6·7
Pen. and Maph. ..	113	2·7	59	10·2
Pen. and Maph. + Bismuth ..	92	3·3	56	14·3
LTA. and Pen. ..	38	0·0	26	0·0
LTA. (A)	84	0·0	67	0·0
LTA. (B)	84	0·0	47	2·1
STA.	38	0·0	42	0·0

reactions were either of the falsely positive type or were due to laboratory errors. Little can be predicted of a case which defaults from surveillance at the second or third month with a serum still positive or doubtful and without any stigmata of clinical relapse. Since the time under surveillance is quite inadequate to disclose the ultimate trend, we have rejected them from our pool of data. Table I shows the percentage of all cases available for follow-up in each series and those rejected for reasons here stated.

In therapeutic trials involving a communicable disease a common difficulty arises in connexion with delimitation of relapses and re-infections. Eighty-five cases in all treatment groups of our series were known to develop additional syphilitic lesions. The venereologist's opinion as stated in the clinical records distributes the later lesions as follows:

Relapses	33
Reinfections	12
Inconclusive	40

It has hitherto been customary (Moore, 1943) to exclude a diagnosis of reinfection unless consonant with all of the three following criteria:

- (i) "There must be proof that the patient had syphilis prior to the occurrence of the suspected second infection, and this proof must rest on the demonstration of spirochaetes in a lesion or the occurrence of a positive blood Wassermann reaction in the blood serum, and not on clinical judgment alone."
- (ii) "After an interval following antisyphilitic treatment and at a site other than that of the primary lesion of the first infection, there must develop a lesion with the characteristics of a chancre in which spirochaetes can be demonstrated."
- (iii) "That at the time of the supposed second infection the serologic test is negative; and that while under observation and during a period in which treatment is purposely withheld, the serologic test becomes positive or the patient develops outspoken secondary syphilis."

The clinical records of our cases do not indicate that the venereologist's opinion relied on the

CUMULATIVE PERCENTAGE RELAPSE RATES

2.4 MEGA UNITS PENICILLIN

coincidence of these three criteria. The first of Moore's criteria (i) was indeed fulfilled in all our cases; but analysis of the sample on the basis of the other two yielded the figures given in Table II.

TABLE II

	Sore at original site		Sore at new site		Total
	Sero-pos.	Sero-neg.	Sero-pos.	Sero-neg.	
Cited as relapse	28	3	2	0	33
Cited as reinfection	3	2	6	1	12
Non-committal	26	7	3	4	40
Total	57	12	11	5	85

Records usually laid emphasis on a history of recent exposure where citing a diagnosis of reinfection. It is reasonable to assume that the 57 cases whose second lesions appeared at the site of the original chancre with coincident positive serum reaction were definite cases of muco-cutaneous relapse. Probably, the 12 cases which were sero-negative when a second lesion appeared on the original sites were also muco-cutaneous relapses. *Inter alia*, Rabut and Hudelo (1924) described 21 such cases in a series of 51. Muco-cutaneous relapse in the presence of a negative or doubtful serum is thus well accredited. The 11 cases whose second lesions were stated to have occurred at different sites from the original chancres at a time when the serum was positive are more difficult to assess. It was clear from the notes of some that the new lesions were sufficiently close to be within the lymphatic watershed of the original site, a fact which might well suggest that they were probably muco-cutaneous phenomena. On the other hand, records of one or two with typical chancres proved to contain *Treponema pallidum* at a site well away from the original chancre and associated with enlargement of lymph glands other than those stated to be enlarged in the original infection, cite a doubtful serum reaction. It is conceivable that such cases were, in fact, reinfections. Of the five remaining cases, none fully satisfies the criteria advanced by Moore. We therefore regard them as relapses, and cite further details with reference to them in Table III.

The evidence that the second sore differed significantly in respect of site from the initial chancre is poor in cases 1, 2, and 4. In case 3, the new lesion was apparently still within the lymphatic

watershed of the initial chancre. Case 5 is the only one in which a negative serum reaction in the presence of the second sore was observed to have become positive before further treatment was instituted. Unfortunately, dark-ground examination was not done until the sore had been present for one month. It was then negative on three occasions. In no case was there evidence that "repeat" blood tests had been used to confirm routine tests.

