INTRAVENOUS SEROTHERAPY OF WEIL'S DISEASE (SPIROCHÆTOSIS ICTEROHÆMORRHAGICA).*

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We have already reported[1] the results of our studies with subcutaneous injections of immune serum in spirochætosis icterohæmorrhagica. In the present article are presented the results of injections made by the intravenous method, which has in the main been employed in the serotherapy of Weil's disease since May, 1916. The number of patients treated in this manner in our clinic from May, 1916, to November, 1916, was 41. We found that the intravenous injection of immune serum far exceeds in potency the subcutaneous injection. An explanation of this finding may be sought in the fact that the therapeutic effect of serum injected directly into the blood stream is 500 times more potent than when it enters the organism by the subcutaneous route (Berghaus).

Experiments to show the comparative effects of the subcutaneous and intravenous administration of serum in Weil's disease were undertaken with seven rabbits, the animals receiving 0.5 to 1 cc. of immune serum per kilo of body weight. At various intervals the blood of the animals was examined for spirocheticidal and spirochetolytic immune bodies. The blood was taken from the ear vein on the side opposite the one in which the intravenous injection was made. The results of these experiments are given in Table I.

The immune bodies could be demonstrated as complete 5 minutes after the intravenous injection of 0.5 cc. of serum per kilo of body weight, while with the subcutaneous method the immune bodies

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[1] Inada, R., Ido, Y., Hoki, R., Ito, H., and Wani, H., *J. Exp. Med.*, 1916, xxiv, 485.

could be detected only 8 hours after the injection and were then not completely absorbed. This passive immunity continued for 3 or 4 days. Complete immunity could not be obtained in man with the use of the small dose injected subcutaneously, but when larger doses

TABLE I.

Immune Bodies in Rabbits Infected with the Blood of Patients Having Weil's Disease.

Animal No.	Method of injection.	Amount injected.	Amount of serum per kg.	Body weight.	Pfeiffer's phenomenon.															
					Before serum injection.	After serum injection.														
						Min.			Hrs.						Days.					
						5	15	30	1	3	5	8	12	24	2	3	4	5	6	7	8
		cc.	*cc.*	*gm.*																	
1	Intravenous.	1.25	0.5	2,500	−		+	+	+							+	+		−		
2	"	2.5	1.0	2,500	−	+		+	+							+	+		−		−
3	Subcutaneous.	2.1	1.0	2,100	−	−		−	−					+	+	+	±		−		
4	"	1.7	0.5	3,400	−			−	−	−	−	−	±	±			±	−			
5	"	1.55	0.5	3,100	−				−	−	−	±	±	±	±	±	±	−			
6	"	3.1	1.0	3,100	−				−	−	−	−	±	±	±	±	±	−			
7	Intravenous.	1.45	0.5	2,900	−	+			+							+	−	−			

Titer of Serum Employed in the Experiments.

Pfeiffer's phenomenon.		Course of disease.	Remarks.
Amount of serum.	No. of spirochetes.		
cc.			
0.001	Liver emulsion (10 spirochetes per field) 1 cc.	Died 5th day of icterus.	Control died 4th day of icterus.
0.005	" " "	" 16th day without icterus. Autopsy negative.	" " "

− indicates no immune bodies; + immune bodies complete; ± immune bodies incomplete.

were given a complete passive immunity was attained also with the subcutaneous method.

The sera used were obtained from horse's blood as follows: No. 2, February 26, 1916; No. 6, August 7; No. 7, August 7; and No. 8, August 19. One of the horses was immunized from the beginning

with a living culture of *Spirochæta icterohæmorrhagiæ;* four others received first an inoculation of the killed culture, followed later by the living culture. The latter procedure can be more readily carried out. The animal receiving the living culture showed on the 7th day a temperature of 39°C. All the horses were immunized by a uniform procedure.

Titer.—The titer of the immune serum was determined by testing

TABLE II.

Titer of Serum.

