II

STUDIES IN THE WASSERMANN REACTION, SHOWING ESPECIALLY THE SUCCESS OF THE IMMEDIATE SALVARSAN AND MERCURY TREATMENT OF ACTIVE SYPHILIS, ALSO THE FAILURE OF THE MERCURY CONTINUATION TREATMENT OF WASSERMANN NEGATIVE QUIESCENT SYPHILIS

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FROM THE THOMPSON YATES LABORATORY OF PATHOLOGY

Introduction.—This paper is a summary by E. E. G. of the chief features of the Medical Research Council's Special Report, No. 107, on "The Effect of Treatment on the Wassermann Reactions of Syphilitic Patients." The statistics have been simplified and reduced to a minimum; they are given in 33 tables and 11 graphs in the Report. The references have been omitted.

Clinical Observations.—The patients attended the Liverpool Royal Infirmary Venereal Clinic under the care of the late Dr. F. P. Wilson. The scheme of treatment throughout the investigation was the following :—

Admission Wassermann. Standard Admission Course lasting 8 weeks, viz., 6 intravenous doses of Salvarsan (total 3.3 grammes) with 8 intramuscular doses of Grey Oil (1 weekly, of 1 gr. Hg.). Rest, 5–8 weeks. Wassermann. Several mercury "Continuation Courses" were next prescribed during the ensuing two years—unless the Wassermann remained or became positive when more Salvarsan was given (p. 87).

The Wassermann reactions and treatment of each patient were represented graphically on a chart; this greatly facilitated our work.

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Seven hundred and eleven male patients were taken from the 3,429 who *first* attended the Clinic between April, 1918, and June, 1922, because they alone received the full Standard Admission Course and had the Wassermann test before and after treatment. Many were followed till December, 1923.

No more than one-fifth of the new patients were available for study, owing to their deplorably irregular attendance. This was partly due to residence—40 per cent. being sailors or other “wanderers.” Nevertheless, the attendance of the “fixtures” was only 10 per cent. to 20 per cent. better. The severity of the disease had practically no influence, because the attendance of patients with typical secondary syphilis was only 2 per cent. to 3 per cent. better than in those with typical primary.

Three-quarters of the selected patients first attended the clinic within two years of the appearance of the primary lesion, nearly half of them within six weeks. This interval between the primary and the first attendance is the “Delay Period.” Only twelve patients had neurosyphilis.

Wassermann Observations.—No. 4 technique of the Medical Research Council was used throughout, the tests being made in the Thompson Yates Pathological Laboratory of the University of Liverpool. The results were recorded for the Clinic in the six grades recommended, but for the Report in three grades, viz., ++ and + ± as +, or positive; + and ± as ±, or partially positive; ± and — as —, or negative. The reagents were distributed by a semi-automatic battery of twelve syringes, simultaneously into batches of twelve sera to be tested. This machine saved time and fatigue, and rendered serious errors in distribution impossible. In fact, the average error in the consecutive distribution of seventy-two doses was only ± 0.96 per cent., with a maximum of 2.4 per cent.

No. 4 technique was very satisfactory. The results were usually definitely positive or negative. Thus the preadmission Wassermann of the 711 syphilitic patients was + in 67, ± in 8, and — in 25 per cent.; but after the Standard Admission Course, + in 25, ± in 12, and — in 63 per cent. The technique was also accurate, as shown by an analysis of the routine retests of 1,071 control sera.

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PART I.—THE SUCCESS OF THE IMMEDIATE SALVARSAN AND MERCURY TREATMENT OF ACTIVE SYPHILIS

A. *The success of the immediate treatment with the Standard Admission salvarsan and mercury course in PRODUCING a negative Wassermann, as demonstrated by the influence of the Admission Wassermann and the Delay Period.*

(a) The effect of this course was studied upon the 711 patients; it was greatly influenced by two factors: (i) the grade of the Admission Wassermann—especially when it was negative. For success was achieved in 92, 78, and 52 per cent. of patients with a $-$, $\pm$, and $+$

GRAPH I. of the percentage of patients whose Wassermann was negative shortly after the Standard Admission Course of Salvarsan and Grey Oil.

