

THE DISTRIBUTION IN THE HUMAN BODY OF SPIROCHÆTA ICTEROHÆMORRHAGIÆ.*

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The material examined came from autopsies performed on forty-three patients who died at various stages of illness, as shown in the table. The ages ranged from 2 to 73 years. There were 36 males and 7 females. 5 patients had cirrhosis of the liver, 9 a mixed infection. In 19 cases, serum was administered in varying quantities; 1 was treated with salvarsan. In a number of cases, only the vital organs were examined. As a rule, these organs were placed in a 10 per cent formalin solution; a few were treated with Orth's fluid. All the material examined was impregnated with silver, according to Levaditi's method.

General Distribution of the Spirochetes.

Inada¹ and Ido have divided the progress of Weil's disease into three clinical stages; (1) febrile, (2) icteric, (3) convalescent. As the distribution of the spirochete varies in the different stages, which are not sharply demarcated, we shall discuss the findings for each stage separately.

Febrile Stage.—This period continues to the 6th or 7th day of illness. The clinical symptoms are fever, intestinal disturbances, headache, muscular pains, hyperemia of the conjunctiva, and albuminuria. The blood is pathogenic for guinea pigs. No immune bodies could be demonstrated by Pfeiffer's test.

Spirochetes in large numbers are present. Their distribution resembles in general that in the experimental guinea pigs. The organisms are lodged mainly

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¹ Inada, R., The clinical aspects of spirochætosis icterohæmorrhagica or Weil's disease, *J. Exp. Med.*, 1917, xxvi, 355.

in the liver, kidneys, and suprarenals. Immune bodies are present as early as the 5th day, and we may assume that they exist even prior to that time, but as death does not usually occur so early in the disease, opportunity was lacking for substantiating this point. In the patient treated with salvarsan, who died on the 6th day,² spirochetes were found in the liver. That organ showed cirrhotic changes, and it is possible that the irregular distribution is related to this condition, although a similar distribution was found in a patient dying on the 8th day, as well as in the animals treated with serum or salvarsan. We believe that the destruction of spirochetes in the liver and their irregular distribution are due to the presence of immune bodies. The spirochetes in the suprarenals of this patient were distributed in groups.

By the 7th day the spirochetes in the liver have been almost completely destroyed, and are found but rarely thereafter.³ We found only a few in 2 cases on the 7th day, in 5 cases on the 8th day, and in 8 cases on the 9th day of illness.

In the suprarenals spirochetes have not been clearly demonstrated on the 7th day, but it is certain that by the 8th day their almost complete destruction has been attained. The organisms are usually found in the kidneys on the 6th and 7th days.

Numerous spirochetes were also found in the pancreas, cardiac muscles, in the intestinal wall, the prostate, testicles, epididymis, the walls of the urinary bladder, and the arteries. The spleen and the lymph glands showed, also in the experimental animals, a small proportion of spirochetes.

The distribution of *Spirochæta icterohæmorrhagiæ* in human beings on the whole parallels that found in guinea pigs, with the exception that in man the organisms are more loosely and irregularly scattered and also show a greater degree of degeneration. These differences are attributable to the immune bodies. It is evident from the infection experiments made with the blood of patients that development of immune bodies is already under way as early as the 5th or the 6th day. No opportunity has presented itself to investigate the distribution of spirochetes at the beginning of illness, before the immune bodies have appeared, but recently we observed a patient who on the 4th day showed numerous spirochetes in the blood, similar to the findings in the guinea pig.

² This case was kindly put at our disposal by Dr. Takeya, Chief of the Second Medical Clinic, to whom we are greatly indebted.

³ Dr. Iida, Assistant in the Second Medical Clinic, in one case found an abundance of spirochetes in the liver of a patient dying on the 8th day.

Icteric Stage.—This stage covers a period from the 7th or 8th to the 12th or 13th day of illness. The icteric condition is then at its height and the mortality is greatest. The proportion of autopsies was twenty-one out of forty-three cases. Further development of the immune bodies takes place during this stage, and they can be demonstrated in the blood.