No. of serum.	Pfeiffer's phenomenon.		Course of disease.	Remarks.
	Amount of serum.	No. of spirochetes.		
	cc.			
2	0.005	Liver emulsion (10 per field) 1 cc.	Died 12th day of icterus.	Control died 4th day of icterus.
	0.01	" " "	Died 18th day without icterus. Autopsy negative.	" " "
6	0.01	Liver emulsion (10 per field) 1 cc.	Well for more than a month.	Control died 4th day of icterus.
7	0.01	Liver emulsion (10 per field) 1 cc.	Died 10th day of icterus.	Control died 4th day of icterus.
	0.03	" " "	Well for more than a month.	" " "
8	0.01	Liver emulsion (10 per field) 1 cc.	Well for more than a month.	Control died 4th day of icterus.

the quantity which would protect a guinea pig weighing 200 gm. against infection from 1 cc. of pure culture containing 10 spirochetes per field (Leitz $\frac{1}{12}$ oil immersion, ocular 3). The spirocheticidal titer of the serum was 0.01 and 0.03 cc.; it has been found that a titer of 0.01 cc. suffices for the serotherapy of Weil's disease. Table II shows the spirocheticidal and spirochetolytic effects of the immune sera.

The experiments were made with sterile sera without preservative (phenol). As shown in Table II, Sera 2, 6, and 8 were more effective than No. 7.

Dose.—As a rule, 60 cc. of serum were injected intravenously, irrespective of the severity of illness, sometimes the entire quantity being given within 24 hours; or 40 cc. in a day, and the remaining 20 cc. the following day; or 20 cc. daily for 3 successive days. We cannot at present state definitely which procedure is to be preferred, and in order to determine this point, it will be necessary to make observations on a larger number of patients than is here presented. In any case, it is clear that the dose depends upon the severity of the disease. The entire amount of 60 cc. is not needed in the treatment of the less severe cases, although this quantity is always put up for an individual dose. In milder cases, the injection of from 20 to 40 cc. of serum is sufficient.

As is the usual custom, the serum was introduced into the vein of the arm. Previous to the injection 2 to 3 cc. of serum were injected subcutaneously into the chest or the thigh of the patient. The arm injection was then made 2 or 3 hours later, the serum being permitted to run in slowly, allowing 5 minutes for the introduction of 20 cc. The serum should be warmed to body temperature before use.

Day of Injection.—This has an important bearing on the course of the disease. As already emphasized, the action of the immune serum is spirocheticidal and spirochetolytic. The best results are obtained when the injection is made at an early stage of the disease. The question now arises: Up to what day of illness may the injections be continued with success? This period can be determined by studying (1) the infectivity of the patient's blood for guinea pigs, (2) the distribution of the spirochetes in the organs at various stages, and (3) from clinical observations of patients receiving the intravenous treatment. Table III gives the infectivity of the blood on various days of the disease. It is based on 42 cases treated recently, and 69 older cases. It will be observed that the infectivity diminishes gradually in the course of the disease. On the basis of these findings it would seem that the intravenous injection is effective up to the 5th day.

The investigations of Kaneko and Okuda concerning the distribution of spirochetes in the organs in Weil's disease indicated that the liver harbors few or wholly degenerated forms on the 7th day. In two patients on whom a post-

mortem examination was made on the 6th day, spirochetes were found in moderate numbers, though not so numerously as in the guinea pig. According to this, as already stated, we may expect the intravenous injection to be successful up to the 5th day. From our clinical observations, an undoubted effect can be obtained up to the 6th day of illness. We had few cases of this kind, however.

Four patients received the intravenous injection on the 3rd day, 9 on the 4th, 6 on the 5th, and 5 on the 6th day. Patients admitted at a later stage received an initial intravenous injection, not fol-

TABLE III.

Infection Experiments on Guinea Pigs with the Blood of Patients Having Weil's Disease.

