

**Experience with salvarsan : Ehrlich-Hata's 606 in the New York Skin and Cancer Hospital / Howard Fox and William B. Trimble.**

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**Publication/Creation**

Chicago : American Medical Association, 1911.

**Persistent URL**

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# EXPERIENCE WITH SALVARSAN

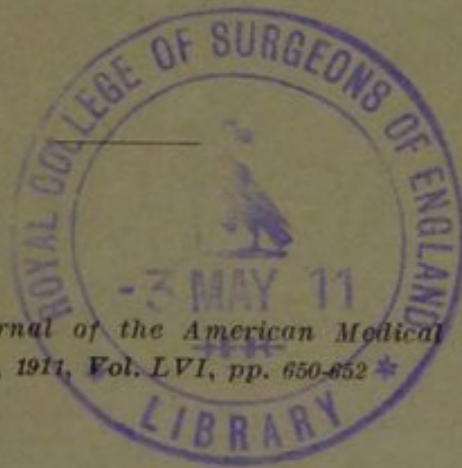
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HOWARD FOX, M.D.

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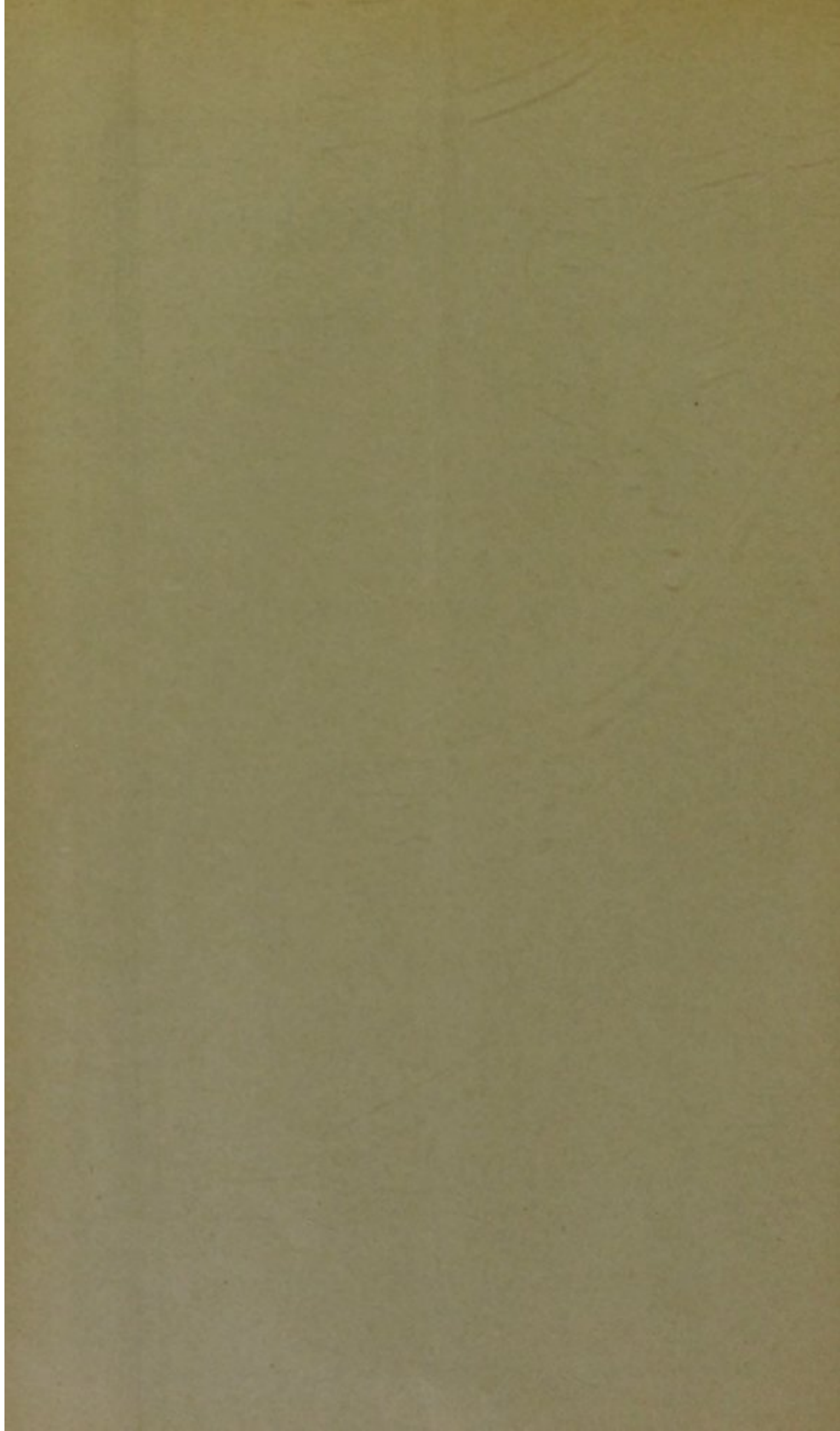
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NEW YORK