In the course of this period the spirochetes disappear from the blood, and infection experiments are usually negative. Destruction of the spirochetes in the organs takes place. They disappear almost completely from the liver and the suprarenals, leaving only a slight degenerated residue,⁴ but can be traced more or less readily in the kidneys, cardiac muscles, skeletal muscles, particularly the gastrocnemius, and rectus abdominis, the walls of the intestine, especially the appendix, large intestine, and stomach, prostate, urinary bladder, testicles, and epididymis, thymus, and uterine muscles. They are most constantly found in the kidneys and the cardiac muscles, but even here the organisms are not very numerous.

On the whole, the spirochetes during this stage are more abundant in the cells (epithelial, muscular, etc.). Those located in the kidneys are found in the tubules. There are massed foci in the interstitial spaces. Frequently the spirochetes are found in coagulated, homogeneous, or hyaline substance, such as urinary casts, degenerated hyaline muscle cells, etc.

Convalescent Stage.—This stage begins variously from the 13th to the 16th day of illness. The immune bodies are then fully developed, and spirochetes are abundantly excreted with the urine.

⁴ The abundance of spirochetes in Dr. Iida's case (8th day) must be considered exceptional.

In the table the following signs are used:

* Cirrhosis of liver.

† Cirrhosis and cancer of liver.

‡ Mixed infection.

+, very sparse distribution of spirochetes; 1 or a few to a specimen. **+**, sparse distribution. Spirochetes can be found readily; 10 to 20 to a preparation, 1 in one or more fields. **++**, spirochetes relatively numerous, 1 or more to a field, many in a preparation. **+++**, spirochetes numerous; some in every field; perhaps many in a single field. **---**, negative. No spirochetes in 1 or more specimens.

The immune serum was given chiefly intravenously; the figures in bold-faced type indicate subcutaneous administration.

Case 12 was placed at our disposal through the kindness of Dr. Iida, Assistant in the Second Medical Clinic of the University; Case 41 by Mr. Onuma, Director of the Chibaken Board of Health. We desire herewith to express our thanks.

No.	Age.	Sex.	Day of illness.	Hours until autopsy.	Treatment.	Fixing fluid.	Liver.	Gall bladder and ducts.	Kidney.	Suprenals.	Spleen.	Lymph glands.	Intestines.	Tongue.	Salivary gland.	Pancreas.	Lung.	Trachea.	Thyroid.	Thymus.	Heart.	Arteries.	Muscles.	Skin.	Nervous system.	Urinary bladder.	Testicles.	Prostate.	Uterus and ovary.	
1	30	M.	5	23	20 cc. serum 5th day.	Formalin.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
2*	59	"	6	18	20 cc. serum 4th and 5th days.	"	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
3	57	"	6	4	20 cc. serum 4th and 5th days.	"	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
4†	48	"	6		Salvarsan.	"	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
5*	45	"	7	25		"	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
6	47	"	7			"	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
7	28	"	8	22		"	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
8	44	F.	8	3	60 cc. serum 4th day; 20 cc. 5th day.	"	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
9	34	M.	8	20		"	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
10	49	"	8			"	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
11	56	F.	8	12	20 cc. serum 6th and 7th days.	"	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
12		M.	8			"	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
13	59	"	9	17	40 cc. serum 6th and 7th days.	"	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
14	22	"	9	16		Orth's fluid.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
15†	70	F.	9	19		"	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

No.	Age.	Sex.	Day of illness.	Hours until autopsy.	Treatment.	Fixing fluid.	Liver.	Gall bladder and ducts.	Kidney.	Suprenals.	Spleen.	Lymph glands.	Intestines.	Tongue.	Salivary gland.	Pancreas.	Lung.	Trachea.	Thyroid.	Thymus.	Heart.	Arteries.	Muscles.	Skin.	Nervous system.	Urinary bladder.	Testicles.	Prostate.	Uterus and ovary.				
33	24	M.	16	12	20 cc. serum 9th day; 40 cc. 12th day.	Formalin.	Extracellular.		Interstitial.																								
34	64	"	16	5	40 cc. serum 10th day.	"			++												+												
35*	35	"	17	2		"			+												+												
36*	41	"	18	2		"			+												+												
37	25	"	18	4	40 cc. serum 12th day; 40 cc. 13th-15th days.	"			++												+												
38	57	"	20	19	20 cc. serum 11th day; 40 cc. 12th-15th days.	"			+												+												
39†	39	"	27	18	20 cc. serum 5th day.	"			+																								
40	32	"	35	13	60 cc. serum 14th-16th days; neo-salvarsan 7th day.	"			++																								
41		"	50			"			+																								
42	51	"	55	16	20 cc. serum 5th and 6th days.	"			++												+												
43†	32	"	?			"			+																								