Day of illness.	Cases previously examined.	Positive cases.	Negative cases.	Per cent positive.	Recently examined cases.	Positive cases.	Negative cases.	Per cent positive.	Total no. of cases.	Positive cases.	Negative cases.	Per cent positive.
2	4	4	0	100.0	0	0	0	0	4	4	0	100.0
3	10	10	0	100.0	4	4	0	100.0	14	14	0	100.0
4	13	13	0	100.0	9	9	0	100.0	22	22	0	100.0
5	12	11	1	91.7	6	5	1	83.3	18	16	2	88.9
6	14	12	2	85.7	5	2	3	40.0	19	14	5	73.7
7	8	4	4	50.0	7	3	4	42.9	15	7	8	46.7
8	4	0	4	0	3	1	2	33.3	7	1	6	14.3
9	1	1	0	100.0	5	0	5	0	6	1	5	16.7
10	0				1	0	1	0	1	0	1	0
11	0				1	0	1	0	1	0	1	0
12	1	0	1	0	1	0	1	0	2	0	2	0
18	1	0	1	0					1	0	1	0
19	1	0	1	0					1	0	1	0
Total No. of cases...	69				42				111			

lowed by others. 12 of the patients showed no icterus on admission, although 4 had a slightly yellowish pigmentation of the conjunctivæ. Of these 12 patients, 6 failed to develop icterus in the further course of the disease. Classified according to the severity of illness, we treated 6 slightly ill, including atypical cases, 9 moderately ill, and 26 severe cases. At the time that the intravenous treatment was being administered, we had in the clinic 11 other patients who re-

ceived no serum treatment; *i.e.*, 4 atypical cases, 1 slightly ill, and 6 moderately ill. There were no severe cases among them. It will be noted that the serum was administered in the main only to those who were severely or moderately ill.

Age.—We treated 9 patients between the ages of 16 and 20 years, 9 between 21 and 30, 6 between 31 and 40, 10 between 41 and 50, 4 between 51 and 60, and 3 who were over 60 years of age. We desire to add here that our patients, in addition to the serotherapy, received the benefit of the other usual methods of treatment in Weil's disease; *i.e.*, the intravenous injection of Ringer's solution and the subcutaneous administration of camphor and cocaine.

Spirocheticidal and Spirochetolytic Effect of the Immune Serum Injected Intravenously.

The spirochetolytic and spirocheticidal effects of the serum can be most readily shown when the spirochetes are demonstrable in the peripheral blood by dark-field illumination. In that case no infection experiments need be made. Up to the present time, however, we have observed this to be true in only 2 out of 100 cases. These 2 cases are discussed below.

Case 1.—M., male; age 47 years. The patient was admitted to the clinic on November 4, 1916, on the 3rd day of illness. This was a severe case. The blood showed by dark-field illumination 1 spirochete in from 70 to 140 fields. 1 hour after the intravenous injection of Serum 6, no spirochetes could be detected in two preparations. Blood was then withdrawn from the arm vein, and two guinea pigs received each an intraperitoneal injection of 1 cc. of the patient's blood. The animals became ill and showed typical symptoms 1 or 2 days later than the control animals, which had received blood withdrawn prior to the injection of serum. Although no spirochetes were found in two preparations, the blood was still infectious.

Case 5.—N., male; age 65 years. He became suddenly ill on May 1, 1916, and was admitted to the clinic on May 4, the 4th day of illness. We were able to demonstrate numerous *Spirochæta icterohæmorrhagiæ* in the blood by dark-field illumination in 14 to 16 specimens of 65 to 70 fields each. As a rule, spirochetes are not readily found in fresh preparations. The findings of spirochetes before and after serum injections were as follows:

2 p.m. Spirochetes in the blood, 14 to 16 in 65 to 70 fields.
3 p.m. 17 cc. of Serum 2 injected subcutaneously.
6 p.m. 14 to 16 spirochetes in 65 to 70 fields.

7 p.m. 10 to 16 spirochetes in 65 to 70 fields.
8 p.m. 20 cc. of Serum 2 injected intravenously.
10 p.m. No spirochetes in 2 preparations.
12 m. No spirochetes in 3 preparations.
1 a.m. 2 cc. of patient's blood injected intraperitoneally into a guinea pig, which remained well (May 14).
1.30 a.m. No spirochetes in 1 preparation.
8.30 a.m. 3 cc. of patient's blood injected intraperitoneally into a guinea pig, which remained well.

2 hours after the intravenous injection of serum in Case 5, we were unable to find any microorganisms. This demonstration of the spirocheticidal and spirochetolytic action of the immune serum in man exactly parallels the results obtained with guinea pigs. The patient died, however, at 5.30 p.m. on the following day. But the unexpected results obtained in this case induced us in later cases to employ only the intravenous injection method.

