THE PATHOGENESIS OF Salvarsan Fatalities

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BY

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ST. LOUIS, MO.

THE FLEMING-SMITH COMPANY
Medical Publishers
Saint Louis
U. S. A.

Translator's Note.

Just what rôle salvarsan and its companion preparation, neosalvarsan, are to play in the future therapeutics of syphilis; whether they are to remain the principal form of treatment of this disease, and whether they possess sufficient spirillocidal power to warrant their unaided employment, are points that the clinical investigations of Professor Wilhelm Wechselmann alone will determine. His vast experience with salvarsan entitles his conclusions on any phase of salvarsan-therapy to the most respectful consideration, and his investigations into the causes of salvarsan fatalities cannot but add in large measure in fixing salvarsan's degree of

toxicity and the bodily factors involved in the fatal process. Whilst it is true that conclusions reached at the present time are subject to revision, for, confessedly, the last word on salvarsan is far from having been written, yet it is safe to assume that much of our present-day knowledge of salvarsan-therapy is sound and worthy of reliance. The translator of this little book believes that all physicians interested in the treatment of syphilis by means of salvarsan and neosalvarsan will find much food for thought in these pages. He hopes, at least, that the reader will see the author's purpose to teach greater caution in salvarsan-therapy.

Clarence Martin, M. D.

St. Louis, Mo., U. S. A.
June, 1913.

ON THE PATHOGENESIS OF SALVARSAN FATALITIES

Of all the clouds which have encompassed salvarsan therapy there yet remains one to darken the horizon, but this is the blackest, viz.: the foudroyant fatalities in consequence of the intravenous injections of salvarsan. There cannot be the least doubt but that these cases are pure salvarsan fatalities, that is, the concerned patients would not have died at the time had it not been for the introduction of salvarsan into their veins.

One can estimate the collateral effects of salvarsan in two ways, just as one can those of any other sort of remedial agents. The one way is that the physician conscientiously register all of the untoward effects and after a time present the ascertained faults; one is thereby, as a matter of course, convinced that these must become more widely extended from day to day, and that one, indifferent as to whether these unfortunate occurrences offer a common type or not, must reach the conclusion that salvarsan is not free from marked dangers. Still wearier and more uncertain is the other way, that one, first of all, free from bias follow the genesis of the fatalities, prove whether or not the same really should be charged against the agent and also how they may be avoided. Only the second is the truly scientific way because it is free from prejudice. It becomes quite clear that this way has led to a knowledge of the causes and

to the control of the collateral effects which from the first presented themselves in the foreground. What Bessel said of inaccurate astronomical instruments, holds good here, viz.: when one has an exact knowledge of an error, then it is an error no longer.

Along these lines we must, therefore, proceed to the investigation of the fatalities of salvarsan and their pathogenesis.

It is best that we base our conclusions not upon those cases of death which have occurred after subcutaneous or intramuscular injections of salvarsan in persons suffering from serious organic changes, but on the contrary upon those which have occurred within a short time after injection—those dying in the acutest manner, as we might say—and in which no organic lesions were present. Such cases should be in the person of young, healthy patients, and there should be no error of technique to influence results.

Millions of salvarsan injections have been given which have been without incident, therefore, a purely toxicologic explanation of these fatalities is out of the question. Also, by reason of the foregoing one cannot draw a connection between the dose and evil ending. I have myself twenty-five times given in quick succession doses of 0.6 and 0.7 without untoward collateral effects. Of neosalvarsan 1.5 has been administered at two-day intervals without harm. But on the other hand, is the single fatal ending occurring in my department, which took place in the case of a young girl, who had received 0.1 and 0.2 of old salvarsan. The other fatalities also fol-

lowed the usual doses. One might think that this bad luck resulted from a preparation which had undergone decomposition changes, but Ehrlich himself, more than once has sent me supplies of salvarsan made under the same circumstances as that which has caused death, and yet when used in my hands no evil results followed. Still more clearly demonstrable of this fact is, that in our case a three gram tube had been made into solution, from which a series of patients received 0.5 and 0.6 without reaction, while the girl who died, and into whom was injected the identical solution, received but 0.2. Portner had a similar experience, injecting four patients with a solution made from the same tube and yet but one became ill and died. Querat injected eight patients from a common mixture, and again only one, the fourth injected, an apparently healthy young man, succumbed, death ensuing after a few hours. Thus it is sure that the drug in itself did not cause death; the determining cause, therefore, for the deadly action must lie within the patient himself.

A hazily outlined hypothesis of a hypersensitiveness has been offered in the way of an explanation. Now this explanation would have value were we able to correctly estimate this hypersensitiveness in a clinical manner, for then before the injection of salvarsan we could preserve the patient from the unhappy termination. On the post-mortem table this hypersensitiveness has a worthless pathological significance, and, therefore, according to its very nature—it could have only a relative clinical value—it must be held to be entirely

unacceptable. Then it must also be remembered that the theory of hypersensitiveness becomes still further weakened by the fact that in the majority of instances, the patients who succumbed to salvarsan did not die after the first injection, but, on the contrary, irregularly after subsequent ones, usually after the second. Also there could not be established the least connection between the hypersensitiveness and the dose employed, in evidence of which may be introduced the case of Klieneberger.* A pregnant waitress, 25 years of age, received on March 29th an intragluteal injection of 0.2; on April 3rd she was given 1.2 intravenously. Apart from an urticarial eruption radiating from the site of injection, and a temperature 38. (100.5 Fahr.), she bore this large dose well. On the 22nd of May she was given another injection of 0.6 whereupon the usual indications of salvarsan badly tolerated set in, and on May 25th death took place.