In the organs, with the exception of the kidneys and the heart, complete destruction of spirochetes has taken place. The kidneys, on the other hand, show the organisms constantly, and particularly in the tubules. In Case 42 they could be demonstrated in the urine up to the 55th day. The experimental animals treated with immune serum and salvarsan also harbored spirochetes in their kidneys for a long time after recovery. It was observed in white rats, mice, rabbits, and occasionally in guinea pigs, that the spirochetes lodge solely in the kidneys.⁵ The relationship of the spirochetes to the kidneys is noteworthy in that the immune bodies are ineffectual against the organisms contained in the kidney tubules. The spirochetes found occasionally in the cardiac muscles are mostly degenerated.

Summarized briefly, the distribution of the spirochetes in the various organs of the human body differs according to the degree of development of the immune bodies. The spirochetes disappear first from the liver and suprarenals, but remain for some time in the muscles, prostate, thymus, appendix, testicles, epididymis, etc. In the kidneys they can be found for a long time. Their mode of disappearance would seem to indicate distribution varying with the different stages of the disease. And not alone the general distribution, but the local position of the spirochetes changes with the different stages. In the early stage, they are located mainly extracellularly, in the interstices; in the later stage, owing to the development of the immune bodies, in the blood, in the main intracellularly, and within the kidney tubules.

Distribution of Spirochæta icterohæmorrhagiæ in the Tissues.

In the first stage of Weil's disease the organisms are located extracellularly, in the tissues.

Spirochetes are rarely found in the epithelial cells, the kidney tubules, and other glands. They are lodged chiefly in the interstitial spaces surrounding the cells, frequently around the periphery of cells. This position is characteristic, and typical in guinea pigs. In man, in whom a development of immune bodies

⁵ Drs. Ido, Hoki, Ito, and Wani, after careful examination of the various organs of house rats were able to find *Spirochæta icterohæmorrhagiæ* only in the kidneys. Ido, Y., Hoki, R., Ito, H., and Wani, H., The rat as a carrier of *Spirochæta icterohæmorrhagiæ*, the causative agent of Weil's disease (spirochætosis icterohæmorrhagica), *J. Exp. Med.*, 1917, xxvi, 341.

takes place in the blood, the distribution is somewhat different. Here the spirochetes are more frequently enclosed in the cells and cell tubes, and increasingly so with the progress of the disease. The spirochetes disappear first from the interstitial spaces, remaining for some time longer in the cells and kidney tubules. This phenomenon is less marked in the liver and suprarenals, where the spirochetes are destroyed at an early stage; it is very marked in the kidneys. Spirochetes proliferate in the kidney tubules and are excreted with the urine.

Muscular tissue, such as that of the heart and skeletal muscles, retains the spirochetes for a relatively long time. The organisms are seen to surround the muscle fibers closely, but are rarely found within them, though this may be the case in late stages of the disease. In a patient dying on the 9th day, we observed densely massed spirochetes in degenerated hyaline muscle fibers. It seems as though the spirochetes were able to penetrate more readily degenerated or broken cells than those that are intact. This is also true of epithelial cells. Smooth muscle reacts in the same manner as striated. The muscular tissue of the prostate, urinary bladder, gall bladder, the vessel walls, and the intestinal walls are lodging places during the second stage. On one occasion we observed numerous spirochetes in the medullary substance of the suprarenals, while the cortex was already free from spirochetes. In smooth muscle, the organisms are not located parallel to the muscle fibers, but cross them irregularly. The spirochetes occur but rarely in the interstices of the nervous system.

