ON THE ASSOCIATED INCIDENCE OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM AND CARDIO-VASCULAR SYPHILIS *

E. D. FRIEDMAN, M.D.

Instructor in Medicine, University and Bellevue Hospital Medical College; Adjunct Attending Physician, Third Division, Bellevue Hospital; Contract Surgeon, U. S. Army

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That syphilis plays an important rôle in the causation of aortic aneurysm and aortitis had been long suspected. Weil thought that every case of fibrous aortitis was due to syphilis. Groen studied 306 cases of visceral syphilis and found vascular changes in 76 per cent. of the men and 49 per cent. of the women. Schultze holds syphilis to be the cause of aortitis in practically all cases. Hampeln says, "A definitely diagnosed, circumscribed aneurysm permits the assumption of luetic infection, eight to twenty years previously." Etienne believed 70 per cent. of all aneurysms to be syphilitic in origin; Gerhardt put the percentage at 53, and A. Frankel at 55. The pathologic work of Doehle, Heller and his pupils, Stadler, Chiari, Benda, Marchand and Eich in Germany; of Mitchell Bruce in England, and the clinical studies of Huchard and Dieulafoy in France, have emphasized the syphilitic origin of aortitis and aneurysm. In this country, Cummer and Dexter, Epstein, Held, Longcope, Symmers, Wallace and McCaskey have made contributions to this subject.

That tabes is of syphilitic origin was emphasized by Fournier and Erb. The latter asserted that 88 out of 100 tabetics were syphilitic. Berger thought 20 per cent. of tabetics were syphilitic. Westphal put the percentage at 33, Remak at 23, Rumpf at 66. Eisenlohr at 52.5, Bernhardt at 60, Fournier at 93, Dejerine at 90, Strümpell at 90. Quincke and Moebius assert dogmatically that every tabes is the result of syphilis. Barker (in Monographic Medicine) says: Tabes is due to syphilis while Dana puts syphilis as the important and essential cause. Starr maintains that 90 per cent. of the cases are due to syphilis; he calls it, however, parasyphilis because it follows syphilis and is not cured by antisyphilitic therapy.[1]

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1. This, however, does not seem a valid argument to us. Hepar lobatum is also incurable, yet no one speaks here of paralues. We cannot cure scars or sclerosis, especially in the nervous system.

Formerly Jews were relatively free from tabes. Now with increasing exposure to infection due to the breaking down of the religious barrier, tabes is quite common among them; this illustrates the etiologic importance of syphilis. The inoculation of rabbits with syphilis by means of cerebrospinal fluid taken from cases of early central nervous syphilis has been accomplished by Uhlenhuth and Mulzer, Hoffman, Nichols and Hough, Kleiner, Volk, Arzt, Kerl and Mattauschek, Marinesco and Minea, Frühwald and Zaloziecki, Reasoner, Dohi and Tanake, Graves, Wile and others.

With the demonstration by Noguchi and Moore of the spirochetes in the brain of general paretics and, though more rarely, in tabes, the confirmation of these findings by Marinesco, Marie and Levaditi and the demonstration of specific changes in the cerebrospinal fluid in syphilitic infections of the central nervous system, we may say with Erb that so-called *meta* or *para* syphilis is syphilis, and only the variations in maximum localization of the process produce the clinical pictures we know.[2] That the heart is frequently involved early has been shown by Brooks, and the early involvement of the meninges is shown in the characteristic changes in the spinal fluid present in the second stage of syphilis. This was first shown by Dreyfus and later confirmed by many other observers.

FREQUENT ASSOCIATION OF SYPHILIS OF THE CARDIOVASCULAR AND NERVOUS SYSTEMS

The frequency of the association of cardiovascular and central nervous syphilis was not noticed until Berger and Rosenbach, in 1879, called attention to the coincidence of tabes and aortic regurgitation. They reported seven cases, but did not emphasize the relationship between the two conditions. Charcot, too, had noted this coincidence, and Vulpian had spoken of anginal attacks occurring during the course of tabes without explaining the association. They both agreed that the cardiovascular lesions came on late in tabes — a fact to which Stadler also called attention.