*Reprinted from The Journal of the American Medical Association*  
March 4, 1911, Vol. LVI, pp. 650-652 \*

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## EXPERIENCE WITH SALVARSAN

EHRlich-HATA'S 606 IN THE NEW YORK SKIN AND  
CANCER HOSPITAL

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HOWARD FOX, M.D., AND WILLIAM B. TRIMBLE, M.D.  
NEW YORK

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Through the kindness of Dr. Flexner of the Rockefeller Institute we received in October twenty tubes of Ehrlich's 606 for experimental use in the Skin and Cancer Hospital. The twenty tubes have been used for the treatment of eighteen patients, a second injection having been given in two of the cases in which relapses occurred. All of the patients remained in bed at least three days after treatment and then continued under observation at the hospital or returned to the dispensary at weekly intervals. All except two of the patients have remained under observation up to the present time.

With the exception of a patient with nodular leprosy to whom the new remedy was experimentally given, the patients selected for treatment were those who presented active syphilitic manifestations and (except in Case 8) a positive Wassermann reaction. The choice of patients was limited to those in whom ophthalmoscopic examination of the fundus and examination of the heart and urine showed no deviation from the normal condition.

The injections<sup>1</sup> of salvarsan were given either in suspension or in solution in doses varying from 40 to 60

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1. In four of the cases (1, 3, 7, 9) the insoluble injections were given according to the method of Wechselmann. This consisted in grinding up the salvarsan in a mortar with 2 c.c. of a 10 per cent. solution of sodium hydroxid. Glacial acetic acid was then added, drop by drop, until precipitation occurred, after which 2 c.c. of sterile water were added. The mixture was then made neutral to litmus by the further addition of either 2 per cent. acetic acid or of sodium hydroxid, according to necessity. When completely neutral the suspension was centrifuged, the supernatant fluid poured or pipetted off, the residue mixed with 10 c.c. of physiologic salt solution and thoroughly shaken. It was then ready for subcu-

centigrams. In the first nine cases the drug was given in a neutral suspension in the subcutaneous tissue of the interscapular region. In one case (10) the injection was made in the quadratus lumborum muscle. In the last ten cases, soluble injections were given in the gluteal muscles, according to the method of Lesser.

Examinations for *Spirochæta pallida* were made with the dark-field illuminator in five of the cases and showed a rapid disappearance of the organisms after injection. In no case could any spirochetes be found at the end of seventy-two hours after treatment, as seen in Table 1.

The Wassermann reaction was performed in every case before the injection was given and was afterward repeated at weekly or somewhat less frequent intervals. It was found to be positive in all except one case (9) in which mercury had been previously administered for

TABLE 1.—RESULT OF EXAMINATIONS FOR SPIROCHÆTA PALLIDA

Case No.	Lesions Examined	Spirochetes Present Before Treatment	End 24 Hours	Hours 48	72 Hours
1	Papules..	Large numbers.	Few.....	None.....	.....
2	Ulcers...	Few.....	Few.....	None.....	.....
5	Chancre..	Large numbers.	Moderate numbers.	Few.....	None.....
8	Papules..	Moderate numbers.	Few.....	None.....	.....
13	Mucous patches	Enormous numbers.	Moderate numbers.	None.....	.....

several months. The original Wassermann method was performed by us, using two antigens for every case, one of the antigens being an alcoholic extract of syphilitic liver that had been found reliable in testing several hundred cases. Active serum from every case was also sent to Dr. Noguchi of the Rockefeller Institute, who

taneous injection. In six of the cases (2, 4, 5, 6, 8, 10) a neutral suspension was made by simply grinding up the salvarsan in a mortar with a 10 per cent. solution of sodium hydroxid. The latter solution was added in the proportion of 1.33 c.c. for each decigram of salvarsan, the mixture being brought up to 10 c.c. in volume by the addition of physiologic salt solution. The salvarsan was prepared for the soluble injections as follows: The drug was added to 15 c.c. of hot sterile water in a graduated glass cylinder containing a few glass beads, and dissolved at once on shaking. Two c.c. of a normal sodium hydroxid solution were then added, causing a precipitation of the salvarsan, which was redissolved by the further addition, drop by drop, of the sodium hydroxid solution. The mixture was brought up to 20 c.c. in volume by the addition of sterile water and an intramuscular injection of 10 c.c. given in each buttock.

