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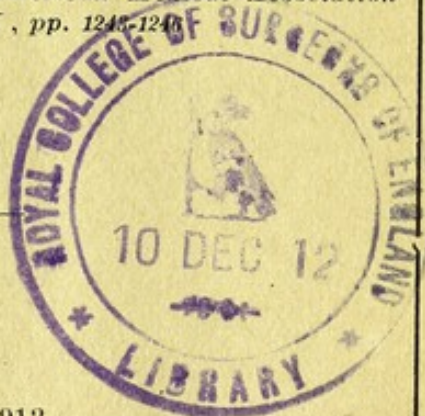
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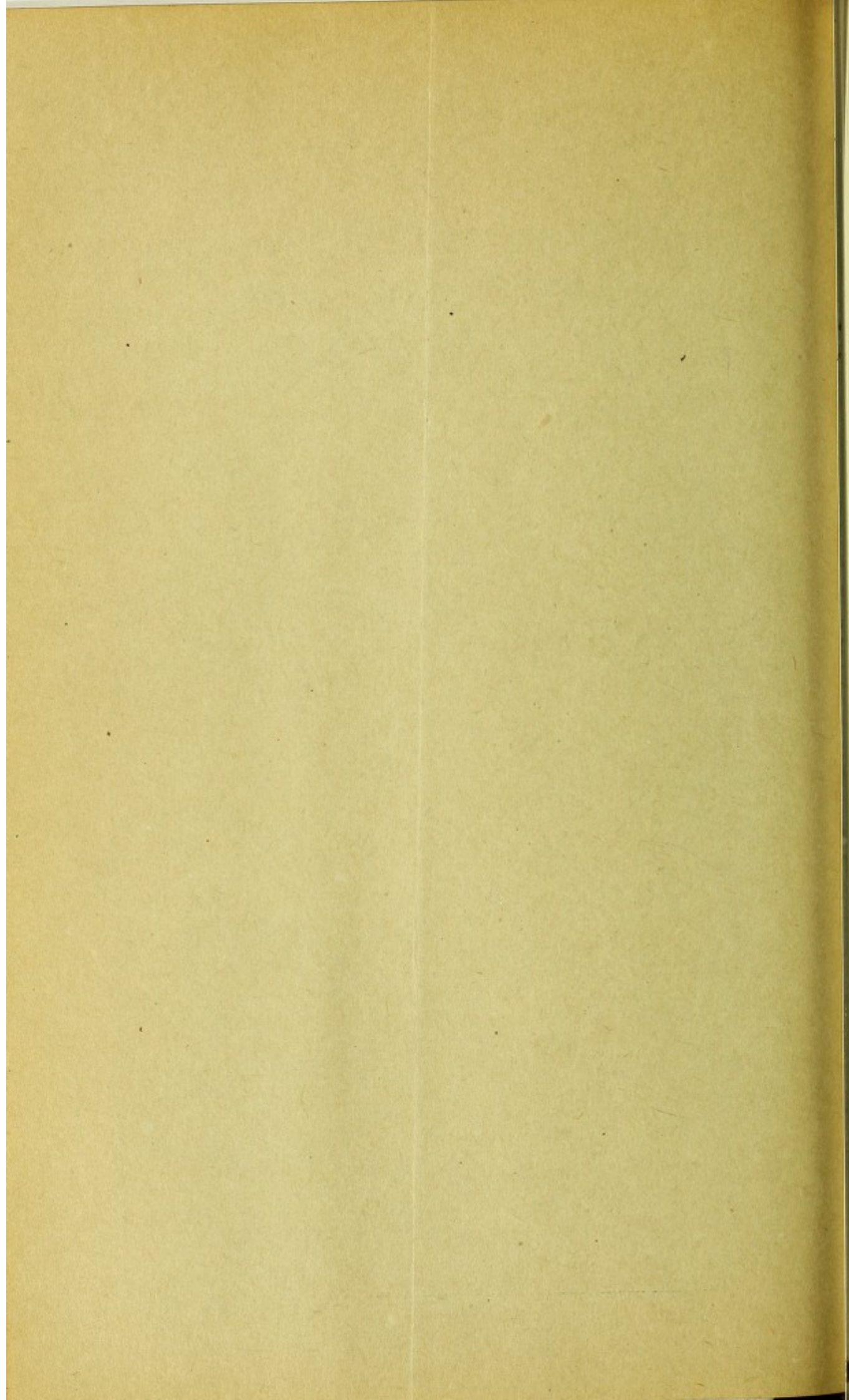
The Relative Value of Mercury and Salvarsan from a Serologic Point of View

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THE RELATIVE VALUE OF MERCURY AND SALVARSAN FROM A SEROLOGIC POINT OF VIEW *

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The action of salvarsan on the clinical manifestations of syphilis is well understood at the present time. Its temporary effect on the Wassermann reaction is also fairly well known. To judge, however, of its ultimate effect on the disease either from a clinical or serologic standpoint will be possible only after many years have elapsed. It will therefore be seen that at the present time a serologic comparison of mercury and salvarsan must of necessity be unsatisfactory.