It shows the advantage of early treatment. Thus success in producing a *negative* Wassermann varies as (1) the duration of the Delay Period, especially when short (Curve III.); (2) the grade of the Admission Wassermann, especially when negative (Curve I.).

The Delay Period also indirectly influences success in the $-$ or $\pm$ Admission Wassermanns, thus the percentage of the $-$ Admission Wassermanns rapidly diminishes, specially at first, as the Delay Period lengthens (Curve IV.).

Wassermann respectively (see also Graph I.); (ii) the duration of the Delay Period—especially when it was short (see Graph I.). This *directly* influenced the success in treating a $+$ Admission Wassermann, which was present in two-thirds of the 711 patients. For in the five "average" * Delay Periods, varying from 2½ weeks to

* See the Report.

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13.3 years, success was achieved in 74, 69, 47, 23 and 8 per cent. (see Graph I., Curve III.).

But the Delay Period *indirectly* influenced success in treating patients with a — or $\pm$ Admission Wassermann; for the longer they were untreated, the greater the probability of the Admission Wassermann becoming positive. Thus, the number of patients with a negative Admission Wassermann rapidly declined from 45 per cent. in the first Delay Period to 1 per cent. in the last (see Graph I., Curve IV.).

Previous anti-syphilitic treatment elsewhere did not appreciably influence these results. For two-thirds of the patients first came to the Clinic with a Delay Period of six months or less, and only 3 per cent. of these remembered previously receiving a salvarsan course; only 11 per cent. remembered receiving "medicine."

(b) *In early syphilis, a — Admission Wassermann may rarely become $\pm$ or even + after the first Salvarsan and Mercury Course.* One hundred and sixty-nine patients had a — Wassermann *before* the Admission Course. But the Wassermann was $\pm$ in 9, and + in 3 of them *after* the course—though it became negative again on further "914" treatment, except in one patient who left prematurely. Nine other patients with a $\pm$ Admission Wassermann remained $\pm$ in 7, and became + in 2 (see Graph I., Curves I. and II., showing that these cases occurred in the shortest Delay Periods).

Such an unexpected result of treatment has been occasionally noted before (Harrison, Dreyer, Houston). MacCormac saw seven cases of primary syphilis which became "positive or suspicious" during the course, but negative by the end. This is the usual experience.

Conclusion.—These statistics of the influence of the Admission Wassermann and the Delay Period in producing a negative Wassermann demonstrate how vital *time* is to success. This is confirmed by animal experiments, for salvarsan will cure syphilitic rabbits, if treatment is begun in the early stages of the infection (Kolle, also Frei, and especially, Chesney and Kemp,* 1926).

B. The success of the immediate treatment with the Standard Salvarsan and Mercury Admission Course in MAINTAINING a negative Wassermann, as demonstrated by

* *Jour. Exp. Med.*, 1926, XLIV., No. 5, p. 589. (Reference not in the Report.)

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the influence of the Admission Wassermann and the Delay Period.

(a) The effect of this course was studied upon (i) 503 patients who had 185 first Wassermann relapses ($94 \pm$ and $91 +$); (ii) 109 patients who had 35 second Wassermann relapses ($20 \pm$ and $15 +$); they were selected from those in Group (i) who had a first Wassermann relapse which again became negative after further treatment—usually with salvarsan. Seven 'relapses' from reinfection were excluded.

The success is most clearly shown by the first Wasser-

GRAPH II. of the percentage of patients with *no* first Wassermann relapse after the Standard Admission Course of Salvarsan and Grey Oil (-----line). It shows the advantage of early treatment, for success in *maintaining* a negative Wassermann varied as with the duration of the Delay Period and the grade of the Admission Wassermann. The Graph also shows the influence of these two factors in *producing* a negative Wassermann (—— line).

mann relapses among a group of 357 patients who became Wassermann negative after only *one* Standard Admission Course. Thus the number with *no* relapse was highest in those with the shortest Delay Period, 70 per cent., or with the — Admission Wassermann, 83 per cent.; it was lowest with the longest Delay Period, 0 per cent., or with the + Admission Wassermann, 57 per cent. (see Graph II., ----- line). The Graph also shows the influence of the Delay Period and Admission Wassermann in *producing* a negative Wassermann (see —— line). The similarity between the two curves is obvious.