The connective tissue contains spirochetes in abundance. It is, in fact, a main repository for them. Carried by the blood stream, they reach first the walls of the capillaries, and from there are spread over the surrounding connective tissue. Hence they are to be found in great numbers in the lumen, the walls, and the perivascular connective tissue of the capillaries. In man by the 6th day the spirochetes have left the capillaries, having proceeded by way of the delicate fibrous strands, deep into the parenchyma. The coarse connective tissue shows a sparse distribution. The spirochetes are assembled mostly in the dividing tissue lying between the connective tissue and the parenchyma, or in the narrow interstitial layer of connective tissue. They disappear relatively early from the connective tissue, though scattered specimens may be observed in the coarse connective tissue for a long time. The spirochetes may also be carried by the lymph channels, though it is difficult to demonstrate them in the lymphatic vessels.

The spirochetes are often harbored for some time in homogeneous substances, such as urinary casts, degenerated muscle fiber, in colloidal masses of the thyroid, and other coagulated masses. They seem to show a preference for substances of this kind, where they can be secure against the action of the immune bodies.

Phagocytosis.—In the early stage spirochetes are rarely found enclosed in leukocytes, endothelial cells, or connective tissue cells; but in the course of the

disease they are increasingly found in phagocytes. This observation was confirmed experimentally. Phagocytosed spirochetes were found in great numbers following the injection of immune serum into guinea pigs. In man, the phenomenon is not quite so marked, owing perhaps to the fact that the development of the immune bodies is a gradual process, while in the animal large numbers of immune bodies are introduced suddenly. The spirochetes contained in phagocytes are in various stages of degeneration. It would appear as if the spirochetes first degenerate and are then taken up by the phagocytes. Organisms not degenerated but showing regressive changes are sometimes found in phagocytes at the beginning of illness. From this we may assume that they actively penetrate the degenerated phagocytes, and are passively received by the latter.

Distribution of Spirochetes in the Organs.

Liver and Bile Ducts.—In our experimental work with guinea pigs we found that the liver contained the densest distribution of spirochetes, while in man the organisms are rather scattered in that organ. Only in one patient dying on the 6th day and in one of Iida's 8 day cases were we able to demonstrate them numerously. In the densest region, ten to twenty were counted to the optical field. As a rule, the organisms are located extracellularly. Within the lobes they are found close to the fine fibrous strands or between the hepatic cells. In our cases they were associated intimately with markedly developed fibrous strands in the periphery of the acini. In the hepatic cells and the stellated cells of Kupffer they are found but rarely, and then in degenerated condition. The spirochetes located between the hepatic cells are bent and adhere with their ends or bent sides to the cells. At times they are located in almost parallel lines on the periphery, giving the appearance of lying in the intercellular bile duct capillaries, but their demonstration within the capillaries is difficult. Only in one instance were we able to observe a spirochete in a somewhat dilated biliary duct. It is not probable that the spirochetes stand in any close relation to the bile duct capillaries. In man they are also not so closely related to the blood capillaries as in the guinea pigs. They are rarely present in the interstices of the lobes; *i.e.*, in the interlobular connective tissue. They are infrequently found massed about the acini and the bile ducts; they enter often into the wall epithelium of the ducts, but almost never into the lumen. They are also rare in the zone of leukocytic infiltration, as well as in the interstitial blood vessels, and are seldom found in the lumen. The spirochetes in the liver are frequently contained in degenerated cell masses and coagulated homogeneous substances. On the whole, distribution within the liver is irregular. In the course of the disease, the spirochetes in the liver are almost completely destroyed, and those found occasionally enclosed in stellated cells are mostly of the degenerated type.

The large bile ducts and the gall bladder were examined in five patients who died during the second stage of Weil's disease. Very rarely were spirochetes found in the subepithelial fibromuscular layer.

Kidneys.—The kidney is characterized by a more or less dense distribution of spirochetes throughout the course of the disease. We were able to demonstrate them up to the 55th day of illness. In cases of mixed infection treated with immune serum, scattered specimens are found in the kidneys after they have disappeared from other organs. In fact the organisms could be found in varying numbers in the kidneys of all cases.