4. CALCULATION OF RELAPSE RATES

All time periods date from the end of the course of treatment. In what follows, the assumption is that we have sorted our data to exhibit:

- numbers of sero-negative individuals (x_{m-1}) still under observation at the beginning of the m th month from date of certification;
- ditto (x_m) still remaining under observation at the end of the m th month;
- relapses (y_m) during the m th month;
- defaulters (d_m), that is, individuals who have ceased to be under observation during the m th month.

The last item is evidently deducible from the others by the relation:

$$d_m = x_{m-1} - x_m - y_m \dots \dots \dots (i)$$

Our problem is to ascertain the chance of relapse during the m th month, denoted below as q_m . If there were no defaulters, this would be the ratio of relapses during the month to sero-negative individuals at the beginning, that is, $y_m \div x_{m-1}$; but d_m defaulters would have accounted for an unascertained number (e_m) of relapses during the same period, so that the correct value is given by:

$$q_m = \frac{y_m + e_m}{x_{m-1}} \dots \dots \dots (ii)$$

Our problem is therefore to estimate e_m . Let us suppose that all the d_m individuals had ceased to be available for further observation on the first day of the m th month after reporting for the census recording x_{m-1} sero-negative individuals at that date. If so, e_m would be the relapses during the month referable to an initial population of d_m sero-negative individuals, i.e.

$$q_m = \frac{e_m}{d_m} \text{ or } e_m = q_m d_m$$

In fact, we are entitled to assume that the stream of defaulters is steady, the mean time during which they were available for observation being $\frac{1}{2}$ a month. We may therefore put approximately

$$e_m = \frac{1}{2} q_m d_m$$

TABLE III

Case	Age	Site of first sore	Sites of adeno-path	Initial serology	Treatment	Serology after treatment to time of development of 2nd sore	Time of appearance of 2nd sore after treatment of 1st	History of new exposure to infection	Site of 2nd sore	Sites of adeno-path	Serology at time of development of 2nd sore	Venereologist's diagnosis
1	42	Left side of glans and sulcus DG Tp +	Inguinal bilateral	(W.R. not done) Kahn negative	Pen. 2·4 mega units	Negative at second month	Third month	3/52 E.M.C. 6 days marital	The meatus Tp +	Inguinal bilateral	(W.R. not done) Kahn negative	" Syphilis early "
2	29	Coronal sulcus DG Tp +	Inguinal bilateral	W.R. and Kahn negative	Pen. 2·4 mega units	Consistently negative	Eighteenth month	2/12 E.M.C. 3 days marital	Coronal sulcus DG Tp + (not on original site)	Inguinal left	(W.R. not done) Kahn negative	" Syphilis early "
3	20	Prepuce and glans DG Tp +	Inguinal bilateral	W.R. and Kahn negative	Pen. 2·4 mega units + maph. 0·6 g.	Consistently negative	Sixth month	6/52 prostitute	Papule in rt. inguinal region DG Tp + penis clear	No adeno-path	(W.R. not done) Kahn negative	" Syphilis primary "
4	33	Fraenum DG Tp +	Inguinal bilateral	(W.R. not done) Kahn positive	Pen. 2·4 mega units	Negative at 2nd month	Third month	Not stated	Prepuce DG Tp +	Inguinal bilateral	(W.R. not done) Kahn negative	" Reinfection "
5	25	Ventral surface of shaft of penis DG Tp +	Inguinal left	(W.R. not done) Kahn doubtfully positive	Maphar-side and bismuth (S.T.A.)	Consistently negative	Seventeenth month	2/12 E.M.C.	Dorsum of penis DG Tp neg. 1/12 after sore appeared	Not stated	Kahn neg. when sore appeared. Became positive before re-treatment	" Syphilis early "

(E.M.C. = extra-marital coitus.)