One is not justified in employing the theory of cumulative action; I have myself given 0.6 doses at two and three day intervals, ten or fifteen times, without any evil collateral effect. These cases showed no cumulative effects. On the other hand, in most instances, death has followed after a total dose of from 0.3 to 0.8.

This confusion is further added to by the pathological findings which reveal in a great number of cases a hemorrhagic encephalitis. For that reason one was disposed, in consider-

*Deutsche med. Wochensch., 1912, No. 36.

ing the nervous manifestations produced by salvarsan, to locate the site of the hypersensitiveness in the central nervous system, and was prone to speak of congestion of the brain.

Pötzl and Schüller who have observed the same brain congestion after the employment of mercury, give the following explanation: "The consequences of the early luetic infection manifest themselves in a permanent change of balance between intracranial and extracranial circulation, as a result of which there may be an increased susceptibility of the brain to toxic influences. The brain then plays a more important rôle in the reaction to toxic influences of various sorts than under normal circumstances." The most that one can say about this explanation is that it is purely hypothetical. Were this hypothesis correct it would still be difficult to understand why, with the well known extraordinarily frequent participation of the brain and meninges in the syphilitic process, a hypersusceptibility to mercury is so rarely seen. That this supersensitiveness to salvarsan is seen so disproportionately oftener indicates in itself that influences other than brain syphilis enter into the question. Then add to this point that, in many salvarsan fatalities, the brain is found to be entirely free from luetic or other changes; furthermore, no illuminating connection can be seen in the age of the infection, for the most casual inspection of statistical information shows that syphilitics in all stages of the disease have met with this sad fate. That the notion of a neurotoxic action is quite untenable is evident in the fact that even in

the presence of encephalitis hemorrhagica following salvarsan, the brain substance does not seem to be affected (still further proven by Nissl's thorough examination of the cells); on the contrary, it is solely the blood vessels which are damaged. That these vessel lesions are caused by noxious influences of a general character is shown by demonstrable hyperemia and hemorrhage in all of the inner organs.

Especially since I have myself experienced a fatality in consequence of the new therapy, I can look at the problem all the more sharply; therefore in presenting my case I shall give every point in connection with it.

Marie St., born on November 21st, 1887, received in the hospital February 26th, 1912. The patient has always been well, knew nothing of her infection and has not been treated. Small papular, universal rash. Plaques on the tonsils. Wassermann ++++. For two weeks has suffered with headache, sleeplessness, and tinnitus on the left side; according to the aural examination the tympanic membranes of both sides are involved, but the findings do not reveal any lesion commensurate with the difficulty. Examination of the eyes reveals a nystagmus claimed to have existed for six years; a sister suffers from the same disorder. The retina is normal. Vision 5/5. Urine normal. Lumbar puncture on February 27th, marked by a forcible escape of fluid. Fluid spurts out in a stream. Cells ++, gold ++, Nonne —, Wassermann —. On March 1st, vomiting. From March 6th to March 18th patient was rubbed daily with 4 grams of ungt. hydr. On March 12th the patient received 0.1 salvarsan in an alkaline solution (0.9 per cent. salt solution). Borne without reaction; temperature 37.6 (99.7 Fahr.). March 13th temperature 38 (100.4 Fahr.). Thenceforth temperature normal. On March 18th,

0.2 salvarsan with immediate rise of temperature to 40.3 (104.5 Fahr.); headache and vomiting; angina and swelling of the glands of the throat. Following the administration of 0.3 (5 grs.) of pyramidon the temperature falls slowly; on the morning of the 20th temperature 36.4 (97.5 Fahr.). Six o'clock in the evening general convulsions suddenly appear with biting of the tongue. The pupils are widely dilated and do not react, coma, marked respiratory distress with deep contraction of the jugular, no cyanosis, trismus and rigidity of the extremities. On March 21st, the advisability of trepanation considered, but as there are no evidences of brain pressure (pulse 120, soft), the idea is set aside and a venesection made, 200 c.c. of blood being abstracted and then a saline infusion of 300 c.c. given. Patient is unconscious. No rigidity of the neck or of the limbs; reflexes present; respiration free but groaning. Temperature in anus 40.7 (105.2 Fahr.). Corneal reflex weak, pupils just a bit dilated, right slightly more so than left, react promptly, motility cannot be tested, retina mildly hyperemic, veins somewhat distended and very dark. Cyanosis of the retina but no hemorrhage, no circumscribed area, no iritis. Function of the bladder not observed. By means of a catheter a small quantity of urine has been evacuated; this contains much albumin, numerous granular casts and formed elements. Without any other changes death ensued at 5 o'clock in the afternoon. Spinal fluid abstracted shortly after death coagulated spontaneously like gelatine. Nonne ++++, gold +++ (10-5000 white) cells +++, lymphocytes: leucocytes 8:1, Wassermann 5 per cent. ++, 100 per cent. ++++.

AUTOPSY (Dr. Auffermann).

Brain.—No changes are to be recognized in the skull. The dura mater, especially in the hind segment, is firmly attached to the skull. Veins and sinuses distended with blood. The inner surface of the dura mater is covered with irregular arterial hemorrhages, arranged in stripes of a bright red color. The more delicate meninges to

a site between the optic nerve and the olfactory tract in front of the chiasma, are transparent. The veins are markedly filled with blood. The brain substance is of a somewhat compact consistence; no gross changes are present. The arteries of the base are reddish blue and quite uniformly thickened. At either side of the crus cerebri and somewhat over it the meninges are hemorrhagic.