Letulle observed that tabes frequently was associated with cardiac lesions, especially aortic regurgitation. His first case came to postmortem. There was degeneration of the posterior columns and atheroma of the aorta and the cerebral vessels. The aortic valve was thickened and retracted. The second case showed a double aortic lesion and tabes. He thought chronic arteritis was the underlying cause of both conditions, and significantly concludes, "If a cardiac lesion is present in tabes, it is generally aortic regurgitation. Both

2. Warthin has emphasized the essential uniformity of the pathologic changes in all forms of syphilis.

are due to a common cause, namely, chronic arteritis." Colgahoun reported two cases of tabes with aortic regurgitation, but thought the tabetic pain caused the aortic regurgitation, and that possibly the vagus played a rôle or that circulatory changes in the cord might contribute to the tabetic condition.

Leyden wrote of anginal attacks and cardiac asthma in tabes and assumed trophic changes in the valves as the cause of aortic regurgitation. In one case of what must have been conjugal syphilis he explained the occurrence of an aneurysm in the wife of a tabetic as having been due to cardiac strain as a result of the wife's nursing her tabetic husband. Balacakis found three cases of aortic regurgitation among fifty-five tabetics, but was not impressed by their association, ascribing the valvular lesions to rheumatism. In reporting two cases Grasset thought tabes was the primary condition and the cardiac lesion due to painful crises. He also thought that the cardiac lesion had long been latent. In the first edition of his text book (1884). Strümpell spoke of the common origin of the two conditions. In a case of Oppenheim's the necropsy revealed tabes, atheroma of the aorta and of the cerebral vessels, and an incompetent aortic valve.

Fournier, Grasset and Letulle thought that on the whole aortic disease was rare in tabes while Charcot, Vulpian and Raymond speak of the relative frequency of the association. With more recent pathologic studies, the view, ascribing both tabes and aortic disease to syphilis, gained ground, and this hypothesis easily explains their coincidence.

Ruge and Huttner found nine cases of aortic regurgitation among 138 tabetics. They conclude: "Those tabetics who develop cardiac disease have it chiefly at the aortic valve. The coincidence of tabes and aortic disease is due to a common cause — lues." Nordmann reviewed the reported cases up to 1894, and found 134 cardiacs among tabetics, 65 being cases of aortic disease. The other 69 involved other orifices alone. He also reported 8 cases of aortitis among 100 tabetics. Schuster found three cases of aortitis among 22 tabetics, and Marie one cardiac to four or five tabetics, most of them with disease of the aortic valve. Hertz examined 98 tabetics and found six cases of aortic regurgitation, two of aneurysm and 16 cases of dilated arch with carotid heaving, elevation of the right subclavian artery, pulsation in episternal notch and inequality of radial pulses In 50 per cent. of his cases of cardiac disease, among tabetics the aorta was involved. In another series he found 48 cases of aortic regurgitation among 76 tabetics with cardiac disease.

Bouveret heads one of his contributions to this subject as follows: "Syphilis-ataxie cardiopathie"—a suggestive title. Enslin reported

seven cases of tabes with aortic insufficiency, and Friedrich Müller a case of aortitis and tabes. There was a to and fro aortic murmur, enlargement of the heart, and at the same time, miotic fixed pupils and ataxia. F. Lesser collected eighteen cases of aortic aneurysm among ninety-six cases of tabes which came to necropsy, and Barthelemy (quoted by Guilly) reported seven cases of tabes with aortic disease.

Guilly reasons as follows: Syphilis is frequent in tabes; it also causes aortitis; hence aortitis and tabes probably have the same etiology, namely, syphilis. He reports thirty-three living patients who have general paresis with ten cases of aortic disease among them, and 200 cases of general paresis which came to necropsy. Forty-one of the latter showed evidence of aortic disease, aortitis, changes at the valve, atheroma. These taken together make a total of fifty-one cases of aortitis among 233 cases of general paresis, that is, one case of aortitis, aortic regurgitation or aneurysm to five cases of general paresis. Aortic regurgitation was the most common lesion during life, and when nothing was found clinically the changes were present at necropsy. As a result of his own studies and a review of the literature, he concludes that aortitis is frequent in the course of tabes. Frequently there is cardiosclerosis with irregularity of rhythm. In general paresis, aortitis is present in about 20 per cent. of the cases, chiefly in the young (under 45), and probably due to syphilis.