It is worthwhile to point out that there is only one arbitrary assumption in the above relation, that is to say, a linear rate of default in the interval. Otherwise the relation is exact for the following reason. Suppose that we divide the month into a large number (s) of intervals in each of which the number of defaulters is $d_m \div s$. At the beginning of each interval the number of defaulters is thus the same; but their contributions to the total (e_m) of unidentified relapses will be different. The first batch with a month before them can contribute to this total $q_m d_m \div s$. The second batch with a residual fraction of a month equivalent to $(s-1) \div s$ can contribute only $s-1 q_m d_m \div s^2$, and so on. The best estimate of e_m is the limiting value of the corresponding sum of the contributions of the batches when s is indefinitely large, that is:

$$e_m = \text{Lt } \frac{q_m d_m}{s^2} \left\{ s + s-1 + s-2 + \dots + 2 + 1 \right\}$$

$$\therefore e_m = \frac{1}{2} q_m d_m.$$

Hence by (i) above

$$e_m = \frac{1}{2} (x_{m-1} - x_m - y_m) \cdot q_m \dots\dots (iii)$$

Likewise by (ii) above

$$q_m = \frac{y_m + \frac{1}{2} q_m (x_{m-1} - x_m - y_m)}{x_{m-1}} \dots\dots (iv)$$

$$\therefore 2 q_m \cdot x_{m-1} = 2y_m + q_m x_{m-1} - q_m x_m - q_m y_m$$

$$\therefore q_m (x_{m-1} + x_m + y_m) = 2y_m$$

$$\therefore q_m = \frac{2y_m}{x_{m-1} + x_m + y_m} \dots\dots (v)$$

The appropriate computing scheme for the estimation of q_m is thus:

Date by month (1st day of)	Residual sero-negative population	Serological relapses	Defaulters from equation (i)	q_m from (v)
0	x_0			
.....	y_1	d_1		q_1
1	x_1			
.....	y_2	d_2		q_2
2	x_2			
.....	y_3	d_3		q_3
3	x_3			

Corresponding to q_m the relapse rate, the survival rate s_m showing the chance of remaining negative throughout the month m is given by:

$$s_m = 1 - q_m$$

The chance of remaining sero-negative to the end of the m th month from the beginning of the follow-up is the combined product

$$\frac{m}{1} s_r$$

With a computing machine the effort involved in extracting the continued product is small; but it is not a necessary operation and the two methods of arriving at a result should be the same. The second is to proceed thus:

Residual sero-negatives	Observed relapses	Estimated relapses	Cumulative estimated relapses
x_0			
x_1	y_1	$y_1 + e_1$	$y_1 + e_1$
			$\sum_{1}^2 (y_r + e_r)$
x_2	y_2	$y_2 + e_2$	

Thus the cumulative relapse rate during m months as a percentage is:

$$100 \sum_{1}^m (y_r + e_r) \div x_0$$

This should be equal to:

$$100 \left\{ 1 - \frac{m}{1} (1 - q_r) \right\}$$

in which $(1 - q_r) = s_r$ of the preceding development.

5. PARTICULARS OF TREATMENTS

Cases which received penicillin fall into the following groups:

1. 2.4 mega units of sodium penicillin by three-hourly intramuscular injections of 40,000 Oxford units over a period of $7\frac{1}{2}$ days with no treatment other than local applications of saline or occasionally Eusol and other antiseptics to lesions;

2. 4.0 mega units of sodium penicillin given as above but for $12\frac{1}{2}$ days;

3. 2.4 mega units of sodium penicillin in $7\frac{1}{2}$ days with a course of intensive arsenotherapy beginning on the second day of penicillin treatment, viz. mapharside 0.06 g. intravenously daily for a period of 10 days;

4. 2.4 mega units of penicillin, 0.4 g. mapharside, and 1.0 g. bismuth given concurrently as above (3) over a period of 10 days.

Standard commercial preparations were used. The proportions of the different crystalline penicillins in these preparations are not known.

"Long-term" arsenic cases call for more detailed specification. Ostensibly, it was the policy to treat all cases of: (a) primary syphilis with at least four courses of arsenic and bismuth given concurrently in a twelve-month period, each course consisting of 5.85 g. of N.A.B. and 2.0 g. of bismuth; (b) secondary syphilis with at least five courses of arsenic and bismuth. In practice, it rarely proved possible to implement this procedure consistently. In fact, cases in our series treated with apparent success received from between 3 to 27 g. N.A.B. and 3 to 18 g. of bismuth over periods varying from 8 to 23 months. Documentation with respect to some cases was poor, only the number of courses being stated. Other long-term cases received, in addition to N.A.B. and bismuth, two weekly injections of 0.06 g. mapharside in place of a single injection of 0.6 g. N.A.B. Cases receiving mercurials (3 per cent. of all) were rejected from the pool of data. The composition of the group was as follows:

		% (437 cases)
N.A.B. Bi.	No. of courses and dosage known ..	61
N.A.B. Bi. mapharside	No. of courses and dosage known ..	16.6
N.A.B. Bi. mapharside	No. of courses known. Dosage not stated	22.4
		100.0

Cases which received mapharside and cases for which treatment dosage was not fully stated make up more than a third of the total material available. So it was decided to retain them. In specifying the equivalent dosage of N.A.B. received by such cases, we equate 0.12 g. of mapharside to 0.6 g. N.A.B.