employed his own antihuman system in determining the reaction. The final results obtained by the two methods were approximately the same with the exception of Case 3, in which the Noguchi method showed a negative result on the fiftieth day, while the Wassermann method continued to show a positive reaction at the time of writing. In five of the cases (1, 6, 7, 11, 12) the reaction has become entirely negative at the end of eighty-five, forty-six, seventy, thirty-three and fifty-four days respectively. In one case it became weakly positive with the Wassermann method (negative with Noguchi) at the end of a month and again changed to a strongly positive reaction coincident with a bad relapse of the clinical manifestations.

In observing the general action of salvarsan we were impressed by the remarkable tonic effect of the drug in a number of our patients. From three to five days after treatment a decided improvement in appetite, color and general appearance was noted, especially in Cases 1, 2, 7. In Case 13, however, in which the result of the injection was most favorable, the general condition of the patient seemed decidedly worse for about two weeks after treatment.

In all of the cases a rise of temperature occurred during the first few days after the injection. As a rule, it appeared at the end of twenty-four hours and continued for two or three days with morning remissions. The highest temperature recorded was 102.6 F.; while in the majority of cases it did not exceed 101. In one case the temperature curve was of an intermittent character. In no case was it accompanied by chills. In the case of leprosy the temperature rose to normal, having been subnormal for several weeks previous to the injection.

While the general febrile symptoms were slight and the cause of little or no disturbance to the patient, the same cannot be said of the local effects of treatment. In almost every case there was considerable pain for the first twenty-four hours following the injections, and as a rule the use of morphin became necessary. In a few cases it was very intense and lasted for about three days. The insoluble injections in the subcutaneous tissue appeared to be more painful than those given in solution in the gluteal muscles. In spite of the unavoidable pain, two of the patients cheerfully submitted to a second injection when relapses occurred.

TABLE 2.—RESULTS OF TWENTY

Case No., Sex, Age and Stage	Lesions	Duration of Lesions	Previous Treatment	Date, Dosage and Method of Injection
1—F.—47—II	Papular syphilid . . . . .	5 weeks.	None . . . . .	10/13/10.— Gm. 0.5 in suspension.
2—M.—19—II	Pustulo crustaceous syphilid of nose, ear, arms and legs.	8 months.	Continuous Hg. treatment by mouth eight months; grew worse under treatment.	10/15/10.— Gm. 0.4 in suspension.
3—F.—32—III	Tuberculo-ulcerative syphilid of face.	2 years.	Hg. at irregular intervals by mouth and injection for two years; disease not controlled.	10/22/10.— Gm. 0.5 in suspension.
4—F.—20—II	Chancre of lip; macular syphilid; mucous patches.	Eruption 6 days.	None . . . . .	10/22/10.— Gm. 0.45 in suspension.
5—F.—27—III	Gumma of clavicle; tubercular syphilid of lip.	Gumma 4 months; lip lesion 12 years.	Hg. at irregular intervals for many years; improved but never cured.	10/22/10.— Gm. 0.45 in suspension.
6—M.—32—II	Papulo-squamous syphilid; extensive mucous patches.	3 months.	Hg. by mouth for one month.	10/28/10.— Gm. 0.5 in suspension.
7—F.—20—II	Papular syphilid . . . . .	3 weeks.	None . . . . .	10/28/10.— Gm. 0.4 in suspension.
8—M.—37—II	Pustular syphilid . . . . .	4 months.	Hg. by mouth for four months without effect on eruption.	10/29/10.— Gm. 0.5 in suspension.
9—M.—21—II	Maculo-papular syphilid	5 weeks.	None . . . . .	10/29/10.— Gm. 0.45 in suspension.
10—M.—34—III	Tuberculo-ulcerative syphilid of arm, shoulder and abdomen; ulceration of palate	4 months.	Hg. by mouth 2 weeks	11/3/10.— Gm. 0.5 in suspension.
11—M.—38—III	Gummatous ulceration of hard and soft palate and ear.	6 months.	Hg. by mouth, inunctions and injections, irregularly one year; Hg. very badly borne.	11/10/10.— Gm. 0.5 in solution.
12—M.—24—II	Mucous patches; laryngitis.	10 months.	None . . . . .	11/10/10.— Gm. 0.45 in solution.
13—F.—46—III	Tuberculo-crustaceous serpiginous syphilid.	1 year.	None . . . . .	11/15/10.— Gm. 0.5 in solution.
14—F.—35—III	Gumma of soft palate and pharynx; gummatous infiltration of access. sinuses; deafness.	3 years.	Hg. and KI by mouth irregularly one year.	12/3/10.— Gm. 0.45 in solution.
15—M.—43—III	Tuberculo-ulcerative syphilid of thigh.	7 months.	None . . . . .	12/5/10.— Gm. 0.45 in solution.
16—M.—38—III	See Case 11. Second injection.	.....	.....	12/15/10.— Gm. 0.6 in solution.
17—M.—19—II	See Case 2. Second injection.	.....	.....	12/22/10.— Gm. 0.45 in solution.
18—M.—40—...	Nodular leprosy . . . . .	6 years.	Chaulmoogra oil, strychnin and mercury.	1/5/11.—Gm. 0.4 in solution.
19—F.—23—III	Gummatous ulceration of leg.	6 months.	None . . . . .	1/12/11.—Gm. 0.6 in solution.
20—F.—32—III	Gumma of nose.....	9 months.	Practically none . . . . .	1/12/11.—Gm. 0.6 in solution.