Rogge and Mueller think that the frequency of this association and its clinical significance are not sufficiently appreciated. Usually one of the two conditions dominates the clinical picture; the symptoms and signs of the latent condition must be carefully elicited. Tabes in a case of aortitis may be very mild. Guilly and Strümpell also note this point. Our own observations confirm the statement. Strümpell speaks of rudimentary tabes. Rogge and Mueller found eight cases of cardiovascular disease among twenty-two tabetics. This percentage is rather high. The average is about from 10 to 20 per cent. In twenty-four selected cases showing this association, the most frequent lesion was aortic regurgitation or aortic regurgitation and obstruction. In 15 per cent. of the twenty-four there were tabes and aortic disease, and in nine there were tabes and aneurysm. Most showed evidences of myocardial degeneration and premature atherosclerosis. In only 58.3 per cent. were there definite cardiac complaints. The cases of sudden death reported in tabes are probably due to sudden dilatation from myocardial degeneration, coronary thrombosis or rupture of an aneurysm. In nine of these cases there was definite evidence of syphilis and in ten others it was probable. In only two was there a history of polyarthritis. "Rheumatism" in these cases usually means

tabetic pain. Seven of the twenty-four patients were women. The average age was about 40. (Bittorf found the average age in non-syphilitc aortic sclerosis to be 55.) The cardiovascular symptoms come later than the nervous phenomena, according to Rogge and Mueller, about four and one-half years later. A lesion in the cord will give symptoms much earlier than one in the aorta. More recently L. Braun reported 103 cases of general paresis with twenty-three certain and five probable cases of aortitis among them. Nobel reported the case of a boy showing aortic regurgitation, with unequal, fixed pupils, exaggerated knee-jerks and ankle-jerks, with dementia, speech disturbance and a positive Wasserman reaction. E. L. Hunt, in the course of an article entitled "Complications of Tabes," mentions the occasional occurrence of aneurysm or aortitis without, however, citing any cases. Dana in the latest edition of his textbook speaks of cardiac crises in tabes, that is to say, dyspnea and angina-like attacks. Starr found nine cases of aortic murmur in 126 cases of tabes, and Levinson has mentioned this association.

SYMPTOMS USUALLY MILD

Tabes in a case of vascular syphilis usually is mild. The pupils may be miotic, rigid, unequal and irregular. The Achilles jerk, alone, may be lost. Hypotonus may be present even in cases with exaggerated knee-jerks and as a result, tabetic flat-foot. There may be girdle sensation zones of hypoesthesia-radicular in type, lancinating pains, gastric crises. Frequently there is retention of urine—another evidence of sacral tabes. Patients will say with a great deal of pride that they can hold their water all day. The Abadie symptom—loss of sensitiveness of the biceps tendon or tendo Achilles to pinching—is a common early sign. There may be ulnaris hypoesthesia. Goodkind described hypoesthesia of the anus and urethra.

On the other hand, cardiac symptoms in a case of tabes or general paresis may be scanty. The absence of history of rheumatic fever or other infectious disease in case of aortic regurgitation, the localization of the murmur, chiefly in second right interspace,[3] and the occurrence of aneurysm in the young are suggestive evidence of cardiovascular syphilis and evidence of this disease should be looked for.

In radiographic examination, aneurysmal bulging may be seen in the first oblique diameter, encroaching on the so-called retrocardiac

3. The murmur of syphilitic aortic insufficiency frequently is loudest in the second right space and not at Erb's point where endocarditic aortic insufficiency usually is best heard. This is said to be due to changes in the wall of the aorta which cause better transmission to the superficially situated ascending aorta.

space. Every case of tabes should be examined radiologically and if possible electro-cardiographically to determine changes in the cardiac musculature to which Brooks in this country first called attention. Usually, as outlined above, one of the two conditions dominates the clinical picture. This may be due to variations in tissue or strain affinities (Reasoner). The spirochetes seem to exert their maximum effect in one system without completely neglecting the other. So patients with myocardial changes occurring early in life — with dyspnea, anginal attacks, palpitation, cough, slight edemas — should be examined for signs of tabes. Careful neurologic examination may illuminate obscure visceral lesions. For example, a fixed pupil may clear up the syphilitic origin of an obscure liver affection, and a lost Achilles jerk may indicate that a stomach syndrome is a gastric crisis. We are fortunate in being able to corroborate our diagnosis by serologic tests, but we must express our admiration for the host of clinicians who could draw accurate conclusions without laboratory aids.