Spinal Cord.—Everywhere the nerve tracts are freshly hemorrhagic; the hemorrhages extend to between the vertebrae. The blood vessels of the cord are distended. The coverings of the cord opposite the middle and upper dorsal vertebrae are somewhat congested. The substance of the cord is rather firm; its appearance is nowhere out of the ordinary. The fluidity of the cerebrospinal fluid is not increased. On the posterior surface are rather firm adhesions between dura and pia mater.

Pharyngeal Organs.—These are somewhat uniformly swollen. The palatine tonsils are larger than a bean.

Thorax.—Position of diaphragm, on the left fifth, on the right fourth rib.

Heart.—The pericardium shows nothing of interest. The heart is rather larger than the fist. The ventricles are contracted. The epicardium over the vessels thickened moderately. In the myocardial substance are to be seen golden and grayish brown stringy streaks, and very numerous striped, dark red foci of the diameter of 1 mm. but without a sharply defined border. Beneath the endocardium of the left ventricle are confluent red specks. The valves are intact.

Lungs.—A few fibrous areas are seen in the covering of the right lung. The left pleura is normal. Both lungs are rather hemorrhagic and lymphedematous, besides they are studded with air-free foci of the size of a hazel nut, some of which are confluent. These foci, through their lighter color and more solid consistency, are quite distinct from the adjacent lung tissue.

ABDOMINAL CAVITY.

Stomach.—Mucosa slightly swollen. There are extensive, light red hemorrhages in the folds of the upper curvature; these are made up of small, distinct foci.

Bowel.—On the valves of the large intestines appear irregularly distributed hemorrhages, in connection with which, here and there, are ulcerations of the mucosa. The follicles are slightly swollen.

Spleen.—14x9½x4 cm. Consistence rather firm. No alteration in structural appearance. Follicle swollen moderately.

Liver.—Somewhat enlarged. Capsules thickened. Consistence soft. Structure indistinct.

Kidneys.—Enlarged. Capsule easily detachable; contains on the inner surface several hemorrhages of the size of a pin head. Surface of the kidney even. Cortex thickened, structural appearance not distinct. Color grayish red. The pyramids, which are also swollen in a marked manner, are filled in their lower third with yellowish white streaks.

Pancreas.—Firm, no change in structural appearance.

Suprarenal Bodies.—Unchanged.

Pelvic Organs.—No change in rectum. Posteriorly in Douglas's pouch numerous old adhesions. Uterus and ovaries in state of menstruation.

Dr. Bielschowsky's microscopical investigation of the brain disclosed no noteworthy alterations which the clinical picture could explain. Sections from the cerebral cortex, the pons and the medulla were examined. In none were inflammatory changes found. Occasional pyramidal cells from the cerebral cortex prepared after Nissl's method, presented signs of a slight swelling with beginning chromatolysis. However, this finding is entirely without significance and could easily have had its origin coincident with death. Probably a note-

worthy point is the normal condition of the blood vessel walls. Hemorrhages are not present. Microscopical examination of the other organs by Prof. Pick discloses the following: Section from alcohol-hardened kidney, stained with hemalaun-eosin, shows: the epithelium of the tubuli contorti of the first order, is variously swollen, cloudy with fine-grained stratifications, with indistinct boundary toward the lumen. Still oftener in these cells the nuclei are missing (necrosis). In the lumen fine-grained coagulated contents. The epithelium of the tubuli contorti, second class, as well as that of the collecting tubules seems to be free from changes. No calcareous deposits in any form were to be found in the specimens examined. The stroma of the cortical layer between the injured tubuli uriniferi is somewhat increased, slightly edematous, noticeably proliferated. Fresh small cell infiltration foci are lacking. In the glomeruli is apparently an increase of nuclear elements.

In general, therefore, a subacute parenchymatous and interstitial nephritis.

Dr. Auffermann made a special examination of the kidneys, and concerning the microscopical stripes in the pyramids, established the following:

Microscopically, in a subdued light, the yellow stripes appear as dark, fairly homogenous casts which correspond to the site of the straight uriniferous tubules. They do not dissolve with the addition of hydrochloric acid, nor is there generation of gas. Fixation in formalin caused them to dissolve, but in denatured alcohol in great part they remain unchanged. Paraffine sections were treated with the usual nucleus and connective tis-

sue stains. These showed severe damage to the epithelium as well as to the tubular systems, as the glomeruli and their capsules. Neither infiltration nor interstitial or blood vessel changes could be found. The nature of the yellow casts was as follows: They appeared entirely amorphous without any tendency toward crystalization, and did not stain with hematoxylin. With nitrate of silver they became of an intensely black color, and also occupied the site of the epithelia. The latter now became only partially recognizable. Notwithstanding the contradictory condition I would claim the casts to be of phosphatic nature. The circumstance that they did not appear to dissolve when treated with hydrochloric acid might be attributed to an error on my part in abbreviating the period of observation. Their solubility in formalin—formic acid—demonstrates this. According to the literature biliary pigment and uric acid are likewise excreted.

Examination of the liver and heart disclosed no special condition (Sections hardened in alcohol, stained as usual).

The chemical examination (Prof. Loeb) shows in blood: Blood sugar 0.089 per cent., free nitrogen (Holweg) 0.0174 per cent, iron 0.210 per cent., total nitrogen 1.454 per cent., therefore marked increase.

Kidneys: Arsenic plainly demonstrable. Mercury very plainly demonstrable.

Brain: Arsenic plainly demonstrable. Only a slight trace of mercury.

Feces: Arsenic demonstrable in slight traces; no mercury.