TABLE IV

MEAN VALUE IN GRAMMES FOR N.A.B. AND BISMUTH AND MEAN VALUE IN MONTHS FOR PERIOD OF TREATMENT IN CASES RECEIVING FOUR COURSES OF N.A.B. AND BISMUTH

Diagnosis	No. of cases	Mean dose N.A.B. (g.)	Mean dose bismuth (g.)	Mean duration of treatment (months)
Primary: sero-negative	36	19.5 $\pm$ 0.6	9.3 $\pm$ 1.3	13.2 $\pm$ 0.5
Primary: sero-positive	66	19.0 $\pm$ 0.5	9.5 $\pm$ 0.4	13.7 $\pm$ 0.6
Secondary	38	19.0 $\pm$ 0.2	9.7 $\pm$ 0.5	14.1 $\pm$ 0.5

and add the quantity of N.A.B. so computed to the actual amount of N.A.B. received.

From analysis (Table IV) of dosage given in four courses to cases with reference to which the information was available, it was possible to distribute the L.T.A. cases among two groups: (i) group A cases receiving more than 19.0 g. of N.A.B. or, where

TABLE VA

ANALYSIS OF CASES RECEIVING MORE THAN 19.0 g. N.A.B. PLUS BISMUTH

Diagnosis	No. of cases	Mean dose N.A.B. (g.)	Mean dose bismuth (g.)	Mean duration of treatment (months)
Primary: sero-negative	28	22.1 $\pm$ 0.9	9.5 $\pm$ 0.6	14.1 $\pm$ 0.9
Primary: sero-positive	50	22.1 $\pm$ 0.4	9.7 $\pm$ 0.2	13.7 $\pm$ 0.4
Secondary	52	22.3 $\pm$ 0.3	10.2 $\pm$ 0.4	14.7 $\pm$ 0.4

TABLE VB

ANALYSIS OF CASES RECEIVING LESS THAN 19.0 g. N.A.B. PLUS BISMUTH

Diagnosis	No. of cases	Mean dose N.A.B. (g.)	Mean dose bismuth (g.)	Mean duration of treatment (months)
Primary: sero-negative	75	13.0 $\pm$ 0.5	8.7 $\pm$ 0.2	12.2 $\pm$ 0.4
Primary: sero-positive	81	14.4 $\pm$ 0.3	9.8 $\pm$ 0.2	14.1 $\pm$ 0.4
Secondary	53	13.4 $\pm$ 0.6	9.5 $\pm$ 0.4	14.0 $\pm$ 0.4

dosage was not stated, four or more courses of arsenic and bismuth; (ii) group B cases receiving either less than 19.0 g. of arsenic or less than four courses of arsenic and bismuth. Tables VA and VB show that the only obviously significant difference between these groups is the dosage of arsenic.

As a result of this analysis, 79 cases receiving between four and six courses of arsenic and bismuth were added to group A, whilst 19 cases receiving between two and three courses only were added to group B. No significant departures from these mean values occurred among cases which were known to have relapsed in the two groups. Analysis of group A and B cases with reference to the incidence of jaundice revealed a highly significant difference (Table VI) between the two groups. This was, of course, the prime reason for the lower average arsenic dose in group B. The incidence of dermatitis was also higher in this group, though it was a minor contributory factor in lowering the arsenic dosage for the group. Differences with reference to incidence of jaundice between the three subdivisions within each group are not statistically significant, though examination of a larger series of cases has shown that maximum susceptibility to jaundice occurs during the very early stage of syphilis.