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The influence of these two factors in maintaining a negative Wassermann was also shown in the second Wassermann relapses. But the effect was less marked, partly because the grade of the first Wassermann relapses influences the grade of the second.

Conclusion.—These statistics demonstrate the vital importance of *time* in the treatment of active syphilis both in producing and maintaining a negative Wassermann. *Therefore, the sooner syphilis is treated, the greater the probability of a preliminary serological cure, and later of a permanent cure.*

PART II.—THE FAILURE OF THE MERCURY CONTINUATION TREATMENT OF WASSERMANN NEGATIVE QUIESCENT SYPHILIS

Introduction.—The first and second relapse incidence among the 503 and 109 patients (p. 87) was studied in five Continuation Periods, dating from the first negative Post-Admission Course Wassermann, viz., 0–6 months, 7–12 months, 13–24 months, 25–36 months, 37–48 months.

A. The incidence of Wassermann relapses, irrespective of the effect of Mercurial Continuation Treatment or of No Continuation Treatment.

The incidence of *first* relapses was greatest in the second half of the first year after the Admission Course, viz., to $\pm$ and $+$ 28 per cent. (corrected),* and to $+$ 13 per cent. (corrected) * (Graph III., upper curves). The incidence of the *second* relapses was remarkably similar (Graph III., lower curves). All the curves show that after the first few months the probability of a relapse diminishes as the Continuation Period increases.

It is of clinical importance that a few patients, after being continuously Wassermann negative for two years, relapsed in the *first half of the third year*. The curves show that second relapses occurred in this period in 10 per cent. (2 to $\pm$), and first relapses in 5 per cent. (3 $+$ and 2 $\pm$); one of the $+$ first relapses, however, probably occurred earlier.

B. The incidence of Wasserman relapses after the Mercurial Continuation Treatment and after No Continuation Treatment.

Introduction.—The efficacy of mercury in removing the

* See the Report.

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clinical manifestations of syphilis, though less than that of arsenobenzol, is proved and universally believed. It is therefore widely believed that mercury *must* be efficacious in preventing, not only clinical relapses, but even Wassermann relapses—for the usual failure of the drug to make a positive Wassermann negative is generally overlooked, despite the observations of Harrison, Genne- rich, Fox, Nelson, Craig, Goodman, Cole, etc. Conse- quently, many practitioners prescribe mercury for about

GRAPH III.

GRAPH III. of the incidence of first Wassermann relapses during various Continuation Periods after the Admission Course ; also of the incidence of second Wassermann relapses. Both show that the incidence was greatest in the second half of the first year ; relapses, however, occurred in the first half of the third year, but not in the second half.

two years after the Wassermann has become negative—to complete the cure.

The Mercury Continuation Treatment of the Wassermann negative patients during the first year was usually two courses of eight grey oils to the "fixtures," and one or more courses of three to four months mercury tablets (three a day) to the "wanderers." During the second year mercury tablet courses were usually prescribed to both fixtures and wanderers. Tertiary syphilitics, however, often received perchloride of mercury and potas-

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sium iodide "medicine." More than a third of the patients received no Continuation Treatment for a considerable period, owing to non-attendance.

The Wassermann relapse incidence of the No Treatment, the Grey Oil, and the mercury tablet groups of patients shows:—

(a) The total ($\pm$ and $+$) first or second relapses in

GRAPH IV. of the total ($\pm$ and $+$) and $+$ first or second Wassermann relapses during the combined 0-12 months Continuation Period, in patients receiving either No Treatment or Grey Oil. The width of the columns indicate the number of patients and the height the percentage of relapses.

The Graph shows that (a) the first relapses were much more frequent after Grey Oil than after No Treatment, viz., about three times for $\pm$ relapses, and one and a half times for $+$ relapses; (b) the second $\pm$ relapses were also about three times more frequent after Grey Oil, but the $+$ relapses rather less frequent, probably because the number of cases and relapses in this group was comparatively few.

the combined 0-12 months Continuation Period were about twice as frequent after Grey Oil as after No Treatment; the oil $+$ first relapses were about one and a half times as frequent as No Treatment; but the oil $+$ second relapses were only about half as frequent—probably because the number of cases and relapses were comparatively few (Graph IV.).