The cerebrospinal fiuid contains 0.05 per cent. arsenic.

The spontaneous gelatinous coagulation of the cerebrospinal fluid drawn off immediately after death, was most extraordinary. The

significance of this condition is not yet sufficiently explained. In this connection it may be added that Mestrezat has made a study of this question. (*Le liquide céphalorachidien,* Paris, 1912, p. 425.)

Here I would remark that neither in arsenic poisoning nor in uremic coma is there any mention of this interesting condition. (In reference to this compare the Thesis by Petit, *Méningite et réactions méningées dans l'urémie,* Paris, 1912, Declose.) The special, extraordinary terminal changes of the liquor, in part, must well have some connection therewith.

An entirely incorrect recital of a case was offered at the July meeting of the Dermatological Society, this being the history of a case which had been twice injected by Dr. Portner and which died in my department.

Portner gave me the following history:

"Franz Ro., 37 years old. At the beginning of April, 1912, infected with syphilis. Hard chancre. May 21st Wassermann was made by Dr. Meier. Positive. One injection of mercury. On May 24th given intravenous injection of 0.4 salvarsan. Ambulatory patient. It is claimed that after the injection diarrhea set in, and after several days a feeling of faintness. Then came a return to normal.

On June 13th another injection of 0.4 salvarsan (Dr. Weber). This was unattended by trouble. Patient was not taken into hospital. After injection a very severe pain seized patient in wrist and ankle joints. The affected limbs could scarcely be moved. After a morphine injection (Dr. Steinitz) pain slightly moderated. Dr. Steinitz found patient in severe collapse, strongly accelerated, scarcely perceptible pulse. Ordered camphor. Fever present. Patient is an inveterate smoker.

Large, corpulent man. Face flushed with fever. Expression of face indicative of suffering. On both thighs marked diffuse reddening of the skin. On the left thigh the redness at the knee is in sharp contrast to the strikingly pale blue color of the lower leg. The toes of the left foot are cyanotic. The left hand also shows from the wrist downwards the same pale blue, lightly cyanotic coloring. Here as on the foot the blue color is most marked at the finger tips. Pulse is very much accelerated and scarcely perceptible. Temperature 38.8 (101.8 Fahr.). No appetite. Therapy: Coffee every two hours; hot hand baths; hot packs to the feet.

June 15th, 1912. Hand pale blue, but color, in general, not so pale as yesterday. But the pale blue color on the lower leg is still strongly marked. As before, the toes are still cyanotic. Pain in the left hand and in left wrist joint in the reclining posture is somewhat less. At an attempt to move the joint the patient cries out at once. Both thighs are brilliantly red.

Patient feels very weak. Occasionally tries to arise from bed hoping to find relief, but staggers and must again lie down. Pulse very small, scarcely perceptible, strongly accelerated. Temperature 39.5 (103.1 Fahr.). More frequent vomiting and difficulty of defecation. Upon taking nourishment (milk) vomiting sets in afresh. Highly smelling urine, light in color, turbid, trace of albumin.

N. B.—On June 13th, three other patients were injected with the same preparation, dose likewise 0.4. Well borne except in the case of a 19-year-old anemic girl, who vomited lightly two or three times."

I proposed to Dr. Portner that after the conclusion of my investigations we publish the case together, but he did not trouble himself to describe the case according to the information he had, so the result was that he erred in needlessly burdening the literature

and further the discussion had to be conducted along false channels.

The report coincided in essentials with that which was published by Portner in the *Dermatol. Zeitschr.,* Bd. XIX, No. 12. There Portner says that he made two further injections with the same solution which he employed in the case of the above mentioned patient, and that no untoward results occurred. Then, he adds thereto (l .c. p. 1091): "In the Virchow Hospital evidently a trepanation was undertaken in the case, well according with the proposal of Ehrlich that in cases of encephalitis after salvarsan, this operation be attempted."

The patient's history and our findings put the case in an entirely different light.

On admission into the hospital on June 15th, patient is somewhat stupified and has headache. Nine years ago underwent a course of mercurial inunctions with Dr. Schmilinski. A week after the first injection the patient felt bad. Vomiting and chills.

The upper half of the face and the forehead are covered with a relapsing erythema. Slight conjunctivitis. The left arm is lame, the left leg is paretic, but can be raised up. Urine dark brown; retention necessitates catheter; bowel movement black and paplike. Patient vomits black masses. Patellar reflex present. Right pulse soft, 120; left cannot be felt in the brachial.

Condition remains unchanged. Urine contains albumin and granular casts. Lumbar puncture on June 16th affords no relief. Nonne +, G. +, C +, Wassermann 500 per cent —. Vomiting black masses. Patient is stupified, but no coma, no convulsions. With ascent of temperature to 38.4 (101.1 Fahr.), and increasing cardiac weakness, death came at 9 o'clock on the morning of June 17th.

Arsenic in the urine and vomitus in abundance (Prof. Loeb).

Through questioning the patient's wife the history of the case was completed as follows: Infection nine years ago, after which one inunction course which was repeated a year later on account of manifestations in the region of the neck.

Patient very intemperate, drinking daily 12 to 15, occasionally 40 glasses of beer and whiskey. Inveterate smoker. At the beginning of May he came under Dr. Portner's care by reason of small blisters appearing on the glans penis. After the first injection on May 24th, he became indisposed on May 30th. Chills on June 1st. Congestion of the eyes. In spite of his condition he went to the race course on June 2nd. On the same day a red eruption broke out on the legs, arms and trunk. Then followed dizziness and weakness. Immediately after the second injection on June 13th, the patient became very much distressed and vomited freely. He complained that the injection had been very painful. On the same day an assistant who was called into the case confirmed the absence of pulsation in the left arm. Patient dragged himself about until 3 o'clock in the afternoon but gave up at four; the left hand and foot became ice cold and the site of agonizing pains. Dr. Steinitz had to give morphine, but notwithstanding this the pains continued to be extremely severe. Patient was very excited and wanted to kill himself.