ECTIONS OF SALVARSAN

Local Effect of Injection	Wassermann Reaction	Result of Treatment
rather severe for 48 hours; induration moderate.	Negative at end of 85 days.	Eruption almost disappeared at end of three months; improvement in general health one week after injection.
moderate, lasting 48 hours; induration moderate.	Weakly positive end of month; then became strongly positive.	Marked improvement for three weeks, when relapse occurred. (See text.)
severe; induration, pain and tenderness marked; slightly red 2½ months.	Positive at end of 87 days.	Improvement began on second day; nasal discharge stopped at end of one week; crusted and ulcerated lesions healed in ten weeks.
moderate and induration moderate and well healed.	Positive at end of 73 days; reaction weaker than at beginning.	Chancre healed in 3 weeks; eruption disappeared at end of 4 weeks; mucous patches healed in 4 days; severe relapse 6½ weeks from time of injection, consisting of mucous patches of mouth and vulva and macular and millary papular syphilid.
moderate; induration moderate and redness very marked at first; persisted 2 months.	Positive at end of 80 days.	Gumma nearly cured end one month (see text); lip lesion disappeared in ten days.
moderate and induration moderate & persistent; no tissue necrosis.	Negative at end of 46 days.	Disappearance of mucous patches in ten days; eruption disappeared end of 2½ months.
moderate and induration moderate.	Negative at end of 70 days.	Marked improvement in general health at end of five days; gained 10 lbs. in weight since injection; eruption practically disappeared.
severe; induration moderate.	Negative before and during entire treatment.	Moderate improvement at end of one week; patient failed to return to hospital.
severe first 12 hrs.; induration moderate.	Positive at end of 16 days.	Slight improvement during three weeks, when patient failed to return to hospital.
severe second day; induration slight.	Positive at end of 3 weeks.	Lesion healed in three weeks.
severe for 12 hrs.; induration moderate 3 weeks.	Negative during entire treatment. (See text).	Astonishing improvement at first; ulceration of palate reduced to half its size at end of one week; marked improvement in general health and appearance; lesions practically healed in 12 days, when relapse occurred. (See text.)
severe pain; marked induration of buttocks 2 weeks.	Negative end of 54 days.	Mucous patches disappeared three days after injection; hoarseness began to improve on second day, and by fifth day voice was normal.
severe pain for 2 days; marked induration of buttocks 3 weeks.	Weakly positive at end of 63 days.	Eruption almost disappeared at end of three weeks; entirely well at end of one month; general condition worse for two weeks as result of treatment, anemia, loss of appetite and weight.
moderate and induration moderate.	Positive at end of 46 days.	Gumma nearly healed at end of six weeks.
severe 5 days; induration marked and lasted 3 weeks.	Strongly positive at end of 43 days.	Lesions entirely healed at end of 3½ weeks.
locally no pain or induration.	Continued to be negative.	Improvement of ulceration marked at end of first week; process then remained about stationary and relapsed slightly at end of third week.
moderate and induration moderate.	Positive at end of 26 days.	Continued slow improvement for a month.
severe; induration moderate.	No examination made after treatment.	Absolutely no effect on lesions; since treatment has been confined to bed, his general condition having become markedly worse.
severe; induration moderate.	Positive at end of 1 week.	Marked improvement in lesions at end of a week.
24 hours; no induration.	Positive at end of 1 week.	Improvement at end of one week.