A group of "long-term" arsenic cases subsequently treated with penicillin started treatment on a

TABLE VI
% JAUNDICED

	No. of cases	Primary sero-negative	Primary sero-positive	Secondary
Group A ..	209	15.2	27.8	20.5
Group B ..	228	54.3	60.6	45.2

TABLE VII
MEAN QUANTITIES OF ARSENIC AND BISMUTH RECEIVED PRIOR TO PENICILLIN THERAPY

Diagnosis	No. of cases	Mean dose N.A.B. (g.)	Mean dose bismuth (g.)	Mean duration of treatment (including penicillin) (months)
Primary: sero-negative	25	7.7 ± 0.6	4.1 ± 0.4	6.4 ± 0.8
Primary: sero-positive	38	7.1 ± 0.5	4.1 ± 0.5	7.0 ± 0.7
Secondary	26	7.9 ± 0.7	4.8 ± 0.6	7.1 ± 0.1

purely "long-term" arsenic basis, but after a variable interval arsenotherapy was stopped; and they were given a routine course of penicillin, 2.4 mega units in 7½ days. Table VII shows the mean values for arsenic and bismuth received prior to penicillin therapy, and the mean period over which therapy (including penicillin) took place.

It can be seen that similar amounts of N.A.B. and bismuth were given throughout and that the period between the beginning of arsenotherapy and the end of penicillin injections was not unduly variable. Amongst cases which are known to have relapsed there were no significant departures from the mean values given above. The three divisions into primary sero-negative, primary sero-positive, and secondary cases refers to the condition at the inception of arsenotherapy. By the time penicillin therapy began, most of the initially sero-positive cases had become sero-negative. Table VIII indicates the proportion of cases in which sero-reversal had taken place, those in which the serum test was still positive, and those who had not had a recent test.

TABLE VIII
SEROLOGY AT START OF PENICILLIN THERAPY

Initial diagnosis	No. of cases	Negative %	Positive %	Insufficient data %
Primary: sero-negative	25	100	0.0	0.0
Primary: sero-positive	38	64.1	10.3	25.6
Secondary	26	80.8	11.5	7.7

Cases which received *short-term arsenic therapy* fell into two groups. The first group comprised cases treated by daily intravenous injections of mapharside of 0.06 g. and intramuscular injection of bismuth over a period of 20 days. On inspection the cases consistently received a total of 2.0 g. bismuth and the treatment period was 20 days with

TABLE IX

Diagnosis	No. of cases	Mean dose mapharside (g.)
Primary: sero-negative	32	1.31
Primary: sero-positive	38	1.30
Secondary	42	1.29

TABLE X
PERCENTAGE RELAPSE RATES

Maximum values shown below were calculated by regarding doubtful cases as relapses, minimum values by regarding such cases as cures. Figures before the sign $\pm$ are thus the means of the maximum and minimum rates and include one half of the doubtful cases.

	Time period (months)	Pen. 2.4 Mu	Pen. 4.0 Mu	Pen. 2.4 Mu and maph. 0.6 g.	Pen. 2.4 Mu, maph. 0.4 g., bi. 1.0 g.	L.T.A. 7 g., pen. 2.4 Mu	L.T.A. (A) (N.A.B. 22 g. Bi. 9g.)	L.T.A. (B) (N.A.B. 14 g. Bi. 9g.)	S.T.A. (maph. 1.3 g. bi. 2.0 g.)
Primary sero-negative	6 12 18	11.0 $\pm$ 0.5 14.0 $\pm$ 2.4 (20.7 $\pm$ 2.2)	(10.8 $\pm$ 0.8) — —	14.6 $\pm$ 1.5 (18.2 $\pm$ 1.5) —	5.0 $\pm$ 0.0 (9.0 $\pm$ 1.9) —	(0.0) (5.7 $\pm$ 0.0) —	0.0 (0.0) —	0.0 (0.0) (0.0)	0.0 (0.0) —
Primary sero-positive	6 12 18	10.2 $\pm$ 0.0 12.8 $\pm$ 0.0 (14.1 $\pm$ 1.3)	(6.3 $\pm$ 0.0) — —	6.7 $\pm$ 0.9 (15.9 $\pm$ 4.5) —	10.9 $\pm$ 0.0 (23.3 $\pm$ 3.3) —	2.6 $\pm$ 0.0 (2.6 $\pm$ 0.0) —	0.0 1.6 $\pm$ 0.0 —	0.6 $\pm$ 0.6 3.5 $\pm$ 0.6 —	5.3 $\pm$ 0.0 (5.3 $\pm$ 0.0) (17.8 $\pm$ 2.5)
Secondary	6 12 18	8.1 $\pm$ 0.5 17.5 $\pm$ 0.5 —	(17.4 $\pm$ 0.0) — —	(6.6 $\pm$ 0.0) — —	(19.2 $\pm$ 0.0) — —	(8.8 $\pm$ 0.0) (12.9 $\pm$ 4.1) —	4.1 $\pm$ 0.9 (11.4 $\pm$ 2.1) —	3.8 $\pm$ 1.2 (9.3 $\pm$ 2.8) —	5.7 $\pm$ 0.0 (10.7 $\pm$ 1.5) (16.8 $\pm$ 3.7)