Besides she reported what the patient had told her, that some years before he had been operated upon by Geh. Rat. Korte for epilepsy. The previous history so cheerfully put at my disposal, runs as follows:

During a brawl on the night of June 13th, 1904, he sustained a blow with a cane which injured the right side of the skull. The injury was dressed at a public dispensary. On June 18th convulsions for the first time seized the patient; during the course of the night and until noon of the next day

he had five seizures. Brought to the hospital by the ambulance at 5 o'clock on the afternoon of June 19th.

Immediately after admission a convulsion occurred which was closely observed by the medical man in charge. Patient draws left arm to the side with light convulsive movements, while at the same time, with the pupils dilated, the head is strongly drawn toward the left. Patient is unconscious; general convulsions have set in. The mouth is widely opened, tongue remains behind the teeth. Lasts for a period of three-quarters of a minute. Following is a light comatose state.

The examination discloses two wounds in the region of the parietal bone, one of which runs in a straight line from front towards the back for an extent of 3 cm. In front of this is an irregular wound connected with two skin fissures which join one another. The length of the single wound is about 1½ cm. Near the first described laceration is a superficial cut 1½ cm. long which the patient, upon the recovery of consciousness, says is an incision made by the attending physician. The wounds are matted with hair, and dressed with iodoform gauze. The borders of the wounds are slightly reddened. Abrasions of the front half of the head. Cleansed with alcohol and ether. Dressed with iodoform gauze.

Pulse, 72, respiration easy. The patient regains consciousness soon after the affair and gives a good account of the circumstances of injury.

During the night had three convulsive seizures of the character described above; similarly during the physician's morning rounds between 8 and 8:30. Patient received morphine 0.01 (1/6 gr.), following which improvement immediately takes place as on yesterday evening (June 19th).

A pronounced paralysis of the left facial nerve is present. The gross motor power of the left arm is plainly reduced. The tongue when extended deviates slightly towards the left.

In the parietal region are three wounds. The one in front extends to the bone, but apparently the others do not. Employment of a crescent-shaped incision with highest point of incision on

line with parietal suture, base over the parietal bone; soft parts are elevated with profuse hemorrhage. Corresponding with the anterior wound, close by the sagittal suture, is a defect in the bone, about the size of a 25 cent piece, with deeply depressed base and edges; between the splinters of bone are blood coagula filling up the site of the injury. Numerous hairs are in wound. Inoculation shows staphylococcic infection.

Operation.—Circling the fracture, the edge of the bone is beveled with a chisel. Three large and numerous small deeply depressed fragments of the external table are removed. Adherent hair may also be seen on these pieces of bone. Moderate extravasation of blood between bone and dura. Removal of all splinters together with thorough cleansing of wound. Tamponed with iodoform gauze.

At seven o'clock on June 20th, an epileptiform attack, resembling the former one, except that head is turned toward the right.

Afternoon of June 21st: The patient feels better; the facial paralysis about gone; patient complains of burning in the operation wound.

Morning of June 22nd: Patient slept well; dressing, which yesterday had to be renewed, has not again become saturated; very slight paralysis of the facial; the left eye can be entirely closed; tongue still deviates a little towards the left.

A difference in the gross muscular power of the two arms is present in a minimum degree.

No lameness in legs; pain entirely gone.

Senses clear. Urine golden yellow, clear, contains no albumin.

On the 22nd of June, at midday, marked convulsize seizure.

On the 24th at 9:20 in the morning, convulsion affecting mainly the left side of the body.

June 25th, during the night at 12:15 and 12:20, further severe convulsive attacks.

Removal of the tampon, wound disinfected, redressed. Patient complains of anxious feeling and dizziness.

June 29th: No convulsive attack since removal of the tampon. Very slight paralysis of the left facialis.

July 12th: Patient again twice had slight twitching of the left arm. Medication: Kal. brom. 1 gram (15 grs.) three times daily.

July 24th: The wound is almost closed; dressing of nitrate of silver salve. Patient feels quite well; no suspicion of any paroxysm; no dizziness; no convulsions. Under close examination twitching in left leg. In the bone is a large defect, in which the pulsation of the brain may be clearly felt and seen.

According to information given by the wife, since the time above mentioned, the patient remained free from epileptic convulsions.

Post-mortem immediately after death (Geh. Rat. v. Hansemann) shows the following:

Anatomical Diagnosis.—Partial defect of calvarium. Yellow softening of brain. Pulmonary emphysema. Thrombosis of the left radial artery. Hepatitis, fatty infiltration. Parenchymatous nephritis. Subendocardial hemorrhage, also of the mucosa of the jejunum.

Trunk and Extremities.—Strongly built male body with well developed musculature and moderate deposit of fat. Over the entire body, particularly left arm, bright red, irregularly outlined spots.

The radial artery in front of the styloid process of the radium for a distance of 4 cm., is entirely occluded by a firmly attached coagulum. The remainder of the radial artery and the brachial and axillary are free.

Thoracic Cavity.—Pericardium without change. Heart: large as the fist; musculature pale red; contracted. Valves and endocardium soft with a greenish yellow color. Ascending aorta shows slight fatty degeneration of the intima. Several hemorrhagic spots beneath the endocardium.