The experiments demonstrate clearly the spirocheticidal and spirochetolytic action of the immune serum, which is capable of destroying the spirochetes in the blood stream within a short period of time.

In the other thirty-nine cases spirochetes could not be readily demonstrated in the blood by dark-field illumination. Hence we conducted infection experiments before and after serum injection, similar to those made with the subcutaneous serum cases (Table IV). Table V gives the results of the infection experiments, the serum administered, and the day of illness when the blood was taken. We have omitted from the table the cases which were negative with the use of blood drawn before serum was injected.

The infection experiments were all negative following the injection of 20 cc. of Serum 2. With Serum 6, only one experiment was positive. In this instance the animal was inoculated 1 hour after the injection of the patient. It appears that Sera 2 and 6 possessed markedly potent spirocheticidal and spirochetolytic properties, while No. 7 was less effective; the titer of the latter serum was 0.03 cc. Although the infection experiments were positive with blood taken after the injection of Serum 7, the animals became typically ill much later than the animals receiving blood drawn before the injection. The difference in the duration of the life of the animals in the two groups was from 3 to 7 days, as in Cases 10, 11, 12, 13, 19, and 25.

TABLE IV.

Infection Experiments with Patients' Blood Withdrawn before and after Intravenous Injection of Serum.

Case No.	Sex.	Day of admission.	Day of illness just before serum injection.	Results on guinea pigs.					No. of serum.	Time between serum injection and withdrawal of blood.	Day of illness after serum injection.
				Before serum injection.		After serum injection.		Amount of serum injected.			
				No.	Result.	No.	Result.				
		1916						*cc.*		*hrs.*	
1	Male.	Nov. 4	3	2	+(7 days). +(8 ").	1	+(9 days).	20	6	1	3
						1	+(9 days).	20		2	3
2	Male.	Sept. 8	3	2	+	2	—	20	7	3	3
3	Male.	Sept. 15	3	2	+	2	—	20	7	3	3
4	Male.	Sept. 22	3	2	+(9 days).	2	+(9 days).	20	7	5	3
5	Male.	May 4	4	1	+	1	—	40	2	5	4
6	Female.	May 30	4	1	+	1	—	20	2	3	4
7	Female.	June 20	4	1	+	1	—	20	2	10	5
8	Male.	Aug. 31	4	2	+	2	—	20	2	3	4
9	Male.	Sept. 22	4	2	+	2	—	20	6	3	4
10	Male.	Sept. 8	4	2	1+(6 days). 1+(8 ").	2	+(13 days).	20	7	3	4
11	Female.	Sept. 19	4	2	1+(6 days). 1+(8 ").	2	+(11 days).	20	7	3	4
						2	—	20		18	5

12	Male.	Sept. 10	4	2	+(7 days).	2	+(12 days).	20	7	3	4
13	Male.	Nov. 19	4	1	+(6 days).	1	+(11 days).	20	8	3	4
14	Male.	Aug. 28	5	2	1+ 1−	2	−	20	2	3	5
15	Male.	Oct. 20	5	2	−	2	−	20	6	3	5
16	Male.	Nov. 12	5	1	+	1	−	20	6	3	5
17	Male.	Nov. 20	5	1	+	1	−	20	6	3	5
18	Male.	Nov. 26	5	1	+	1	−	20	6	3	5
19	Male.	Sept. 6	5	2	+(7 days).	2	1+(12 days). 1+(13 ").	20	7	3	5
20	Female.	May 28	6	1	−	1	−	20	2	4	6
21	Female.	June 26	6	1	−	1	−	20	2	3	6
22	Female.	Aug. 23	6	1	?	1	?	20	2	3	6
						1	−	40		9	7
23	Male.	Oct. 16	6	2	1− 1?	2	−	20	6	3	6
24	Female.	Oct. 26	6	2	−	2	−	20	6	3	6
25	Male.	Sept. 10	6	2	+(8 days).	2	+(13 days).	20	7	3	6