In earlier stages the spirochetes are present mostly in the interstices, more numerous in the cortex than in the medullary substance. They are found in the fibrous strands (*trabeculæ*), in the tissue spaces, and in the interstitial cells. They are intimately related to the capillaries. In the kidney tubules they are found surrounding the *tunica propria*. They are rarely contained in the epithelium and the lumen of the kidney tubules. In the course of the disease part of the spirochetes are gradually destroyed, but even in later stages, numerous organisms can be detected in the tubules. In the convalescent stage, innumerable, thickly grouped spirochetes are found in the tubules. It is evident, therefore, that the spirochetes proliferate in the tubules. The number found in the kidneys does not parallel the course of illness. In a patient dying on the 8th day without complicating symptoms, the organisms were sparse, while in one dying on the 10th day, spirochetes in large numbers were found. The latter case was of interest because the spirochetes were thickly grouped in the interstices. In the densest regions, the organisms covered the whole area of the interstitial space and closely surrounded the tubules. It was possible to observe them by low power of the microscope as black dots or spots. Occasionally one sees a case in which the organisms are found mainly in the tubules.

The spirochetes in the tubules lie in the pockets of the lumen, close to the epithelium. They are to be found in the detritus mass or in urinary casts, seldom in epithelium, sometimes in vascular desquamated epithelium.

The spirochetes in the tubules are frequently located in the border zone between the cortex and the medullary substance, the free organisms in the convoluted tubules, and those enclosed in casts in the straight tubules.

In man the spirochetes were never observed in the glomeruli, though in guinea pigs they were found there in sparse numbers. We may conclude, therefore, that the spirochetes in the tubules are not flooded out by means of the glomeruli, but rather that those contained in the interstices migrate through the walls of the tubules directly into the lumen, where they are preserved and may proliferate.

Suprarenals.—The suprarenals, like the kidneys, are characterized in the guinea pig by a dense distribution of spirochetes. Many were seen in a patient dying on the 6th day. They were contained in the interstices, combined with the interlobular fibrillæ of the upper cortex layer. In the cortex cells and their sheaths, they were scarce. They were irregularly distributed, and were found mainly in the subcapsular layer, almost never in the medullary, and the deep cortex layer. After the 8th day, only a few degenerated residual forms are present. The latter lodge in the cortical layer and in the interstitial cells. Occa-

sionally spirochetes are located extracellularly, between the cortical cells and in the interstices. In a patient dying on the 8th day we observed a number of intact specimens in the medullary muscles.

Spleen, Lymph Glands, and Bone Marrow.—The hematopoietic organs showed throughout a sparse distribution of spirochetes. In the spleen the organisms are found at an early stage in the pulp, trabeculæ, and capsular tissue, very rarely in the Malpighian bodies. In the experimental animals it was also difficult to find spirochetes in the Malpighian bodies, particularly in the center. In the pulp tissue, the spirochetes are found mainly in the lattice fibers and the fibrous strands of the sinus and vessel walls. They are likewise present in the pulp cells and in the phagocytes. The phagocytized spirochetes are mostly degenerated. On the other hand, the spirochetes found in the trabeculæ and other coarse fibrous tissue are relatively well preserved. Spirochetes are sometimes found in the walls of large arteries and in their vicinity.

Further on in the disease, spirochetes are rarely present in the trabeculæ, in coagulated masses, and in phagocytes. They are then mostly degenerated in type, though sometimes in good condition in the trabeculæ.

Numerous organisms are contained in swollen lymph glands at the beginning of illness. At first, they are present in the regions of the lymph vessels and sinuses. On the 2nd and 3rd day of illness they appear deeply seated in the fibrous tissue of the parenchyma. The vessel walls, the trabeculæ, and the perivascular tissue also show them. Spirochetes are found extracellularly in the peripheral zones of the follicles. Phagocytized spirochetes are rare. On the 3rd and 4th day we find them numerous in the lumen of the vessels. It would seem, therefore, that the organisms gain access to the lymph channels through the local lymph glands. From there they go into the parenchyma and blood vessels. This phenomenon was confirmed on animals. After the 7th day, it is difficult to find spirochetes even in swollen lymph glands. In the mesenteric glands, they are more numerous, but degenerated and contained mostly in phagocytes. They are rare in fibrous strands. Later on, only scattered residual forms are seen in phagocytes and fibrous tissue.