(b) After mercury tablets, the total ($\pm$ and $+$) first or second relapses were about one and a third times as

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frequent as after No Treatment ; the + first and second relapses were about equally frequent as after No Treatment (Graph V.).

Graph VI. (p. 92) gives the relapse incidence after No Treatment, Grey Oil, and Mercury Tablets respectively in another way, viz., during the various Continuation Periods.

Investigation showed that the greater incidence of relapses after mercury was not due to greater clinical

GRAPH V. of the total (± and +) and + first or second Wassermann relapses during the combined 0-12 months Continuation Period, in patients receiving either No Treatment or mercury tablets. The width of the columns indicates the number of patients and the height the percentage of relapses.

The Graph shows that the first and second ± relapses were about twice as frequent after mercury tablets than after No Treatment, but the + relapses were slightly less frequent.

severity of the disease in patients receiving the drug, to differences in the Delay Period, the Admission Wassermann, to the length of the Admission Courses, the length of time observed, or to the occurrence of a spontaneous Wassermann fluctuation in late syphilis, etc.

These figures of relapse incidence have been examined by statisticians, who found that "the incidence of Grey Oli first relapses was, on the whole, statistically significant," but those of the Grey Oil second and the mercury tablet first and second relapses did not give "conclusive

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evidence of an essential difference," nevertheless, the evidence pointed in "the same direction as the Grey Oil first relapses."

Conclusion.—(i) *Mercury tablet courses certainly did not diminish the relapse incidence, as expected—they very probably increased it.* (ii) *Grey Oil courses definitely increased the relapse incidence.*

These conclusions are corroborated by:—

(a) Some of the clinicians of the last generation, notably Sir Patrick Heron Watson, of Edinburgh, who taught that "on no account must the course of mercury

GRAPH VI. of the incidence of total ($\pm$ and $+$) first or second relapses after Grey Oil (———), mercury tablets (- - - - -) and No Treatment (.....) during the various Continuation Periods. The Grey Oil was only administered for two years (first relapses) and one year (second relapses).

be given to prevent the occurrence of manifestations of syphilis at a future date," and Sir Jonathan Hutchinson, who said, "I feel sure that in certain cases in which it (mercury) fails to cure, it may greatly protract the malady (syphilis) by increasing the distance between the stages."

(b) By Fildes and Parnell who—unknown to us—studied the effect of Mercury Continuation Treatment given for several months after a "914" course in 129 cases of primary and secondary syphilis. They concluded: "It is clear that these observations lend no support to the generally accepted view that the administration of mercury after a course of arsenical treatment has a beneficial influence upon the number of relapses which may be expected."

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(c) Recent statistics of the Life Insurance Medical Directors of New York, showing that the expectation of life in 100 syphilitics "thoroughly treated" with mercury only was slightly less than that of 174 syphilitics "not thoroughly treated," etc., instead of being much greater—as mercury enthusiasts would anticipate.

Objection that these conclusions must be fallacious because mercury is beneficial in clinically active syphilis.

This objection is not valid. The pathological condition requiring treatment is entirely different in (i) clinically active syphilis, when the Wassermann is positive, except in the early primary stage; (ii) quiescent syphilis, when the Wassermann has become negative.

Recent research, particularly, by the infection of monkeys or rabbits, has shown that in clinically active syphilis the spirochætes are numerous, active, often in the blood and generally accessible; thus the mercury can attack them easily and in relatively high concentration. But in Wassermann negative quiescent syphilis the spirochætes are few, more or less inactive, practically never in the blood, and generally inaccessible—being protected either in fibrotic lesions which may not be histologically "specific," or in indurated lymph glands, spleen, testes, or in bone-marrow; so the drug can attack them less easily and only in a lower concentration.

A. *The mercury possibly acts on the residual spirochætes* first by producing mercury resistant strains (Noguchi, Klauder and Launoy). Second, by stimulating or "provoking" these resistant spirochætes into increased activity, as suggested by the laboratory experiments of Ehrlich with spirochætes, Browning with trypanosomes, etc. This view is probably incorrect, because:—(i) the relapses were more frequent and severe after intensive treatment with Grey Oil than after the milder treatment with mercury tablets; (ii) observations by King, Stokes and O'Leary, Pollitzer, O'Leary, and Dunlop, indicate that the clinical provocative reaction is much less easily produced than was originally believed.