Bracketed figures are based on samples of less than 30 cases

exceptional and minor variations (e.g. ± 0.2 g. bismuth and ± 1 day respectively). Mapharside dosage varied between 1.2 g. and 1.6 g. for the course. Table IX shows, however, that the mean dosage was 1.3 g.

The second group comprised only about 40 cases treated by semi-intensive courses of mapharside, or neohalarsen, and bismuth over a minimum period of thirty days. The variability of dosage and treatment period were, however, too great to allow of standardization in such a small group of cases. We therefore present the relapse rates for the twenty-day treatment group only.

6. RESULTS

Appendix 1 cites crude figures with reference to relapses, and failures and doubtful cases; and Appendix 2 cites cases remaining at the end of specified intervals after end of treatment. Table X shows cumulative relapse rates at the end of six and twelve months for the different treatments. With regard to some, it was possible to follow sufficient cases for eighteen months. Figures can be regarded only as trends owing to the small size of some samples. All failures as defined above have been excluded. It is evident that the penicillin

courses are comparatively unsuccessful except when following long-term arsenic. The two L.T.A. schemes are apparently the most efficient, particularly for treatment of primary syphilis, and in contrast to other forms of therapy are the most successful treatments of secondary syphilis. Short-term arsenotherapy takes an intermediate position.

It is interesting to note the comparative relapse rates of S.T.A. (mapharside 1.3 g. and bismuth 2.0 g.) with: (a) penicillin 2.4 mega units and mapharside 0.6 g., and (b) penicillin 2.4 mega units and mapharside 0.4 g. + bismuth 1.0 g. Duration of treatment was much the same for each of these therapies. The relapse rates of S.T.A. are consistently smaller than those of either form of combined therapy. The least difference occurred in cases of sero-positive primary and in cases of secondary syphilis between S.T.A. and penicillin 2.4 mega units and mapharside 0.6 g. Since penicillin alone, in the two dosage schemes investigated, is least efficacious of all, these relapse rates suggest that penicillin may in some way mitigate the effect of arsenic on *Treponema pallidum*. It is, however, necessary to point out that the dosage of mapharside received by the S.T.A. group was at least twice as great as that given to the penicillin cases.

TABLE XI
ANALYSIS OF TREATMENT FAILURE CASES

Percentage of treatment failure cases (defined as cases remaining persistently sero-positive for four months or more after treatment) as a percentage of total numbers of cases (within each treatment).

	Pen. 2.4 Mu	Pen. 4.0 Mu	Pen. 2.4 Mu and maph. 6.0	Pen. 2.4 Mu, maph. 0.4 g., bi. 1.0 g.	LTA 7 g. and Pen. 2.4 Mu	LTA (A) NAB 22 g. Bi. 9 g.	LTA (B) NAB 14 g. Bi. 9 g.	STA 1.3 g., bi. 2.0 g.
Primary sero-positive	2.9 $\pm$ 0.0	1.6 $\pm$ 1.6	0.8 $\pm$ 0.8	5.5 $\pm$ 0.8	0.0	0.0	0.0	0.0
Secondary	7.8 $\pm$ 3.2	3.8 $\pm$ 3.8	2.5 $\pm$ 2.5	2.8 $\pm$ 2.8	0.0	0.0	5.0 $\pm$ 0.0	10.7 $\pm$ 6.0

Our data sustain the accepted conclusion that the prognosis for arsenotherapy is less favourable if treatment does not start until the sero-positive primary stage. Contrary to results reported by Moore (1943) and others, they would also suggest that the prognosis for sero-positive primary cases is better than that for secondary cases. Our results do not suggest any consistent differences in these respects with regard to penicillin therapy. Although attenuation of our material owing to the introduction of penicillin shortly before demobilization compels us to state only guarded conclusions with respect to the long-term prognosis of penicillin therapy, the picture disclosed by the diagram suggests that the risk of relapse among cases treated in the primary stage reaches a limiting value of about 14 per cent. within the first twelve months.