In attempting to collect statistics of various observers on the serologic action of the two remedies, we are confronted with very great difficulties. In the case of mercury the figures vary greatly according to the thoroughness of treatment, the preparation and administration of the drug and the stage of the disease at which the remedy is given. Indeed, there is even now no absolute agreement as to the very best method of using mercury. In the case of salvarsan the difficulties are still greater owing to the newness of the remedy. A large number of the reports deals with methods of treatment (subcutaneous and intramuscular injections) which at the present time, except in the case of children, are practically discarded. A further difficulty in judging of the action of salvarsan alone is due to the fact that at present the majority of syphilographers are using it in combination with mercury. Again, the number of serologic reports on the action of salvarsan is very small in comparison with the enormous number dealing with the clinical aspect of the subject.

* Read in the Symposium on Mercury and Salvarsan in the Treatment of Syphilis in the Sections on Pathology and Physiology and Dermatology of the American Medical Association, at the Sixty-Third Annual Session, held at Atlantic City, June, 1912.

In attempting a comparative study that appeared to be rather hopeless at the outset, I have realized the difficulty in drawing conclusions from statistics. It would be possible, I feel, for a prejudiced observer to prove his case in favor of either mercury or salvarsan. My efforts would have indeed been discouraging if it were not for the striking results that have been noted in the abortive treatment of the disease, which will be later discussed.

In judging of the serologic action of mercury I have compiled the records (Table 1) of twenty-one observers. Most of these reports deal with cases that were thoroughly treated by inunctions or injections, in all stages of the disease. The percentage of negative results is perhaps too favorable for mercury, as some of the tests were made after a course of treatment. Omitting three reports that included among the negative results cases in which the reaction was weakened, there were 1,634 cases giving an average of 64.8 per cent. of negative reactions following the use of mercury.

In judging of the serologic action of salvarsan one is struck by the great discrepancies in the results of different observers, particularly in the case of subcutaneous and intramuscular injections. I have tabulated the results of thirteen observers who treated a total of 987 cases by these methods with an average of 47.4 per cent. of negative results. The variations in the results are seen by glancing at Table 2, in which Schreiber and Hoppe reported 92.3 per cent., Lange 61 per cent., Treupel and Levi 25 per cent. and Goldenberg and Kaliski 8.8 per cent. of negative reactions.

The results obtained by intravenous injections, especially when repeated or combined with intramuscular injections, are much more favorable. By the use of triple intravenous injections Gutmann obtained 74 per cent. of negative results, while Zimmern found 68 per cent. after two or more injections. By a combination of intravenous and intramuscular injections Linser obtained 70 per cent. and Micheli and Quarelli 86 per cent. of negative results, while from this method Spiethoff states that a negative reaction was obtained in a majority of his cases.

In a serologic comparison of the different methods of administration of salvarsan, McIntosh and Fildes found 80 per cent. of negative results after intravenous injection.

TABLE 1.—CASES OF SYPHILIS TREATED WITH MERCURY

No.	Name	No. of Cases	Method of Treatment	Percentage of Negative Results
1	Müller	48	One to three courses.	37.5
2	Lederman	{ 92	Four or more courses.	26
3	Bering	{ 59	Well-treated chronic intermittent method.	52
4	Citron	69	84
5	Fischer	58	46.5, 75.8 including weak reactions.
6	Blumenthal and Roscher	62	48
7	Lesser	95	One to five "Kuren".	51 negative or weakened.
8	Blaschko	115	Well treated; at least four good "Kuren".	62
9	Mauriac	90	84 negative or weakened.
10	Pürckhauer	33	Well treated	60
11	Höhne	{ 116	One or more "Kuren".	65
		{ 54	One to four "Kuren".	68.5
		127	Thoroughly treated by injections and inunctions.	52
12	Jesionek and Melrowsky	{ 216	Calomel	66
		{ 130	One to three "Kuren".	45
13	Bruck	{ 49	Four to eight "Kuren".	61
14	Harrison	{ 69	70
15	Seligman and Pinkus...	{ 166	Two courses inunctions or injections.	22
		{ 38	Six to eight courses.	59
		112	One to three "Kuren".	25
16	Feuerstein	102	Four to ten "Kuren".	55
17	Almkvist	231	42.8
18	Boas	139	Mercury alone or combined KI, arsenic and quinin.	70
19	Gavini	200	Little treatment	79
20	Marcus	124	Energetic treatment	23
21	Gennerich		Majority; ten "Kuren" by injections.	85
			Calomel injections and inunctions.	87
			75

tions, as opposed to 53 per cent. after intramuscular injections. On the other hand, Craig in a comprehensive paper states that he obtained 78.6 per cent. of negative reactions after intramuscular injections (mostly single), as opposed to 63.8 per cent. after combined intramuscular and intravenous methods.