TABLE IV—*Concluded.*

Case No.	Sex.	Day of admission.	Day of illness just before serum injection.	Results on guinea pigs.				Amount of serum injected.	No. of serum.	Time between serum injection and withdrawal of blood.	Day of illness after serum injection.
				Before serum injection.		After serum injection.					
				No.	Result.	No.	Result.				
		1916						*cc.*		*hrs.*	
26	Female.	Nov. 19	6	1	+	1	—	20	8	3	6
27	Male.	July 25	7	1	+	1	—	60	2	11	8
28	Female.	June 24	7	1	+	1	—	20	2	3	7
29	Male.	July 6	7	1	—	1	—	20	2	3	7
30	Female.	Aug. 31	7	2	—	2	—	20	2	3	7
31	Male.	Sept. 2	7	1	—	2	—	20	2	3	7
32	Male.	Oct. 12	7	2	1+ 1—	2	—	20	6	3	7
33	Male.	Sept. 15	7	1	—	1	—	20	7	3	7
34	Male.	May 20	8	1	—	1	—	20	2	8	8
35	Female.	Nov. 15	8	1	—	1	—	20	7	3	8
36	Female.	Nov. 22	10	1	—	1	—	20	2	3	10
37	Male.	Sept. 15	11	2	—	2	—	20	6	3	11

Cases 1 and 4 are exceptions. It is evident that the serum was potent after 3 hours, although it was incapable in this short period of time of destroying completely the spirochetes contained in the blood. This is true also of Serum 8.

The time elapsing between the injection of serum and the withdrawal of blood varied from 1 to 18 hours, the usual interval being 3 hours. Table VI gives the infection experiments carried out with

TABLE V.

Infection Experiments with Patients' Blood Withdrawn before and after Intravenous Injection of 20 Cc. of Serum.

Positive Infections.

No of serum.	Day of illness.									
	3		4		5		6		7	
	Before injection.	After injection.	Before injection.	After injection.	Before injection.	After injection.	Before injection.	After injection.	Before injection.	After injection.
2			4	0	1	0	1	0	2	0
6	1	1	1	0	3	0	1	0	1	0
7	3	1	3	3	1	1	1	1		
8			1	1			1	0		

TABLE VI.

Infection Experiments with Blood Withdrawn after Serum Injections.

Time between serum injection and withdrawal of blood.	Infection experiments before serum injection.	Infection experiments after serum injection.
hrs.		
1–3	+ 19	− 13
		+ 6
Over 5	+ 5	− 4
		+ 1

blood withdrawn after serum injection. These results show that serum having a titer of 0.01 cc., given intravenously in doses of 20 cc., after 3 hours destroys completely spirochetes contained in the peripheral blood, which then is incapable of infecting guinea pigs. While with the use of sera having a titer of 0.03 cc., we found 3 hours after injection incomplete destruction of spirochetes in the blood,

the animals became typically ill later than the controls. It would appear, then, that the spirochetes had become reduced in number or had lost some of their virulence.

Behavior of the Immune Bodies in the Blood.

Experiments were conducted with the blood of twenty patients. Owing to a shortage of guinea pigs, we were not able to inject the animals immediately after withdrawal of the blood, and the fluid was placed in the refrigerator until it could be used. Unfortunately, most of these specimens became contaminated. The results of our investigation for the presence of immune bodies in the blood during the course of the disease, after intravenous injection of immune sera, are shown in Table VII.

The immune bodies appear in the blood much earlier with intravenous than with subcutaneous injections. They are present as

TABLE VII.

Appearance of Immune Bodies in the Serum of Intravenously Injected Patients.

Case No.	Day of illness when serum was injected.	Day of illness when blood was withdrawn.						
		6	7	8	9	10	11	12
8	4	−						+
4	3		−		+			
2	3		−					
11	4			+				
10	4			+				
7	4			+				
6	4	±(+ 7)		+				
14	5				+			
38	5		+					
19	5		+					
15	5		±(+ 4)					+
23	6	−		+				
24	6	+		+				
21	6				+			
20	6			+				
30	7		−		+			
33	7							
28	7				+			
29	7				+			
34	8				+			

early as the 8th or 9th day, which does not, as a rule, occur when the patient has received no serum treatment. They may be observed after the introduction of 60 cc. of immune serum.

In one of the cases referred to the immune bodies appeared as early as the 6th day, before the administration of serum was begun. It is possible that in this instance an error has been made in computing the day of illness, inasmuch as we have never observed a similar result with other non-serum-treated cases.