B. *The mercury probably depresses the patient's immunity to the residual spirochætes.*

There is no doubt that immunity, both natural and acquired, plays an important part in destroying the residual spirochætes—though it may be increased or diminished by drugs. This is shown by the variation in

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the resistance of different races of rabbits to inoculated syphilis, by the occurrence of antibodies in the serum of human syphilitics (Eberson), and by the fact that the therapeutic action of certain drugs on infections from spirochætes, the malaria parasite, the dysentery amœba, or the trypanosome, depends chiefly or entirely upon their combination with the *patient's tissues* to form the lethal derivatives.

Now, the only effect of mercury treatment was to *raise* the level of the relapse incidence for the first three or four Continuation Periods ; further, the level was higher after the more intensive Grey Oil treatment (see Graph VI.). This is statistical evidence that a depressed immunity is the main factor in increasing the relapse incidence. For relapses from the development of mercury-resistant spirochætes would be more numerous in the later, and those from provocative reaction in the earlier periods.

Mercury may diminish the patient's immunity by damaging his general health or his reticulo-endothelial system, or lastly by being administered before the liver has recovered from the salvarsan—though we found no statistical evidence of this.

The Danger of a Positive Wassermann.—Positive Wassermann relapses were associated with clinical relapses in 10 per cent. of our patients. It is significant, however, that the clinical relapse incidence was only 9 per cent. and 7 per cent. after No Treatment and mercury tablets, but 17 *per cent. after Grey Oil.*

In latent syphilis, a positive Wassermann sometimes indicates that the spirochætes are only *potentially* injurious ; for their activities may be confined to the bone marrow, lymphatic glands or spleen. Eberson, also Trinchese, state that such patients may still infect their wives. W. Mayo * mentions nine cases of late syphilis at his clinic, in which the Wassermann persisted in spite of treatment, till an enlarged spleen was excised.

A positive Wassermann in latent syphilis usually indicates an attack upon more important organs, as the heart, arteries, or nervous system (see the clinical observations of Stokes, Craig and Faber, of Medical Boards in the War,† and of Life Insurance Directors of

* *Mayo Clinic*, 1924, Vol. XV., p. 779. (Reference not in the Report.)

† *Brit. Med. Jour.*, 1920, Vol. I., p. 334. (Reference not in the Report.)

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New York, also the pathological observations of Turnbull, Warthin, etc.).

Those who regard a positive Wassermann in late syphilis as not necessarily signifying spirochætal activity, admit that it always does so in early syphilis—though clinical evidence of this may be absent. Such an attitude is illogical. The onus falls upon the sceptics to demonstrate at what period of the disease the Wassermann substance mysteriously changes its character, and, therefore, its significance!

The remarkable *steadiness* of Curve III., Graph I., of the effect of the Delay Period upon the Admission Course in patients with a positive pre-treatment Wassermann, is strong evidence of a positive reaction *always* indicating that the spirochætes are not only alive, but also active.

The partial relapses (comprising about half the total relapses) were about 20 to 40 per cent. more frequent in the treated than the untreated, though the reason for this was not discovered. Yet these partial relapses are also dangerous, at least potentially. First, because a partially positive Wassermann is more significant of disease in a proved and treated syphilitic than in an undiagnosed and untreated patient (Med. Res. Special Report No. 14; also Browning and MacKenzie). Second, because, in our experience, an untreated partial Wassermann in a proved syphilitic will probably become positive in two to four months.

PART III.—MODIFICATIONS IN THE ROUTINE CONTINUATION TREATMENT OF SYPHILITICS, RECENTLY "CURED" AND WASSERMANN NEGATIVE, SUGGESTED BY THE FAILURE OF MERCURY CONTINUATION TREATMENT

The fundamental difficulty in the after-treatment of a case of clinically active syphilis, which has recently become Wassermann negative, arises from the fact that "you never can tell" whether any quiescent residual spirochætes may still be lurking in the patient's vitals. The provocative reaction is little help, for its diagnostic value is less than was formerly believed (p. 93).