The value of the reports on salvarsan that have been quoted is lessened by the fact that the period of observation of the cases was short as a rule, seldom more than a few months at best. One of the most valuable communications from the standpoint of the number of cases as well as duration of observation has recently been published by Heidingsfeld, whose latest statistics I am able to quote through the kindness of a personal communication. In his series of 333 cases, treated mostly by single injections, 256, or 76.9 per cent., changed from a positive to a negative reaction. Of these cases 101 remained negative one year or more, fifty-eight, nine months or more, forty-five, six months or more, fifty, from one to three months, giving a total average of eight and one-fifth months per negative case.

From the figures of the different observers that have been thus far quoted it is, I think, apparent that no positive conclusions can be made as to the comparative serologic value of mercury and salvarsan. The case is entirely different with regard to the results recently reported from the abortive method of treatment by salvarsan alone or in combination with mercury. From this method of treatment some very strikingly good results have been obtained from a serologic as well as a clinical point of view.

By the early administration of mercury, it has generally been found to be impossible to abort syphilis if we except the almost immediate application of the drug (first eight hours) at the site of inoculation. Even when the early administration is combined with excision of the chancre, the eradication of the disease does not follow. While such early treatment probably shortens the course of the disease, it is nevertheless true that the subsequent use of the drug is almost invariably required.

While it is too early to judge of the permanent results of abortive treatment by salvarsan it can be asserted that they are at least very hopeful and worthy of our most careful consideration. One of the first reports on the abortive method by the use of salvarsan was that of

TABLE 2.—CASES OF SYPHILIS TREATED WITH SALVARSAN

No.	Name	No. of Cases	Method of Treatment	Percentage of Negative Results
22	Schreiber and Hoppe...	52	Subcutaneous and intramuscular.....	92.3
23	Neisser and Kuznitzky.	100	Intramuscular; small doses.....	44
24	Fraenkel and Grouven..	75	Subcutaneous	9, 24 including weak reactions.
25	Lange	250	Subcutaneous and intramuscular.....	61
26	Jeanselme and Touraine	32	One large dose (?).....	75
27	Lesser, E.	66	Intramuscular	25
28	Plaut	46	Subcutaneous	4, 10.9 including weak reactions.
29	Scholtz, Salzberger and Beck.....	80	Subcutaneous	26
30	MacRae	54	Subcutaneous and intramuscular.....	12.9, 29.6 including weak reactions.
31	Weller	40	Intramuscular	50 became negative or an original negative remained so.
32	Treupel and Levi.....	115	Subcutaneous and intramuscular.....	25
33	Freund	43	Mostly subcutaneous	35
34	Goldenberg and Kaliski.	34	Subcutaneous and intramuscular.....	8.8; a number also gave weakened reactions later.
35	Noguchi	102	Subcutaneous, intramuscular and intravenous.....	33.7, 52 including weak reactions.
36	Fox and Trimble.....	71	Intravenous and intramuscular.....	39
37	Engman and Buhman..	32	Intramuscular and intravenous.....	28
38	Craig	150	Intramuscular	78.6
39	McIntosh and Fildes...	36	Intravenous	53
40	Gutmann	26	Combined	63.8
41	Zimmern	21	Intramuscular	53
42	Kromayer	27	Intravenous	80
43	Linser	132	Three intravenous	74
44	Spiethoff	30	Two or more intravenous.....	68
45	Micheli and Quarelli...	135	Repeated small intravenous.....	26
46	Heldingsfeld	90	Repeated intramuscular and intravenous.....	70
		34	Combined intravenous and intramuscular.....	Negative in majority of cases.
		333	Combined intravenous and intramuscular.....	86
			Mostly intravenous	76.9

Finger, who treated thirteen cases of primary syphilis by a single intramuscular or subcutaneous injection. During an observation period of twelve weeks to six months, six cases remained or became Wassermann negative.

In a series of twenty-three cases of primary syphilis treated by Milian by two to four injections (intravenous alone or combined with intramuscular), seventeen cases became negative and remained so from two to eight months and showed no clinical manifestations during this time. Milian writes, "It is certain that these statistics show that salvarsan is not a constant abortive remedy, but that among such remedies it is at the present time the most efficacious and powerful."

Of twenty-one cases treated by Emery by three intravenous injections thirteen became negative and remained so for a period of three weeks to two and a half months.

McDonagh treated twenty-two cases by two intravenous injections at intervals of ten days and writes, "I have twenty-two cases of primary syphilis treated in this way, ranging from twelve months to the present time, which have never given a positive Wassermann reaction or developed secondary symptoms."

Géronne and Gutmann report a series of thirty-seven cases, seventeen of which were positive and twenty negative before treatment. The abortive method was successful in twenty-nine cases, the majority of the patients being observed over six months. Ten cases were under observation from twelve to sixteen months.

Of fourteen cases treated by Stern, eight remained negative and showed no clinical symptoms for periods varying from four to fourteen months.

Queyrat reports a series of seventy-eight cases treated by three intravenous injections at intervals of seven days. He found that fifty-one cases became negative and remained so for periods averaging about three months. None of them showed any clinical manifestations.

Favorable as some of these reports appear, it would seem that still better results in the abortive treatment are possible when salvarsan is combined with mercury. In a valuable communication Gennerich reports on eighty-three cases of primary syphilis treated by intravenous injections of salvarsan combined with injections of calomel. The calomel was given as soon as the diag-

TABLE 3.—RESULTS OF ABORTIVE METHOD OF TREATMENT BY SALVARSAN ALONE OR IN COMBINATION WITH MERCURY

No.	Name	No. of Cases	Method of Treatment	Period of Observation	Percentage of Negative Results
47	Finger	13	One intramuscular or intravenous.....	12 weeks to 6 months...	46
48	Milian	23	Two to four intraven. or combined intraven. and intramusc.	2 to 8 months.....	73.9
49	Emery	15	Three intravenous injections.....	3 weeks to 2½ months...	86.6
50	McDonagh	22	Two intravenous injections.....	12 months to present...	100
51	Gérone and Gutmann.	37	Two and three intravenous injections.....	Majority over 6 mos.; 10 cases from 12-16 mos.	78.3
52	Stern	14	4 to 14 months.....	57.1
53	Queyrat	78	Three intravenous injections.....	Average three months....	65.3
54	Gennerich	83*	3-6 intravenous injections; 6-12 calomel injections.....	37 cases ½ to 1 year....	63.5
55	Löwenberg	24	Two intravenous injections of salvarsan combined with course of mercurial inunctions.	20 cases more than 1 yr.	20
56	Arning	45	One intravenous; one intramuscular injection combined with mercurial inunctions.	At least six weeks.....	100
57	Hecht	15†	Two intravenous injections combined with mercurial inunctions.	Average four months....	100
				4-11 months	66.6

* Sixty-three negative at outset; twenty positive at outset. † Negative at outset.

nosis was made by finding the spirochetes. This was followed in one or two days by intravenous injections of salvarsan given at intervals of a few days, in some cases six injections being given. Of sixty-three cases which were negative at the beginning of treatment, all except four remained negative. Of twenty cases that were positive before treatment all except four became negative and remained so. The figures of Gennerich are especially valuable owing to the comparatively long time of observation, thirty-seven of the cases having been followed for six months to a year and twenty of the cases for more than one year.

Löwenberg treated twenty-four cases of primary syphilis by a combination of two intravenous injections of salvarsan and a course of mercurial inunctions. All of his cases remained Wassermann-negative and free from symptoms at the end of a minimum period of six weeks' observation.

Equally good results were obtained by Arning in the treatment of forty-five cases of primary syphilis and twenty-six cases showing the earliest secondaries, in which the average period of observation was four months, the longest being eleven months. His method consisted of a course of inunctions combined with an intramuscular and, ten days later, an intravenous injection of salvarsan. All of his seventy-one cases showed negative reactions and freedom from symptoms at the last period of observation.

Finally, Hecht has treated cases of primary syphilis by a course of mercurial inunctions combined with two intravenous injections of salvarsan, together with excision of the chancre (in a few favorable cases). Of fifteen cases that were Wassermann-negative at the outset, all except one remained negative during a period varying from four to eleven months.

Before giving the conclusions of my statistical paper, it should be said that in a serologic comparison of the two drugs, salvarsan is perhaps at a disadvantage. While a great deal of experimental work has already been done with this new remedy, the last word still remains to be said as to the best method of administration. We do not know as yet the limit of the number of doses that can be given. In the case of mercury, on the other hand, there is a fairly general agreement as to the best form of treatment.

The question of the serologic effect of a combination of the two remedies has not been discussed except in the case of the abortive method, as the reports on this aspect of the subject, though favorable, are yet very few in number.

CONCLUSIONS

1. In the primary stage of syphilis, especially before the Wassermann reaction becomes positive, salvarsan is a most valuable remedy from both the serologic and clinical standpoint.

2. Repeated intravenous injections at this stage give promise of aborting the disease in a considerable percentage of cases.

3. No such promising results have ever been reported by the early administration of mercury alone.

4. It is probable that the abortive method will prove still more effective when a combination of the two drugs is used.

5. A serologic comparison of mercury and salvarsan in later stages of syphilis fails to show any decided advantage in favor of either remedy.

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