Mortality.

The total mortality with the use of the intravenous injections was 23.7 per cent. Of forty-one patients under observation, twelve died. We have not included in our tabulations a patient who after recovery from the disease died on the 55th day from complications, a patient admitted to the clinic in moribund condition who died after 29 hours (numerous spirochetes could be demonstrated in the blood), and another, admitted when moribund, who died after 31 hours. The mortality of patients receiving no serum was 30.6 per cent. In the subcutaneously injected patients, the percentage was 17.3. This low mortality in the case of the subcutaneously injected patients is attributable to the fact that in this group, which entered before the 8th day of illness, only five patients were over 40 years of age, while in the group of intravenously injected patients, twelve were over that age.

Since in the moderate and slight forms of Weil's disease death results from complications, we shall consider particularly the severer cases of the disease. As the serum is effective only when administered in the initial stage, we have not considered in our study patients admitted after the 6th day. The mortality of patients who were admitted before the 7th day and received no serum was 57.1 per cent, of the subcutaneously injected patients 40 per cent, and of the intravenously injected patients 38.5 per cent.

It is clear that the total mortality figures, particularly the mortality of the severer cases, is considerably lower in the case of intravenous and subcutaneous serum administration than in the non-serum-treated cases.

In judging the results, one should take into account factors which strongly influence the prognosis. Among these factors must be counted the age of the patient, the severity of the illness, the season of its occurrence, and above all the day of illness on which serum was first administered. One must also consider whether the cases occur in epidemic form or sporadically. The difficulty of estimating the results is further increased by the fact that often at the onset it is not possible to judge precisely the degree of severity of the disease, while on the 6th or 8th day an error in prognosis is unusual. Table VIII shows the influence of the age of the patient upon the prognosis.

TABLE VIII.

Mortality and Age.

Age.	Without serum treatment.		Intravenous serum treatment.
	Inada.	Nagao.	
yrs.	*per cent*	*per cent*	*per cent*
Up to 20	12.5	60.0	0
21–30	21.0	17.9	12.5
31–40	23.5	20.0	0
41–50	21.4	35.0	42.8
51–60	75.0	50.0	33.3
Over 60	50.0	75.0	100.0

Of 21 patients less than 40 years old, admitted from the 3rd to the 7th day of illness, who were treated by intravenous injections of serum, only 1 died. This was a patient admitted on the 7th day. The 21 cases included 4 slightly ill, 7 moderately ill, and 10 severely ill patients. Of the 12 patients over 40 years of age—2 slightly ill and 10 severely ill—7 died. Prior to the age of 40, a good result is insured from the serum injections, but after 50 the outlook is not favorable; the older persons constitute, in fact, the severest cases of the disease. When we compare 10 severe cases below 40 years with 10 above that age, we find among the first only 1 death as against 7 deaths in the older group. It is evident that the years above 40 exert an unfavorable influence on the prognosis of Weil's disease, and this is especially true when the disease appears in severe form.

Effect of Intravenous Serotherapy on the Spirochetes in the Organism.

The spirochetolytic action of the immune serum upon the spirochetes in the human body is more pronounced with the intravenous than with the subcutaneous injection. Kaneko and Okuda have studied this phase of the subject.[2]

Effect of Serotherapy upon the Symptoms and Course of Weil's Disease.

Severity of Illness.—When the serum is administered early, the disease appears to assume a milder form. As already stated, it is difficult at the beginning to judge the precise degree of illness. We observed one patient moderately ill and another slightly ill, who after the serum injection could be grouped with the atypical cases. It is, however, not possible to assert that this change is wholly attributable to the serum; it may be that the disease in these cases would have run a less severe course without the administration of serum. But when we study the influence of the intravenous injection upon the different symptoms, we find that on the whole they are considerably diminished and shortened in duration.

Fever appears not to be influenced by the serum to any extent, even in cases where serum is administered early in the disease. In fact we often observed a rise in temperature after an injection, though it is not possible to say that this was due to the action of the serum.