The conditions in the lymphoid tissue of the various organs and the tonsils resemble those of the lymph glands.

The bone marrow, particularly that of the tibia, was studied in a few cases. In a patient dying in the second stage, no spirochetes were found. In guinea pigs, on the other hand, spirochetes were as numerous in the bone marrow as in the blood.

Digestive Tract and Pancreas.—In guinea pigs closely packed spirochetes are found in the subepithelial mucosa of the intestinal wall. In man their distribution in the intestinal wall was rather scanty on the 7th day and throughout the second stage. In the appendix wall and that of the large intestine and stomach, the spirochetes are more numerous at this stage. They are scattered throughout the mucosa, somewhat more numerous in the submucosa and muscular layer.

They are found free in the tunica propria or in phagocytes, and are often lodged close to the epithelial layer, rarely in the layer itself. They are present for a long time in the muscular layer, and often in considerable numbers. In the convalescent stage, spirochetes do not occur in the intestinal wall; but occasionally a few are found in the intestinal crypts and lumen, though we are unable to say definitely that the organisms were *Spirochæta icterohæmorrhagiæ*, as they were very closely grouped and well formed, which are not characteristics of this spirochete. Moreover, in the silver preparation they did not appear granular, and similar organisms are often found in healthy persons. Dark-field illumination is required to decide this point.

Judging by analogy with the kidneys, it may be supposed that the *Spirochæta icterohæmorrhagiæ* wander out into the intestinal lumen. Infection experiments carried out on guinea pigs with intestinal contents were occasionally positive. In some cases, the organisms may be identified with certainty in the intestinal lumen. These spirochetes are clearly granulated and are located in desquamated epithelium and detritus masses.

The esophagus, tongue, and salivary glands also harbor the spirochetes in varying numbers. As a rule, they lodge in the interstices early in the disease, and later on in the cells.

The pancreas showed spirochetes on the 6th or 7th day. In the densest region a number of specimens appeared in the optical field. They occur mainly in the interstices, closely surrounding the body of the gland and the excretory duct, rarely in the lumen and in the epithelial cells. Later in the disease only a few degenerated forms were found, mostly in the cells.

Respiratory Organs, Thyroid, and Thymus.—The lungs contain but few spirochetes, only a small number being found in the alveoli on the 6th day. They were enclosed in desquamated epithelium, blood, and blood coagulum. Later on, it is almost impossible to find them; very rarely one finds degenerated forms in the alveolar epithelium and coagulated masses.

In the trachea spirochetes were present in the interstices on the 7th day in considerable numbers. In another individual, dying on the 8th day, they were scattered.

A few spirochetes were present in the interstices and capsule of the thyroid in a patient who died on the 6th day. At a later stage they are rarely found in the colloidal masses

The thymus, which was examined in two cases, showed a relatively thick distribution of spirochetes. In a patient dying on the 10th day, they were found rather plentifully in the capsule and septum tissue, and also enclosed in thymus cells. The other patient, who had died on the 12th day, had received serum treatment. Here also numerous organisms were present, mainly degenerated forms, located extracellularly.

Circulatory System.—In the search for spirochetes in man, particular attention has been paid to the heart, for the number there is much greater than in guinea

pigs. On the 7th day of illness and throughout the second stage, spirochetes are more or less numerous; a few were seen in an optical field. Early in the disease they are found in the epicardium and endocardium, and most constantly in the muscular layer. They occur first in the interstices, later on in muscle cells. In the interstices they are found in the perimysium, closely surrounding the muscle cells, in the neighborhood of the capillaries, in coagulated venous blood, and in phagocytes. Those enclosed in cells are found in the periphery and in the centers of muscle cells, independent of the striation. On the whole, they are more numerous in the right side of the heart than the left. The sinoauricular region also showed a dense distribution. During convalescence spirochetes are found here and there, mostly degenerated.

In the arterial walls of the aorta, carotids, brachials, and radials, spirochetes are present more or less constantly during the second stage, chiefly in the media, seldom in the adventitia. They are not numerous. In the lumen of the brachial artery, we observed a single specimen in a patient dying on the 9th day. This was located in coagulated blood near the wall.