Now, the physician may try to assist Nature to destroy any residual spirochætes, by giving drugs; but the spirochætes will be in protected and inaccessible lairs, where the drugs can only reach them in low concentration.

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Therefore common sense demands that they should be attacked by a remedy proved to be far more spirochæticidal than mercury, namely, arsenobenzol. The extraordinary efficiency of arsenobenzol, as compared with mercury, has been conclusively demonstrated by laboratory experiments, by clinical observations, and by the almost invariable failure of mercury to make a positive Wassermann negative (p. 89).

Arsenobenzol is also preferable to mercury, because laboratory experiments suggest that resistant strains of spirochætes are produced by a prolonged administration of the latter, but not of the former.

MODIFICATIONS IN THE ROUTINE CONTINUATION TREATMENT

(a) The incidence of our Wassermann relapses was greatest in the second half of the first year, after the "914" Admission Course. Therefore, although the liver occasionally takes six months to recover from the "914" course, it is best, in the absence of contrary indications, to risk giving the first Continuation Course of 6.3 gm. of "914" *after a rest interval of two months only.*

(b) The grade and incidence of our Wassermann relapses varied directly with the grade of the Admission Wassermann; therefore, patients with a positive or partial Wassermann should be given an extra "914" Continuation Course, if possible, about three months after the first. A second "914" Continuation Course should be given in the first half of the second year.

(c) Grey Oil is unjustifiable in Wassermann negative quiescent syphilis, when prescribed alone; yet it may still be *an adjuvant* with Salvarsan—as Lehnhoff-Wyld found that minute doses of one metal activated the therapeutic action of another in trypanosome infections.

We have no data from our Clinic regarding this point. Colonel Harrison, however, who supports the treatment suggested under (a), (b), and (d), is convinced that mercury should be prescribed with the Salvarsan. (Private communication.)

(d) If the Wassermann becomes positive at any time, salvarsan should be given at once—unless contra-indicated. If the Wassermann remains persistently positive, it may be advisable to stop all drug treatment.

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GENERAL CONCLUSIONS

A study of the Wassermann reaction as a guide in treating male syphilis at a venereal clinic during 1918-23 inclusive has led to the following conclusions:—

(1) *The sooner a patient who has contracted syphilis is thoroughly treated, the greater the probability of making his Wassermann negative, of keeping it negative, and so of completely curing the disease.*

(2) (a) *It is unjustifiable to treat syphilis—Wassermann or Sachs-Georgi-negative—with mercury alone as a routine, to prevent clinical or Wassermann relapses, and finally cure the disease by destroying any quiescent residual spirochætes.*

For (i) Grey Oil courses definitely increased, instead of greatly diminishing as expected, the tendency to Wassermann relapse; (ii) Mercury tablet courses certainly did not diminish as expected, but very probably increased, the tendency to Wassermann relapse.

(b) A Wassermann relapse (even a partial one) signifies renewed spirochætal activity, and, therefore, injury to the patient—though this is sometimes only potential.

(c) Assuming, for the sake of argument, that mercury tablet courses have *no effect* on the Wassermann relapses, it is still unjustifiable to prescribe long courses of this recognised cumulative poison, for no definite clinical advantage. Far less poisonous drugs, when used as food preservatives, are officially condemned—notably boracic acid.

(d) This frequent failure of mercury in Wassermann-negative quiescent syphilis, contrasting with its usual success in clinically active syphilis, is due to the different pathological condition treated—though it rarely removes a positive Wassermann in the latter. Most probably the mercury, being unable to attack the inaccessible residual spirochætes, simply depresses the patient's *immunity*. For upon immunity—which may be indirectly increased by drugs—the destruction of these spirochætes chiefly depends.

(3) Salvarsan is a more potent spirochæticide than mercury; besides, resistant strains of spirochætes are probably developed by prolonged administration of the latter, but not of the former. *Therefore, extra courses of salvarsan, carefully given, will be more successful than*

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those of mercury, in preventing Wassermann relapses and destroying any residual spirochætes.

To avoid misapprehension, it must be stated that our criticisms of the value of mercury refer only to its administration in Wassermann-negative quiescent syphilis. The value of mercury in clinically active syphilis is admitted.