Our definition excludes the occurrence of failures among sero-negative primary cases. Table XI shows an analysis of those cases remaining sero-positive for four or more months. Penicillin has a comparatively higher rate of failure among sero-positive primary cases, but among secondary cases, particularly when combined with mapharside, compares not unfavourably with S.T.A. and the smaller dosage group (B) of L.T.A. For most treatments the prognosis in this respect of secondary cases is less favourable than the prognosis of primary cases.

SUMMARY

Relapse rates during a twelve-month period of cases of early syphilis respectively treated with eight different therapies are contrasted and disclose the following conclusions:

1. Long-term arsenic in a mean dosage of 22 g.

N.A.B. given in four or more courses proved to be the most effective therapy for all forms of early syphilis. In dosages averaging 14 g. in fewer than four courses, it was the next most efficacious.

2. For primary cases in the doses, and for the period, specified in the text, penicillin alone was inferior to either long-term or short-term arsenotherapy both with respect to prognosis of relapse and resistance to treatment.

3. The data of this enquiry give no conclusive indications of synergism with reference to simultaneous use of penicillin and arsenicals with bismuth, being suggestive, if at all, of the reverse.

4. Though the data recorded admittedly antedate recognition of the importance of the K-fraction, the results at least emphasize the need for long-term follow-up before replacing arsenotherapy by penicillin.

5. On the other hand, it is necessary to admit the possibility that greater frequency and/or duration of penicillin treatment in contradistinction to greater aggregate dosage might reverse the unfavourable verdict which our data compel us to record.

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APPENDIX 1

The relative distribution of relapses and treatment failures in the various treatment groups and their subdivision into primary sero-negative, primary sero-positive, and secondary cases. Space does not permit of indication of the relationships of relapses to time intervals after treatment. Crude figures.

	Primary sero-negative			Primary sero-positive					Secondary				
	Clin. relapse	Definite sero-relapse	Doubtful sero-relapse	Clin. relapse	Definite sero-relapse	Doubtful sero-relapse	Definite treatment failures	Doubtful treatment failures	Clin. relapse	Definite sero-relapse	Doubtful sero-relapse	Definite treatment failures	Doubtful treatment failures
Pen. 2-4 ..	11	1	3	15	3	1	4	0	8	4	2	5	7
Pen. 4-0 ..	5	0	1	1	0	0	0	1	2	1	0	0	1
Pen. and maph.	10	1	2	5	1	3	0	1	3	0	0	0	2
Pen., maph., and bi. ..	5	0	1	6	1	1	3	1	6	1	0	0	2
LTA and pen.	2	0	0	2	0	0	0	0	0	3	1	0	0
LTA (A) ..	0	0	0	0	1	0	0	0	0	0	6	0	0
LTA (B) ..	0	0	0	1	1	0	0	0	0	4	0	2	0
STA ..	0	0	0	2	2	2	0	0	1	5	0	2	5
Total ..	33	2	7	32	9	7	7	3	20	18	9	9	17

APPENDIX 2

Numbers of cases in each treatment group (subdivided into primary sero-negative, primary sero-positive, and secondary) and the numbers of cases remaining under surveillance after six and twelve months. It will be noted that relatively small numbers of cases in the LTA, LTA + Pen., and STA groups were, in general, followed over a longer period than the other cases.

		Pen. 2·4	Pen. 4·0	Pen. and maph.	Pen., maph., and bi.	LTA and pen.	LTA (A)	LTA (B)	STA	
Primary sero-negative	Total treated	114	57	108	105	25	44	75	32	
	Remain- ing 6/12	80	20	30	51	23	30	64	31	
	Remain- ing 12/12	41	0	6	5	8	10	34	23	
Primary sero-positive	Total treated	163	41	110	89	38	84	84	38	
	Remain- ing 6/12	122	14	31	42	31	64	63	35	
	Remain- ing 12/12	52	0	6	2	17	31	31	29	
Secondary	Total treated	118	28	53	48	26	67	46	42	
	Remain- ing 6/12	86	8	25	20	19	48	36	39	
	Remain- ing 12/12	32	0	5	4	9	26	20	28	Total cases
Total treated		395	126	271	242	89	195	205	112	1,635