Left Lung: Agglutinated with easily soluble adhesions; everywhere filled with air; especially in marginal regions where it is inflated.

Right Lung: Same condition as left.

Larynx and pharynx without change.

Abdominal Cavity.—Peritoneum smooth and glistening.

Spleen: Slightly enlarged; surface smooth; color dark red; structure distinct.

Liver: Of natural size; capsule smooth; consistence normal; color bluish red with large yellow areas.

Left Kidney: Of natural size; capsule detachable; surface smooth; color grayish red; structure changed through tissue proliferation; cortex increased.

Right Kidney: Same condition as in left.

Suprarenal bodies, pancreas and stomach without change.

Bowel: In first part of the jejunum isolated mucous hemorrhages; color of the feces dark grayish blue.

Pelvic organs without change.

Head and Spinal Column: Brain remains *in toto;* in the right parietal bone, in the region of the parietal convulsion, is a defect the size of a dollar, the edges are smooth, and the whole is covered with dural tissue. Brain is adherent at this point and shows defect (the size of a chestnut), has yellowish color. Over wound is a skin scar.

A microscopic examination carried out by myself reveals:

Kidneys: In the uriniferous tubules flat, granular masses (albumin), hyaline casts, vacuolar state of the epithelium of the tubuli contorti. Glomeruli rather richer in nuclei than normally, but without important changes.

Liver: Moderately rich in fat. Large drops of fat within the cells with well colored nuclei. No necrosis. Interstitial proliferation such as seen in a drunkard's liver.

Spleen: Congested; the inner lining of the artery of the duct here and there inlaid with

a somewhat homogenous substance (probably hyaline); beyond this no changes.

Bowel: Leucocyte infiltration in the superficial layer of the mucosa; no necrosis.

In the left radial artery fresh thrombosis (blood plates, leucocytes, erythrocytes, no organization).

Dr. Bielschowsky found nothing in the brain indicating an acute inflammatory process. But there was found an old fibrous leptomeningitis which was most pronounced where the two hemispheres met. There were further chronic changes in the cells of the lamina pyramidalis and chronic fibrous tissue proliferation. In general, the picture was that of chronic alcoholism. As always, there were also present a few acutely changed cells, but these had no bearing on the diagnosis.

There cannot be the slightest doubt but that the heavy drinking and the former epileptic attacks should have been a sufficient notice of the possibility of chronic cerebral changes. A further cause for care should have been the drug exanthem following the first injection as well as the indisposition which lasted for days. That in all probability, the injection was made into the radial artery after recognition of the clinical picture and the condition of the artery, is, to say the least, not without significance.

The entire clinical picture and the pathological findings of our only case do not indicate arsenic poisoning. And furthermore, the majority of the other cases which have been carefully and thoroughly examined give only an irregular picture of the usual symp-

toms of arsenic poisoning. Most authors give special prominence to this in their discussions. For example Almkvist and Hedren say: "At autopsy there were no characteristic pathologic changes of acute arsenic poisoning, such as bowel paralysis, fatty degeneration of the kidneys, the liver, the heart muscle and the intima of the blood vessels. Furthermore, there was no hemorrhage in the different organs such as occurs in acute arsenic poisoning, except in the brain. That this case cannot be considered as an ordinary poisoning by arsenic as a result of the dose of salvarsan (0.6), is clear without question."

"Busse and Merian take the opposite viewpoint. Should, however, any doubt yet exist, it may be dissipated through study of the older and half-forgotten, yet helpful, literature on the organic changes of arsenic poisoning. From the description of isolated cases of poisoning as well as from experimental studies, one is led to conclude that in some instances arsenic, just as exactly as with the new preparations, has an individual, distinctive action, and that, at other times, it gives rise to the same changes which are observed in the modern treatment of syphilis. I shall pass over the quite extraordinary, varying action of arsenic on the different organs, such as the stomach, intestinal tract, liver, kidneys, etc., for I wish to refer here only to the similar, not to say identical, changes in the central nervous system produced by acute and chronic arsenic poisoning which may be observed, as in our case. The multiple hemorrhages in the central nervous system, particu-

larly in the spinal cord, have been the object of various investigations (Popoff, Kreyssig, Wolkow, Silbermann, Heinz, *et al.*); they were investigated jointly with the thrombotic obliteration of vessels, whose nature and manner of formation in arsenic poisoning was quite closely studied especially by Heinz, and explained by the appearance of thrombi (thrombi of blood corpuscles and mixed thrombi). It must also be emphasized that in these cases of arsenic poisoning inflammatory infiltrations of the tissue occur, and, indeed, not only following subcutaneous injections but, on the contrary, also in cases where the poison reaches the tissues through oral administration."

"From this it appears that the unwelcome, severe and at times even fatal collateral effects following the administration of salvarsan and neosalvarsan, are to be accepted as toxic actions of the introduced drug, and so it seems, principally of its arsenic constituent."