AUTHOR'S OBSERVATIONS

My own observations were made first on fifty cases of tabes at the Central Neurological Hospital, New York City. Those with definite rheumatic history were excluded. There were seven cases of cardiovascular syphilis among them. One other case showed at the same time an uncomplicated aortic insufficiency and left-sided cerebral thrombosis with motor and sensory paralysis, astereognosis, motor aphasia, and mimic facial palsy. Concerning this case we could not say definitely whether the cerebral lesion was due to embolism from the diseased aortic valve or to autochthonous thrombosis. The absence of evidence of embolism anywhere else and the stationary character of the valvular process would seem to point to the latter.

ILLUSTRATIVE CASES

CASE 1.—Man, aged 51, contracted syphilis eighteen years ago. Circulatory: Aortic regurgitation; aortitis; Corrigan pulse. Nervous: Pupils, unequal—left smaller and sluggish to light; knee jerks only with reinforcement; ankle-jerks, absent; Abadie's sign, positive; ulnaris hypesthesia; cochlear and vestibular function lost on the right; undue retention of urine; impotence. Serologic: Blood Wassermann, + +.

CASE 2.—Man, aged 42, became infected with syphilis twenty years previously. Circulatory: Diastolic murmur at apex; to and fro murmur at Erb's point and second right interspace; Corrigan pulse; manubrium dulness; pulsation in episternal notch. Nervous: Pupils, fixed; hypotonus; knee-jerks and ankle-jerks, absent; Romberg sign, positive; incontinence of urine. Serologic: Blood Wassermann, + + +.

CASE 3.—Man, aged 33, was infected with syphilis fourteen years ago. Circulatory: Cardiac asthma; decompensation; no murmurs (even after return of compensation); arrhythmia. Arrhythmia not altered by injection of atropin (myogenic). Nervous: Pupils were unequal, miotic and irregular, sluggish to light; ankle and knee jerks, absent; hypotonus; Romberg sign, present; undue retention of urine; Abadie's sign, positive; vibratory sense, absent. Serologic: Spinal fluid was weakly positive.

CASE 4.—Woman, aged 49, had syphilis. She was well up to three years ago when she had pain in the left leg and had to watch her feet. Later there was pain in her right leg with numbness and tingling and she was unsteady on her legs. Circulatory: Systolic murmur in aortic area transmitted upward into vessels of the neck; dulness over manubrium; pulsation in episternal notch. The roentgen ray revealed a dilated aorta. Nervous: Pupils, equal, Argyll Robertson; pallor of left disk; deep muscle and joint movement sense, impaired in all extremities; vibration sense lost; ataxia; knee and ankle jerks, absent. Serologic: Wassermann on blood and spinal fluid was negative; fluid showed increase of globulin and 22 lymphocytes to the cubic millimeter.

CASE 5.—Woman, aged 43, with no history. Circulatory: Systolic murmur in aortic area, transmitted upward; dilatation of ascending aorta. Nervous: Pupils, fixed; ankle jerks, absent; bladder symptoms. Serologic: Blood Wassermann, + +.

CASE 6.—Woman, aged 44, had been a prostitute. Circulatory: Systolic murmur in aortic area; loud diastolic at Erb's point and second right interspace; pulsation in episternal notch. Roentgen ray revealed a dilated arch especially at junction of transverse and descending aorta. Nervous: Argyll Robertson pupils; Romberg sign, present; knee-jerks, absent; radicular anesthesias. Serologic: Both Wassermann tests, positive.

CASE 7.—Woman, aged 40, gave no history. Circulatory: Aortic systolic murmur; very loud aortic second sound without elevation of blood pressure. Diffusely dilated arch, especially ascending aorta. Nervous: Argyll Robertson pupils; knee-jerks, absent; Romberg, present; ataxia; bladder symptoms. Serologic: Both Wassermann tests were weakly positive; increased globulin in spinal fluid and 24 cells to the cubic millimeter.

COMMENT

There were two additional cases in this series, but their respective ages were 55 and 57, and they both showed hypertension. Since in these cases dilatation of the arch of the aorta and aortic murmurs may have been the result of simple atherosclerosis without syphilis, we did not include them in our series.

We have recently been able to observe forty cases of syphilis of the central nervous system, admitted to the Third Medical Division of Bellevue Hospital. Among these there were seven cases of cardiovascular disease affecting chiefly the aorta.