The immune serum has a favorable effect on the duration of the icterus. The exact time of disappearance cannot be definitely stated on the basis of an examination made of the skin and mucous membranes, inasmuch as anemia usually follows recovery. We have, therefore, taken as an index Gmelin's urine test, which has been used in our clinic during the past 10 years. Without serum treatment, the icteric condition usually continues for a period of 20 days or more in the severe cases, sometimes as long as 30 days; and in the moderately ill 14 to 30 days, occasionally more than that time. In the cases receiving subcutaneous serum treatment, the icterus continued for an equal length of time. No definitely favorable effect was observed, even in the cases receiving an injection as early as the 3rd or 4th

[2] Their work is reported in detail on page 305 in this *Journal*.

day of illness. On the other hand, the icterus of the intravenously treated patients in most cases disappeared within 20 days, in the earliest case on the 13th day. No such finding was ever observed in the non-serum-treated cases or in those receiving subcutaneous injections. Of the severe cases receiving the intravenous injection prior to the 6th day, in only two did the icterus last more than 20 days. The longest period was 12 to 14 days in moderately severe cases. When the injection of serum is deferred until after the 6th or 7th day, the icteric condition will continue as long as it would if no serum had been given. We cannot state definitely whether an injection made on the 1st or 2nd day is capable of suppressing the icterus completely, but this is probable. Of the eight patients who received serum treatment on the 3rd or 4th day and at that time showed no signs of icterus, three remained without jaundice throughout. In any event we may say that the duration of the icterus is shortened considerably when the intravenous injections are given early in Weil's disease. The intensity of the icterus in most cases is greatly diminished by the intravenous injections (Tables IX, X, and XI).

The serum has likewise a decided influence upon hemorrhages. This was observed to a slight extent also with the subcutaneous injections. As a rule, cutaneous hemorrhages continue, but they are less pronounced in character. The percentage of petechiæ in the patients receiving intravenous treatment was 70.7, while in those receiving no serum it was 72.2. Although there is little difference in the figures, the duration of this symptom in the first group was considerably shorter. In half of the non-serum-treated cases the petechiæ continued for 10 days, while in the cases which received serum intravenously (admitted from the 1st to the 6th day of illness) only a third showed this symptom for more than 9 days. The number and size of the petechial spots were also reduced. Hemorrhage from the nose occurred also with serum treatment, but the percentage was somewhat smaller; that is, 29.3 against 32.7 per cent. Hemorrhages from the mucous membranes, gums, and tongue, and hematoma of the buccal mucosa continued to occur. In the intravenously treated cases the proportion was 41.5 per cent, in the non-serum-treated cases, 43.5 per cent. When the intravenous injection

was given early, within the first 6 days, the percentage was 30.6. This is true of intestinal hemorrhages, which may be reduced one-half by the intravenous injections. Table XII gives in percentages the

TABLE IX.

Duration of Icterus with Intravenous Serum Injection.

Day of illness when serum was injected.	Degree of illness.	Duration of icterus.
		days
3 (four cases).	Atypical.	Without icterus. Icterus only of conjunctiva bulbi.
	"	13
	Severe.	17
	"	
4 (five cases).	Atypical.	Without icterus.
	Severe.	15
	Moderately severe.	14
	Severe.	15
	"	23
5 (five cases).	Moderately severe.	Without icterus.
	Severe.	8
	Moderately severe.	12
	Severe.	16
	"	21
6 (six cases).	Atypical.	Without icterus. Icterus only of conjunctiva bulbi.
	Slight.	11
	Moderately severe.	12
	Slight.	13
	Moderately severe.	18
	Severe.	
7 (six cases).	Severe.	16
	Moderately severe.	14
	" "	16
	Severe.	17
	"	23
	"	30
8 (two cases).	Moderately severe.	16
	Severe.	28
9 (two cases).	Moderately severe.	13
	Severe.	23
Total 30		

hemorrhages occurring in the non-serum-treated cases, the intravenously treated cases, and of the latter those receiving serum injections at an early stage. The table also shows the percentages of hematemesis and epistaxis.

TABLE X.

Duration of Icterus with Subcutaneous Serum Injection.