It is quite past understanding how the authors can find sufficient support in the cited literature to sustain their position that in arsenic poisoning "similar, not to say identical, changes in the central nervous system may be observed, as in our case." Let one search the literature as he will, yet nothing can be found which could be offered as a parallel. In the Handbook of Experimental Pharmacology by Heinz nothing on the subject is to be found. In his Breslau *Habilitation* thesis (1891) he throws light on the occurrence of thrombi in the capillaries as well as larger vessels due to arsenic poisoning, this being based on

varied experimental work, but nowhere does he mention human pathology and certainly not hemorrhagic encephalitis. Silbermann's investigation (*Virchow's Archiv.,* 117, p. 304), so far as this point is concerned, contains just as little. Wolkow (*Virchow's Archiv.,* 127, p. 477) concerns himself with an investigation into degenerative and progressive liver changes. Popoff (*Virchow's Archiv.,* 113, p. 385) finally tries to prove in his dissertation that acute arsenic, lead and mercury poisoning can produce acute myelitis, a point that Kreyssig opposes. Popoff cites a fatal case of arsenic poisoning, but this died with gastro-intestinal symptoms and heart failure (cf. below) and without coma. Hemorrhages and plastic exudates were found in the spinal cord of this case. This is the only case in point which can be brought forward in substantiation of these claims, and even it offers an entirely different clinical picture from that of a salvarsan fatality.

In sharp contrast to this is to be mentioned that the acute arsenical poisoning described in the literature plays no role whatever as regards hemorrhagic encephalitis (*vide* literature by M. B. Schmidt, Ziegler's contributions, VII supplement, Laignel Lwastine and Voisin, *Archiv. de méd. exp. et d'anat, path.,* 1907, No. 1 and Meyer Frankfurt, *Zeitschrift für Pathologie,* No. 5, 1910). Furthermore, in Grote's valuable investigation, conducted under the guidance of Pick and Stadelmann, on the pathological anatomy of arsenical poisoning (Berlin, 1912), the condition of the brain

is described in an entirely different manner; there is nothing on hemorrhagic encephalitis.

Now, there is an acute arsenical poisoning which corresponds to the picture of arsenical asphyxia. Concerning it, Grote says: "These cases which proceed to a promptly fatal termination, this occurring even within ten hours can run their course quite entirely without any trouble referable to the intestinal canal. Finally the picture of narcosis predominates yet the convulsive forms are also observed. Taylor* reports a case of this character which terminated fatally within twenty minutes. This form is not so rare; Harvey** was able to find it in 36 out of 697 cases.

Seidel in Maschka's Handbook of Medical Jurisprudence, No. II, p. 241, says concerning the cerebral form: "The picture of gastroenteritis appears in the background with perhaps distress or occasional vomiting, but nothing else; these may be entirely lacking; in the foreground stands the extraordinary weakness with small pulse, cool skin, the occasional dizziness, pain and a feeling of numbness in the extremities preceding. The patient falls into a deep swoon, after recovery from which he is sleepless and finally becomes delirious. Thereafter follows a deep coma, now and then light convulsions and death comes in the midst of general paralysis with complete unconsciousness. The course is very rapid. Death may ensue as quickly as six or eight hours, and occurs at least in the course of the first day."

Die Gifte, übers. von Seydler, 1862.
***Ind. Med. Gaz.*, 1876.

Heinz also says on this score (Handbook of Experimental Pathology and Pharmacology, Nos. 1, 2, p. 929): "The acutest form of arsenical poisoning, in which a large quantity of arsenic has been taken at one time, corresponds irregularly to the customary 'gastro-intestinal' form, showing, principally, evidences of impairment of the central nervous system and weakness of the heart—the paralytic form. The last form (especially rare in human beings) begins with an uneasy sensation and vomiting, yet these signs may be entirely lacking. The principal features are marked weakness, very weak pulse, and decline of temperature; the memory quickly wanes; gradually come delirium, loss of consciousness and then coma until finally, without any special sign, death ends the scene. Death comes quickly; usually within a few hours, not often longer than ten."

That does not correspond to the picture of a salvarsan fatality. Especially in the cerebral type of cases there is a latent period lasting for hours and even several days; this does not correspond, as Fischer has emphasized, to the picture of an acute poisoning.

The question has occurred to me, whether the cerebral symptoms making up the clinical picture really constitute its central feature. In view of the fact that in all of these fatalities coma appears prominently in the foreground, I directed my efforts at an investigation of the uremic phenomena. A prominent characteristic of uremia, as pointed out by v. Noorden* is its tendency to present strange

*Handbuch der Pathologie des Stoffwechsels, Bd. I, p. 1002.

and unexpected manifestations. As a matter of fact, Prof. Loeb found urea in the spinal fluid in the proportion of 0.5 gram to the litre, and marked increase of rest nitrogen in the blood. (0.0174 per cent., Holweg 0.21 per cent. iron, total nitrogen 1.454 per cent.)

If, after full consideration, we give this accumulation of nitrogenous products its most complete significance, we cannot, in view of Holweg's investigations,* consider it as absolutely indicative of uremia, but it is, however, certainly an expression of kidney insufficiency. This opinion conforms also to the quantitative investigations made by Mestrezat,** who found in suspension of the renal function without uremia 0.25 to 1, in non-fatal uremia 0.98 to 2.55, in fatal uremia 3 to 6.34 grams of urea.

According to its urea-content our case belongs to the first group.

Insufficiency of the kidney, therefore, and not hypersensitiveness of the brain, is the point of the entire question of salvarsan fatalities.

It thus becomes evident, as a matter of fact, that in intravenous injections of salvarsan the overburdened organ is the kidney and not the brain.

The largest quantity of salvarsan disappears rather quickly from the blood, for injected salt solutions do not remain in the vessels.

**Ueber das Verhalten des Reststickstoffs des Blutes bei Nephritis und Uraemie. Archiv. f. klin. Med.*, 104 Bd., 3-4. *Bei der Uraemie erreicht sie sehr hohe Grade nach Strauss (Reststickstoff in seinen Beziehungen zur Uraemie).* Ebenda, Bd. 106.