CASE 8.—Man, aged 53, had a chancre twenty years previously. Circulatory: Heart displaced downward and to the right; very loud aortic second sound. The roentgen ray revealed an aneurysm of the descending aorta with distortion of cardiac outline. Nervous: Pupils were miotic and fixed; knee and ankle jerks, absent. Serologic: Blood Wassermann, + +.

CASE 9.—Man, aged 42, had a chancre when 26 years old. Circulatory: Systolic murmur in aortic area; metallic ringing aortic second sound. The roentgen ray revealed a diffusely dilated arch. Nervous: Pupils were miotic and fixed; knee and ankle jerks, absent; hypotonus; undue retention of urine; sensory changes; genu recurvatum; marked ataxia. Serologic: Both Wassermann tests, + +.

CASE 10.—Man, aged 46, had a chancre twenty years previously. Circulatory: Myocardial insufficiency with decompensation; dilated arch. Also large nodular liver, after return of compensation (hepar lobatum). Nervous: Pupils were irregular and sluggish; knee and ankle jerks were much diminished. Serologic: Blood Wassermann, + + + +.

CASE 11.—Man aged 51, had a chancre thirty years ago. Circulatory: Aneurysm of common carotid artery; metallic aortic second sound; valvular first sound of heart; blood pressure, 140/90; large nodular liver; dyspnea. The roentgen ray revealed a widening of the aorta especially in the descending portion of arch. Nervous: Pupils were small and sluggish to light; ankle jerk, absent; incontinence of urine. Serologic: Blood Wassermann, + + +.

CASE 12.—Man, aged 38, had a chancre ten years ago. Circulatory: Apex beat was in the sixth space in the anterior axillary line; double aortic murmur; dulness over manubrium; pulsation in episternal notch; throbbing carotids; Corrigan pulse; systolic tone in vessels; systolic thrill in aortic area. Nervous: Pupils were unequal, both Argyll Robertson; ptosis of upper lid; ankle jerk very much diminished; undue retention of urine. Serologic: Not studied.

CASE 13.—Man, aged 36, denied that he had syphilis. Circulatory: Double aortic murmur; systolic murmur transmitted into vessels of the neck. The roentgen ray revealed a diffuse dilatation of the arch, especially marked in transverse portion (fusiform aneurysm). Nervous: Basilar meningitis involving the fifth, seventh and eighth nerves on the left; knee and ankle jerks were absent. Serologic: Blood Wassermann, + +; spinal fluid, globulin increased, 1,000 cells to the cubic millimeter.

CASE 14.—Man, aged 53, denied syphilitic infection. He had had anginal attacks for two years. Circulatory: Double aortic murmur with visible diffuse pulsation; dulness of upper sternum. The roentgen ray revealed a dilated arch. Nervous: Pupils were irregular, very sluggish to light; hypotonus; knee and ankle jerks were absent. Serologic: Blood Wassermann, + + + +.

Finally I have selected several cases from my own records which illustrate this association. Out of a total of thirty-five cases of syphilis of the central nervous system, there were five cases showing coexisting cardiovascular syphilis.

CASES OBSERVED PERSONALLY BY THE AUTHOR *

CASE 15.—Man, aged 44, denied that he had syphilis. He complained of "fainting spells," loss of memory, mental deterioration, that he was clumsy and awkward in his work (that of plumber) for last year. Circulatory: Systolic murmur in the aortic area; blood pressure, 140/100. The roentgen ray revealed a very much dilated aortic arch. Nervous: Pupils were miotic and fixed; weakness of the right lower facial; tongue deviates to right; deep reflexes exaggerated on the right, abdominals diminished; dysarthria; motor aphasia (?); tremor of face and tongue. Serologic: Blood Wassermann, + +.

CASE 16.—Man, aged 57, had syphilis sixteen years previously. Circulatory: To and fro murmur in aortic area; much diminished aortic second sound; right radial showed less pulsation than left; blood pressure, 140/70. The roentgen ray revealed a dilated aorta. Nervous: Pupils were very sluggish, miosis; knee jerks increased; Babinski sign on the right. Mendel-Bechterew and Rossolimo, positive on both sides; abdominalis diminished; tremor in right facial; mental changes; speech defect; vertigo. Serologic: Blood Wassermann, + + + +; spinal fluid showed the globulin increased 35 cells to the cubic millimeter; Wassermann reaction, + +.