Day of illness when serum was injected.	Degree of illness.	Duration of icterus.
		days
3 (one case).	Atypical.	4
4 (one case).	Severe.	22
5 (three cases).	Severe. Moderately severe. Severe.	16 20 24
6 (six cases).	Slight. Severe. Moderately severe (approaching slight form). Severe. Moderately severe. Severe.	14 18 20 20 29 33
7 (three cases).	Severe. " "	20 24 30
8 (five cases).	Slight. Moderately severe (approaching slight form). Moderately severe. " " " " (approaching severe form).	10 20 24 25 26
9 (one case).	Severe.	20
13 (one case).	Severe.	17 (died on 34th day).
Total 21		

From the above considerations we may conclude that the early intravenous injection of immune serum has a decidedly favorable influence upon the hemorrhagic tendency of Weil's disease, and particularly upon hemorrhages from the mucous membranes.

TABLE XI.

Duration of Icterus without Serum Treatment in Thirty-Six Cases.

Degree of illness.	Duration of icterus.
	days
Atypical.	Icterus only of conjunctiva bulbi.
"	5
Slight.	11
"	12
Moderately severe.	14
" "	14
" "	17
Slight.	17
Moderately severe.	18 (died on 18th day).
Severe.	20
"	20
Moderately severe.	21
Slight.	22
Moderately severe.	22
Severe.	24
"	24
"	24
"	25
"	25
Moderately severe.	22
" "	25
" " (approaching severe form).	25
" "	26
" "	28 (had beri-beri).
" "	29
" "	30
" " (approaching severe form).	30
Severe.	30
"	31
"	34
"	37+
Moderately severe.	37+
" "	38+
" "	24+
Severe.	24+
"	29+ (died on 38th day).

TABLE XII.

Percentage of Hemorrhages in the Serum-Treated and Non-Serum-Treated Cases.

Symptoms.	Without serum treatment.	Intravenous serum treatment.	Intravenous serum treatment (26 cases admitted from 3–6 days).
	per cent	*per cent*	*per cent*
Hemorrhages from tongue and mouth	43.5	41.5	30.6
Intestinal hemorrhages	30.2	22.0	15.3
Hematemesis	11.3	9.7	7.6
Bloody stools	15.1	7.3	7.6
Petechiæ	72.2	70.7	69.2
Epistaxis	32.7	29.3	
Complications—suppurative processes	24.0	14.6	4.9

We have not observed a decidedly favorable influence of the serum upon the pulse, although arrhythmia was a less frequent symptom. It occurred in 20 per cent of the cases, while in the non-serum-treated cases the figure was 50 per cent.

Complications such as suppurative processes—parotitis, skin abscesses—were found in 14.6 per cent, in patients admitted from the 3rd to the 6th day only in 4.9 per cent, and in patients receiving no serum treatment in 24 per cent of the cases. Thus these complications are greatly reduced with the early use of the serum.

Summarizing the observations on such symptoms as hemorrhage, particularly of the mucous membranes, heart rhythm, and suppurative processes, which play a large part in the outcome of the disease, we are justified in saying that the intravenous injection of immune serum has a definitely beneficial effect.

The after-fever was found to occur somewhat more frequently—in 34.1 per cent—while without serum treatment it occurred in only 28.2 per cent. The greater frequency of this symptom is probably referable to the fact that the most severely ill patients who recover from the disease are included in this category. As the time of greatest mortality of Weil's disease lies between the 8th and the 18th days, and the after-fever, as a rule, does not begin until the 13th or 15th day, it is evident that this symptom does not usually occur in the cases ending fatally. The percentage of after-fever is found to increase as the mortality decreases.

On two occasions following the injection of Serum 7, and once after Serum 2, the patients had chills followed by a rise in temperature. Serum rash occurred three times after the administration of Serum 2. There were no anaphylactic manifestations.

Among 18 patients who returned for examination after several months we found 8 who showed more or less marked ocular disturbances. These 18 cases comprised 10 severe, 5 moderately severe, and 3 atypical forms of the disease. The 8 patients showing ocular disturbances were as follows: 5 from the severely ill group, 1 from the moderately ill, and 2 from the atypical group. 1 patient showed, on examination in the ophthalmologic clinic, iridocyclitis, hypopyon of the right eye, and opacity of the vitreous humor; in another only the last symptom was present. These after-effects seem to occur more frequently in the severe types of the disease. We cannot say at this time to what extent the sequelæ are influenced by serum treatment.