***Le liquide céphalo-rachidienne*, p. 592.

The blood is not subjected to elimination because it contains no free water, on the contrary all water is associated as hydration-water with the colloid which is here present. Conversely, a salt solution disappears quickly from the circulatory system because it contains free water.* It has been shown by Saynisch** that oftentimes in so short a space as an hour after the injection, arsenic could no longer be demonstrated in the blood, a point which control experiments have further confirmed. Abelin† found the salvarsan reaction of the blood after one hour to be very weak; after an hour and a half still less certain and after two hours and a quarter scarcely appreciable. Yet, as regards this point, it must be remembered that, as Prof. Loeb has shown me, there are marked individual variations.

After intravenous introduction, salvarsan, in largest measure, is eliminated through the kidneys.

It is a well known fact that the kidneys always tend to free themselves from foreign substances as quickly as possible, and possess much less tolerance to such than to the physiological urinary constituents. Also immediately, or at least in a few minutes after the injection, one may, by means of Abelin's test, demonstrate salvarsan in the urine,†† and, gen-

*Hoga and Martin H. Fischer. *Theorie und Praxis der Transfusion in Ostwald, Kolloidal-chemische Beihefte*, III, 10-11.

***Deutsche Med. Wochenschr.*, 1912, No. 44, p. 2070.

†*Muenchner med. Wochenschr.*, 1912, No. 2, p. 81.

††*Abelin. Abhandlungen über Salvarsan*, Bd. II, p. 51.

erally speaking, its entire elimination is accomplished in five or six hours. As a rule, the kidneys easily take care of this extra burden, and through careful examination albumin is rarely found. Schlasberg* who quite recently has thoroughly investigated these circumstances mentions the same fact; he frequently found, however, occasional hyaline casts. We, too, have had urinary examinations made in 80 cases after intravenous injections but without being able to demonstrate hyaline casts. In isolated instances, however, we have discovered albumin; Weiler reports the same condition. While it is a very rare occurrence, yet our work confirms Weiler's observations. Apparently, in these cases the question is, whether the affected patients did not have at a previous time a kidney lesion which progressed undiscovered until the injection and subsequent urinary examination.

Now comes the question: How does an altered kidney, especially a luetic kidney, function during the elimination of salvarsan? We know that nephritis occurs during the preroseolous stage of syphilis but more especially during the secondary period. In general, the syphilitic kidney bears salvarsan well; we even have reports of improvement and cure of syphilitic nephritis, and this, too, in instances where mercury has failed. But this result is not without its exceptions. Thus Marlot** reports in a presentation on the action of ar-

Gesammelte Abhandlungen über Salvarsan, Bd. II. p. 387.

***Les néphritis de syphilitiques et l' Arsénobenzol. Thése. Lille.* 1912.

senobenzol in regard to syphilitic nephritis, two cases that died in uremic states.

As a rule, however, salvarsan is excellently borne in the presence of nephritis and only exceptionally are bad results registered. Therefore, there apparently is offered the contradiction that plainly pathological kidneys stand the full burden of salvarsan without reaction, while on the other hand, seemingly normal kidneys are rendered insufficient. The judgment of such cases in no way depends upon the pathological state which is ascertained to be present; a nephritis may cause death without offering an anatomical picture even approximately in keeping with the severity of the clinical manifestations of the disease. Through the labors of Schlayer* it has been shown that the anatomical investigation of the organs does not always disclose as much damage of the renal arterial system as clinical findings would indiate is present. Notwithstanding the most careful studies of the glomeruli, particularly in acute nephritis, we have, in no sense, progressed so far as to be able to determine positively the state of their function from the anatomical picture presented in such cases. Schlayer and Heubner have shown that patients with a severe glomerulonephritis may offer only the most insignificant glomerular changes.

We encounter with extraordinary frequency in the literature on salvarsan fatalities, instances of death occurring with anuria or suddenly appearing albumin. In many cases

Ergebnisse der inneren Medizin, No. 2, p. 576.

little or no attention whatever has been paid to the urinary function. By chance one may note that the patient has fallen into this condition, accidentally discovering that but a small quantity of urine is being eliminated.

Let me cite a few examples of this class:

Tucker's Case. (*The Therapeutic Gazette*, No. 9, 1911).

Patient well developed, muscular, 30 years old. Three weeks before chancre appeared on prepuce. Has always been healthy. Heredity without interest. The clinical examination disclosed nothing abnormal in heart or lungs. A trace of albumin, however, in urine. Skin pale, hot and damp. Extirpation of right inguinal glands (adenitis) on April 29th. On May 5th, a maculo-papular eruption broke out on trunk and limbs. Patient complained of pains in joints. A few leucocytes in urine. Wassermann, +++. At half past two in the afternoon of May 12th, patient received an injection of 0.6 of salvarsan. In one hour the injection was followed by nausea, chills, vomiting and diarrhea. Temperature rose to 39 (102.2 Fahr.), pulse 126. In the morning patient felt quite well, no more diarrhea but since the time of injection has not urinated. The bladder upon catheterization found to be empty. Forty-eight hours after the injection the condition of patient grew worse, the cord-like pulse slowed down and symptoms of dyspenea appeared. Death took place two and one half days after injection with patient entirely conscious. No autopsy.

Luque Morata's case (*Revista de Medicinia y Cinejica Practicas*, Feb. 28, 1911).

Student 21 years old. Infected two years before. Treated for one year with injections of grey oil. Mucus patches in mouth and pharynx. Patient very emaciated, weight but 91 pounds. No albuminuria, heart and lungs without findings of interest. On January 31st, received injection of 0.4 of salvarsan in 200 c.c. 0.9 per cent physiological salt solution, alkaline. