A CLINICAL STUDY OF THE REACTIONS FOLLOW-
ING THE INTRAVENOUS ADMINISTRATION
OF ARSPHENAMIN IN NONSYPH-
ILITIC PERSONS *

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Ten years have now elapsed since arsphenamin (salvarsan) was first introduced by Paul Erlich and his associates, and during that space of time many thousands of doses of this remedy have been administered. Almost from the beginning and extending to the present, untoward symptoms have been noted following the intravenous administration of arsphenamin. Many hypotheses have been advanced to explain these reactions, but as yet no method has been suggested which would eliminate these untoward reactions.

In this study, arsphenamin (Dermatological Research Laboratory) of the same serial number was administered to both syphilitic and nonsyphilitic patients, and the reactions following their intravenous administration were noted. It was believed that a study of this nature might throw some light on the possible cause or causes of these untoward symptoms.

SYMPTOMS IN SYPHILITIC AND NONSYPHILITIC PATIENTS

The reactions following the intravenous administration of arsphenamin are classified into: (1) immediate, (2) early, and (3) late symptoms. We shall concern ourselves in this discussion with a study of the early symptoms which were noted following the intravenous administration of arsphenamin to the nonsyphilitics and compare them with the symptoms observed when the identical product was administered to syphilitic patients.

The symptoms observed in the nonsyphilitic series were headache, chills, fever, nausea, vomiting, diarrhea, and backache. Two patients

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of this series developed cutaneous manifestations; one of the eruptions was scarlatinoid in character, and the other presented the characteristics of a vesicular eczema. Both patients made uneventful recoveries.

In all, 114 injections were administered to nonsyphilitic patients. Table 1 details the results obtained in our syphilitic series.

TABLE 1.—REACTIONS TO ARSPHENAMIN IN NORMAL PERSONS

Case	Lot	Dose	Reaction
1	3586	0.5	No reaction
2	2586	0.5	Fever, chills, headache, nausea, vomiting, pains in stomach
3	3586	0.5	No reaction
4	3586	0.5	Chills, nausea, loose bowels, no appetite
5	3586	0.5	Chills, fever
6	3586	0.5	Slight fever and loose bowels
7	3586	0.5	Slight nausea
8	3586	0.5	Chills and headache
9	3586	0.5	Headache, nausea, loose bowels, backache
10	3586	0.5	Slight chills and headache, nausea, loose bowels
11	3586	0.5	No reaction
12	3586	0.5	Chills, headache, nausea, loose bowels, no appetite
13	3586	0.5	Headache
14	3586	0.5	Fever, chills, headache, nausea, loose bowels
15	3586	0.5	Fever, chills, headache, nausea
16	3586	0.5	No reaction
17	3540	0.45	Fever, chills, headache
18	3540	0.45	Fever, chills, headache, nausea, loose bowels
19	3546	0.5	Chills, headache, nausea, vomiting, loose bowels, no appetite
20	3546	0.5	No reaction
21	3546	0.5	Headache, nausea, loose bowels
22	3546	0.5	Chills, headache, nausea, loose bowels
23	3546	0.5	Fever, chills, headache, nausea, vomiting, loose bowels
24	3546	0.5	Nausea, loose bowels
25	3546	0.5	Nausea
26	3855	0.5	Fever, chills, headache, nausea, loose bowels, aching of kidneys
27	3855	0.5	Fever, headache, nausea, vomiting at hospital, loose bowels
28	3855	0.5	No reaction
29	3855	0.5	No reaction
30	3843	0.5	Chills, headache, nausea, loose bowels, dizzy
31	3843	0.5	Fever, headache, loose bowels
32	3843	0.5	Nausea, vomiting, sleepy
33	3829	0.5	No reaction
34	3829	0.5	No reaction
35	3829	0.5	No reaction
36	3829	0.5	No reaction
37	3829	0.5	Nausea
38	3829	0.5	Fever, headache
39	3829	0.5	Headache, nausea
40	3829	0.5	Fever, nausea
41	3829	0.5	Chills (little)
42	3829	0.5	Headache (slight)
43	3829	0.5	Slight fever and headache
44	3829	0.5	Nausea
45	3829	0.5	Chills, nausea, vomiting
46	3829	0.5	No reaction
47	3829	0.5	Fever, chills, nausea, loose bowels
48	3829	0.5	Headache, vomiting, loose bowels, backache
49	3829	0.5	Nausea
50	3829	0.5	Fever, chills, headache, nausea, vomiting, loose bowels
51	3829	0.5	No reaction
52	3829	0.5	No reaction
53	3829	0.5	No reaction
54	3829	0.5	Slight nausea, backache
55	3829	0.5	No reaction
56	3829	0.5	Fever, headache, vomiting, loose bowels
57	3829	0.5	No reaction
58	3829	0.5	Chills, headache
59	3829	0.5	No reaction
60	3829	0.5	No reaction
61	3829	0.5	Headache, nausea, loose bowels
62	3884	0.5	Fever, chills, nausea, loose bowels
63	3884	0.5	Chills, nausea and loose bowels
64	3884	0.5	No reaction
65	3895	0.6	Loose bowels
66	3895	0.6	No reaction

TABLE 1.—REACTIONS TO ARSPHENAMIN IN NORMAL PERSONS—(Continued)

Case	Lot	Dose	Reaction
67	3900	0.5	Headache
68	3900	0.5	Headache, nausea, vomiting, loose bowels
69	3878	0.6	Fever, chills, headache, nausea, vomiting, loose bowels
70	3903	0.6	Chills, loose bowels
71	3903	0.6	Nausea, loose bowels
72	3895	0.5	Chills, headache, nausea, loose bowels
73	3895	0.5	Headache
74	3895	0.5	Headache, nausea, vomiting, loose bowels, backache
75	3895	0.6	Fever, chills, headache, nausea, vomiting
76	3895	0.5	No reaction
77	3895	0.6	Fever, chills, headache, nausea, loose bowels, weak and nervous
78	3895	0.5	Fever, chills, headache, nausea, vomiting, loose bowels
79	3900	0.5	Headache, nausea, loose bowels, pain in shoulder blade
80	3900	0.5	Chills
81	3900	0.5	Headache
82	3900	0.5	Headache, nausea, vomiting, loose bowels
83	3900	0.5	Chills, nausea
84	3900	0.5	No reaction
85	3900	0.5	Vomiting, constipation
86	3900	0.5	No reaction (drowsy)
87	3900	0.5	Headache, nausea
88	3900	0.5	Fever, chills, headache, nausea, vomiting, loose bowels
89	3900	0.5	Headache
90	3900	0.5	Loose bowels
91	3928	0.45	No reaction
92	3928	0.45	No reaction
93	3937	0.6	No reaction
94	3928	0.6	Headache, loose bowels
95	3903	0.5	Headache, nausea, loose bowels
96	3903	0.5	No reaction
97	3903	0.5	Loose bowels
98	3903	0.5	No reaction
99	3903	0.5	No reaction
100	3903	0.5	Nausea, vomiting, loose bowels
101	3903	0.5	No reaction
102	3903	0.5	Fever, headache and loose bowels
103	3902	0.5	No reaction
104	3937	0.5	Nausea, loose bowels
105	3937	0.5	Loose bowels
106	3937	0.5	No reaction
107	3937	0.5	Fever
108	3937	0.5	No reaction
109	3937	0.5	Headache
110	3937	0.5	Loose bowels
111	3937	0.5	Loose bowels
112	3937	0.4	Loose bowels (slightly)
113	3937	0.5	No reaction
114	3855	0.5	Loose bowels

Of this number seventy-seven, or 67 per cent., gave evidence of some reactive symptoms. Twenty-five, or 32 per cent., complained of fever; thirty-one, or 40 per cent., of chills or chilliness; forty-six, or 60 per cent., of headache; forty-seven, or 60 per cent., of nausea; eighteen, or 23 per cent., of vomiting; forty-six, or 60 per cent., of diarrhea, and five, or 6 per cent., of backache.

Table 2 gives in detail the reactions reported by the syphilitic patients, receiving the arsphenamin of the same serial numbers as the nonsyphilitic patients. The symptoms complained of were identical in both classes of subjects.

In all, the records of the reactions of ninety-three syphilitics were tabulated. Of this number, sixty-two, or 66 $\frac{2}{3}$ per cent., reported some evidence of reaction. Twenty-five, or 40 per cent., complained of

fever; twenty-six, or 42 per cent., of chills and chilliness; thirty-seven, or 60 per cent., of headache; thirty-seven, or 60 per cent., of nausea; twenty-six, or 40 per cent., of diarrhea; eleven, or 18 per cent., of vomiting and four of backache.

TABLE 2.—REACTIONS TO ARSPHENAMIN IN SYPHILITIC PERSONS

Case	Lot	Dose	Reaction
1	3586	0.5	No reaction
2	3586	0.5	Fever, chills, headache, nausea, loose bowels, pains in body
3	3586	0.5	No reaction
4	3540	0.5	No reaction
5	3540	0.5	No appetite
6	3540	0.5	No reaction
7	3540	0.5	Slight chills, nausea and loose bowels
8	3546	0.5	Headache, heart and body hurts her
9	3546	0.5	Headache
10	3547	0.5	No reaction
11	3546	0.5	Chills, nausea, loose bowels, heart-burn
12	3855	0.5	No reaction
13	3855	0.5	No reaction
14	3855	0.5	Chills, headache, body hurts and face is swollen
15	3855	0.5	Fever, chills, headache, nausea, loose bowels, pains through body
16	3855	0.5	Fever, headache, stiff joints
17	3855	0.5	Vomiting, tired feeling in back, also slight pains
18	3855	0.5	Fever, chills, nausea, loose bowels, nervous
19	3855	0.5	Chills, headache, nausea, pains in legs
20	3843	0.5	Fever, chills, headache
21	3843	0.5	Headache, loose bowels, feet hurt
22	3843	0.5	Fever, headache, stiff joints
23	3843	0.5	No reaction
24	3843	0.5	Nausea, nervousness
25	3829	0.45	No reaction
26	3829	0.45	Fever, headache, constipated, stiff joints
27	3829	0.5	Headache
28	3829	0.45	No reaction
29	3829	0.45	Chills, headache, nausea, vomiting
30	3829	0.45	Nausea, itching on calf and shins
31	3829	0.45	No reaction
32	3829	0.5	Headache, nausea, vomiting
33	3829	0.45	Fever, chills, headache, loose bowels
34	3829	0.5	Chills, nausea, vomiting, loose bowels
35	3829	0.45	Fever, chills, headache, nausea, loose bowels, pains in body
36	3829	0.5	No reaction
37	3829	0.45	No reaction
38	3829	0.5	No reaction
39	3829	0.5	Chills, headache, nausea, pains in legs
40	3829	0.5	Fever
41	3829	0.5	Fever, chills, nausea and loose bowels
42	3829	0.5	Headache, nausea, loose bowels
43	3829	0.5	Loose bowels
44	3829	0.5	Vomiting, dull feeling in head, tired limbs
45	3884	0.5	Headache, nausea, vomiting
46	3884	0.5	Headache, nausea, loose bowels
47	3884	0.5	Fever, chills, headache, loose bowels
48	3884	0.5	Chills, headache, nausea, loose bowels
49	3884	0.5	Nostril trouble
50	3895	0.45	Fever, headache, nausea
51	3895	0.45	Nausea, loose bowels
52	2895	0.45	Nausea, vomiting, loose bowels, tired in limbs
53	3900	0.45	Headache
54	3900	0.45	No reaction
55	3900	0.45	No reaction
56	3878	0.3	No reaction
57	3878	0.3	Chills, headache
58	3903	0.4	No reaction
59	3903	0.4	Fever, headache, nausea, weakness, pains in knees
60	3895	0.5	Fever, chills, headache, nausea
61	3895	0.5	(Spitting)
62	3895	0.5	Fever, headache, joints ache
63	3895	0.4	Fever, headache, nausea, loose bowels
64	3895	0.5	No reaction
65	3895	0.45	No reaction
66	3895	0.4	Vomiting, loose bowels, tired feeling in limbs
67	3895	0.5	No reaction
68	3895	0.5	No reaction

TABLE 2.—REACTIONS TO ARSPHENAMIN IN SYPHILITIC PERSONS—(Continued)

Case	Lot	Dose	Reaction
69	3895	0.5	Fever, chills, headache, nausea, loose bowels (arm swollen and sore)
70	3895	0.4	Headache, nausea, loose bowels
71	3895	0.5	Chills, nausea, pains in back
72	3895	0.4	Fever, chills, headache, nausea, vomiting
73	3895	0.5	Pains over eyes
74	3900	0.5	Fever, chills, headache, nausea, loose bowels
75	3900	0.5	Nausea, pains in chest and shoulders
76	3900	0.5	Fever, headache, nausea, loose bowels
77	3900	0.5	Fever, chills, nausea
78	3900	0.5	No reaction
79	3928	...	Chills, headache
80	3928	0.4	No reaction
81	3928	...	No reaction
82	3937	0.4	Nausea, vomiting
83	3937	0.4	Loose bowels
84	3937	0.4	No reaction
85	3928	0.4	Fever, chills, headache, nausea, vomiting, pains in the legs
86	3928	0.4	Nausea
87	3928	0.4	Weak
88	3903	0.45	Nausea
89	3903	0.45	Fever, chills, headache, loose bowels
90	3903	0.45	Feels tired
91	3903	0.45	Headache, nausea, loose bowels
92	3937	0.45	No reaction
93	3937	0.45	No reaction

It is to be noted from the study of these tables that the percentage of reactions was equal in both the syphilitic and nonsyphilitic series. The statistical analysis of the tables recorded shows these results:

Fever as a symptom was recorded in 40 per cent. of the syphilitic patients and in 32 per cent. of the nonsyphilitics; diarrhea in 60 per cent. of the nonsyphilitics and in 40 per cent. of the syphilitics; chills in 40 per cent. of the nonsyphilitics and in 42 per cent. of the syphilitics; vomiting in 23 per cent. of the nonsyphilitics and in 18 per cent. of the syphilitics, and headache and nausea occurred in 60 per cent. of both the syphilitic and nonsyphilitic patients.

It will be noted that the percentages of the reactive symptoms registered approach one another so closely in the syphilitic and nonsyphilitic series that no definite conclusions can be drawn from the figures per se.

CAUSES OF REACTIONS

The causes of the reactions following the intravenous administration of arsphenamin can be classified into: (1) factors relative to the patient; (2) factors relative to the technic, and (3) factors relative to the chemical compound employed.

1. *Factors Relative to the Patient.*—There can be but little doubt that the mental state of a patient at the time of treatment influences the occurrences of reactive symptoms. Not only is this true of the intravenous injections of arsphenamin but also of mercurial preparations and other medicinal substances which at times are administered intravenously.

One of us (A. Strickler) gave a series of intravenous mercurial injections to a group of syphilitic patients that had received a large number of arsphenamin treatments. A percentage of these patients that had received these mercurial injections reported some of the reactive symptoms, such as headache, nausea, and chilliness which occur after injections of arsphenamin. Similar reactive symptoms were also reported by patients suffering from nonsyphilitic dermatologic affections who had received intravenous injections of mercurial preparations. •

2. *Factors Relative to the Technic.*—Under this caption belongs the discussion of the water error of Wechsellmann. Wechsellmann believed that water impurities, chiefly bacterial proteins, were largely responsible for febrile and gastro-intestinal reactions. Gennerich believed that organic contamination of water by saprophytes was the cause of a certain number of unfortunate consequences.

In 1910, Neisser advanced the view that the febrile symptoms were due to the rapid destruction of innumerable spirochetes and the setting free of endotoxins which reached the blood stream and induced the symptoms. E. H. Martin, in a discussion of the treatment of syphilis, believed that the temperature and bowel symptoms were due to the endotoxins liberated from killed spirochetes, and nausea and vomiting caused by idiosyncrasy.

Our clinical investigation seems to disprove the views of Neisser. Our records show definitely that the reactive symptoms were just as numerous among the nonsyphilitics that had received intravenous injections of arsphenamin, as among the syphilitic patients that received the same medicament of the same serial number. Our evidence seems to point to the fact that the so-called "syphilitic state" of the patient plays either no rôle or a very minor rôle in the causation of reactive phenomena. There are other faults in technic which at times may be responsible for some reactive symptoms, such as the temperature of the water employed, acidity or excessive alkalinity of the solution, too rapid infusion of the solution and the preliminary preparation of the patient.

3. *Factors Relative to the Medicament.*—We are of the impression that the most important factors in the causation of the reactions following the intravenous injections of arsphenamin are to be found: (a) in impurities in the drug, and (b) in the chemical reactions which probably take place between the arsphenamin and the chemical constituents of the blood.

Arsphenamin is an extremely complex substance, and before its final elaboration numerous intermediate products must be prepared. Arsphenamin cannot be regarded as an absolutely pure compound

because it cannot be purified by repeated crystallization. Arsphenamin does not give arsenic values quite up to the theoretical amount, and furthermore, there are elements present which have no place in the chemical formula. Analyses have shown that arsphenamin contains on the average from 1 to 2 per cent. of sulphur. In view of these statements, it is entirely possible that a medicinal substance, which requires numerous steps for its preparation before its final elaboration, and which is of such complexity, should be capable of producing untoward symptoms when introduced into the blood stream.

SUMMARY

1. Both syphilitic and nonsyphilitic patients may experience similar reactions following the intravenous injections of arsphenamin.

2. The endotoxins, produced presumably by the rapid killing of spirochetes in the blood stream of syphilitic patients, play either no rôle or a very unimportant one in the causation of reactive symptoms.

3. The percentage of reactive symptoms following intravenous injections of arsphenamin is equal in both syphilitic and nonsyphilitic patients.

4. It is our impression that the two most important factors in the production of arsphenamin reactions are (1) the patient and (2) the medicament.

5. Of these two factors, the medicament is far more potent in causing reactive symptoms; the untoward phenomena may be produced either by some impurity in the arsphenamin or by some chemical reaction between the arsphenamin and the chemical constituents of the blood, or both factors may be operative at the same time.

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