CASE 17.—Man, aged 50, denied that he had syphilis. He had dyspnea for some time, was impotent and could not pass his urine at will. Circulatory: Dulness over manubrium; embryocardia; loud ringing second aortic; blood pressure, 140/90; pulsation in notch; liver enlarged, edge was hard and sharp, no tenderness. The roentgen ray revealed a typical aneurysm. Nervous: Right pupil was irregular, both fixed; knee and ankle jerks diminished; Abadie's sign, +; definite ulnaris hypesthesia. Serologic: Blood Wassermann, + + +; spinal fluid not examined.

CASE 18.—Man, aged 45, was infected with syphilis twelve years previously. He had a lesion on his neck which refused to heal; bleeding from nose; ulcerating lesions in the throat. He was treated for diphtheria, but with no benefit. He had diffuse abdominal pain with passage of tarry stools. There was a stellate scar on the right tonsil. Circulatory: Blood pressure, 110/70; vessels sclerosed; spleen palpable; probable thrombosis of intestinal vessels. The roentgen ray revealed a hypoplastic heart. Nervous: Pupils were miotic and irregular, sluggish reaction to light; knee and ankle jerks absent; loss of sense of fulness of bladder; hypotonus; gastric crises (?). Serologic: Both Wassermann tests were negative; spinal fluid shows simply increased globulin; luetin test positive.

CASE 19.—Man, aged 49, had a chancre twenty-five years ago. A number of times he could not pass urine at will. Circulatory: Systolic murmur in aortic area; very loud second aortic; blood pressure, 150/90; liver palpable, nodular (hepar lobatum). A roentgenogram revealed a definitely dilated arch. Nervous: Pupils were unequal, fixed; ankle-jerk much diminished; left abdominal reflexes, absent; Rossolimo, positive on left; anal crises; disks grayish. Serologic: Blood Wassermann, + + + +.

To my mind the pupillary changes in aneurysm are rarely due to pressure on the cervical sympathetic. They are rather the result of the associated syphilis of the nervous system.

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* Several of the cases cited showed the picture of parenchymatitis luetica, a term coined by Brauer to denote simultaneous involvement of all parenchymatous organs; heart, liver, kidney, and nervous system. (Cases 10, 11, 17 and 19.)

FURTHER OBSERVATIONS

Through the courtesy of Dr. Douglas Symmers, I have had access to the postmortem records of the State Hospital for the Insane at Morristown, N. J., for the period of 1907-1915. There were eighty-three patients who had general paresis. Of these, I have selected only those about 45 years old or less who had changes in the aorta indicative of syphilis. There were forty-nine such cases, and among the remaining older cases the lesion in the aorta was aortitis luetica in thirteen, making a total of sixty-two cases with syphilitic aortic disease, that is, 75 per cent.

SUMMARY

Summarizing my own observations, I may say that among 125 cases of syphilis of the central nervous system, there were 19 cases of cardiovascular disease — an incidence of 14 per cent. Of these, 13 showed disease of the aortic valve either alone or in combination with aneurysm or dilatation of the aortic arch. There were two cases of myocardial degeneration with resulting decompensation. Two showed typical aneurysms without demonstrable disease of the aortic valve. In the series was one carotid aneurysm and one patient showed the clinical picture of premature atherosclerosis with probable occlusion of mesenteric vessels.

INTRASPINAL TREATMENT

A word on intraspinal treatment. That the cerebrospinal fluid is poor in antibodies is shown by the necessity of taking larger quantities of it than we do of blood serum for the Wassermann test. We also know the value of serum in cerebrospinal meningitis when the antibodies are introduced from without. Attempts to treat general paresis with nucleic acid and tuberculin injections really resolve themselves in efforts to stimulate the antibody mechanism which we now know is intimately associated with fever. So too, it seems to the writer, it is not so much a question of introducing arsphenamin into the cerebrospinal fluid; it is rather one of introducing antibodies. The value of a preliminary intravenous injection of arsphenamin would consist in the destruction of spirochetes with consequent calling into play of the antibody mechanism of the blood. The injection of the patient's own serum would then furnish the antibodies which seem to get into the cerebrospinal fluid with difficulty. It would be for the immunologist to devise a means of concentrating the antibodies in the blood and then making use of them for therapeutic purposes.

74 East Ninety-First Street.

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