Skeletal Muscles and Skin.—The skeletal muscles showed on the 7th day (second stage) a relatively dense distribution, particularly in the calf muscle and rectus abdominis, where the histological changes were most marked. On the 9th day a few specimens were seen. The spirochetes found in muscles occur as a rule in the interstices, *i.e.*, the perimysium, and they surround the muscle fibers closely. Only once did we find thickly grouped spirochetes in degenerated hyaline muscle fibers. At a later stage the organisms are rarely seen in muscle fiber.

The outer skin rarely shows spirochetes. We could discover them only in two out of four cases—in the one contained in prickly cells, in the other in the corium. None were found in the lumen of the sweat and sebaceous glands.

Nervous System.—At an early stage (the 6th day) spirochetes were found in the interstices and the spinal meninges. In rare instances they were present in the interstices of the central and peripheral nervous systems. In the gray and white substance of the brain and spinal cord, degenerated forms were found on a few occasions. Once they were present in the neuroglia.

Urinary Bladder and Genital Organs.—On the 7th day, and during the second stage, a large number of spirochetes were present, particularly in the muscular layer of the bladder. In the testicles and epididymis, well preserved specimens were seen on the 6th and 7th days (second stage), in the fibromuscular tissue, but seldom in the tubules. The prostate shows an unusual condition. On the 7th day (second stage), numerous spirochetes were found in the fibromuscular tissue. The muscular layer of the uterus and the fibrous tissue of the ovaries may show scattered spirochetes, those in the uterus being in well preserved condition.

Factors Influencing the Distribution of Spirochæta icterohæmorrhagiæ.

Severity of Illness.—Those cases of Weil's disease, in which the pathological changes are particularly marked, show in the main the densest distribution in the various organs. In guinea pigs also the distribution of spirochetes is more or less paralleled by the degree of icterus and hemorrhage.

Mixed Infections and Complications.—Suppurative or septic infections, which often accompany Weil's disease, greatly influence the distribution; the spirochetes in the organs thus become reduced in number. They are often absent from all the organs, except the kidneys and the cardiac muscles. Cirrhosis of the liver does not seem to affect the distribution.

Serum and Salvarsan Treatments.—The spirocheticidal action of immune serum has been previously described.⁶ The statements then made are supported by our postmortem findings. Very few spirochetes are discovered in the organs, with the exception of the kidneys, where they remain for a long time. The spirochetes in other organs had evidently been destroyed.

Types of Spirochete in Human Tissues.

In comparison with those found in the experimental guinea pigs the spirochetes in man are irregular in type. They show greater rigidity than those in the animals. They are atrophic and shrunken, and of varying thickness. The edges are not smooth and the curves are irregular; many small waves are observed. At one or both ends, or in the middle, a circumscribed thickening may be present. Sometimes one-half of the spirochete differs in thickness from the other. The circumscribed thickening can be distinguished from the bud, as the latter is more markedly granular. The spirochetes may appear as large, irregularly distributed chains of granules. One end often shows an enlarged, granular bud. This rare form was distributed in a number of organs. It seems to arise through a loosening and

⁶ Inada, R., Ido, Y., Hoki, R., Ito, H., and Wani, H., The serum treatment of Weil's disease (spirochætosis icterohæmorrhagica), *J. Exp. Med.*, 1916, xxiv, 485.

enlargement of some of the granules of the spirochetes. Abortive forms (rod-like, comma-shaped, or bent) arise through the breaking off of parts of the spirochete. One end may give the appearance of having dissolved. The large bud may be present at one end of a markedly shrunken spirochete. Such deformed types are often found in phagocytes.

In the group, where the spirochetes are closely assembled, many small granules or rings are seen; these stain black when impregnated with silver. The granules are globoid or irregularly formed, and are from two to five times as thick as the spirochetes. They are detached, fused buds or broken parts of spirochetes. The rings referred to above are round or somewhat irregular, also from two to five times as large as the thickness of the spirochete. Their origin is identical with that of the granules. On the other hand, the ring type of spirochete which has already been described, is large and irregular, and can be readily distinguished from the rings referred to above.

We are led to believe that these forms are degenerated products, caused by the action of the immune bodies. This point requires further investigation.

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