The induration following the insoluble injections varied considerably in the different cases. It was generally well marked for the first week. In no case has it absolutely disappeared at the time of writing. In three cases (3, 5, 6) it was very severe, accompanied by redness and was the cause of considerable discomfort for about two weeks. No abscesses occurred, although in one case (6) there was a slight necrosis of tissue, followed by a serosanguinolent discharge for three weeks. The induration resulting from the soluble injections in the buttocks was extremely variable in the different cases. It was greatest, as a rule, on the third day after treatment. In some of the cases it was slight and occasioned very little inconvenience. Two of the patients, however, complained of considerable lameness for about two weeks. While the pain and induration were by no means unbearable they were severe enough to make it very desirable to continue our experiments with other methods of injection, concerning which we hope to report in a later communication.

The result of the twenty injections from a clinical standpoint were in some respects encouraging, in other disappointing. The most brilliant symptomatic result was obtained in Case 13, in which a superficial tuberculo-crustaceous syphilid disappeared at the end of a month. Even in this case it is not impossible that a single injection of calomel or one or two injections of salicylate of mercury might not have accomplished the same results. An excellent result was also obtained in Case 5, in which a mild tubercular syphilid of the lip that had existed for twelve years (according to the patient's statement) disappeared at the end of ten days. A gumma at the sternoclavicular point occurring in the same patient was also healed at the end of a month. In three of the cases (1, 6, 7) presenting early papular syphilids, the results were apparently not so good as those that might have been obtained from mercury. The lesions, however, finally disappeared in each case, and the Wassermann reaction became negative.

In three tuberculo-ulcerative cases (3, 10, 15) and in a case of gumma of the pharynx and palate (14), the results were satisfactory from a clinical standpoint, although the Wassermann reaction has not as yet become negative. The result of treatment in Case 3 was especially gratifying, as it had been very difficult to control

the disease with mercury. In three cases in which mucous patches were present (4, 6, 12) there was a most rapid disappearance of the lesions after injection. The result of treatment in the case of leprosy was most unsatisfactory. No change whatever occurred in the lesions and the patient's general condition has become decidedly worse.

Relapses occurred in three cases, in two of which we thought at first that splendid results had been obtained. One of these cases (2) presented a pustulo-crustaceous syphilid of somewhat malignant type that had grown worse under internal administration of mercury. The patient improved rapidly for a month, the Wassermann reaction becoming nearly negative and the ulcerated lesions of the nose, ear, arms and legs healing almost completely. He then suffered a severe relapse, his condition becoming nearly as bad as at the outset. He was given a second injection and the manifestations have again almost disappeared.

A disappointing relapse was also shown by a patient (Case 11) with extensive gummatous ulceration of the hard and soft palate. The improvement was most striking at first, the ulcerated area being reduced to half its original size at the end of a week. A relapse then occurred and the patient was given a second injection which was again followed by a relapse. As it is almost impossible to administer mercury to this patient it is our intention to give him one or two more injections of salvarsan in the near future.

It would be unwarranted to draw any general conclusions from our limited material. It must be admitted, however, that the effect of the new remedy, in causing lesions to disappear rapidly, has been striking in several of our cases. In other cases, however, the lesions have disappeared rather slowly. In comparison with what might have been expected from a vigorous mercurial treatment, the results do not appear to be especially brilliant. In several of the cases the disease had not been controlled by mercury and responded very favorably to salvarsan. Indeed in one case (11) the patient had found it practically impossible to take mercury in spite of persistent attempts to administer the drug by mouth, inunctions and injections.

In the limited number of cases in which we have used salvarsan it has seemed to us that the lesions of the

mucous membranes have yielded more quickly than those of the cutaneous surface. As has been said, the brilliant results in some cases have been only temporary and the relapses that have occurred have followed the improvement with discouraging rapidity. Our results are favorable enough to make us willing to continue our experiments with salvarsan in a larger and more varied number of cases than the ones that are here reported.

In conclusion we wish to thank Dr. George Henry Fox for much of the material and for the privilege of treating the cases at the Skin and Cancer Hospital; to Dr. Udo J. Wile for the spirochete examinations, and to Dr. Robert G. Reese for the ophthalmoscopic examinations.

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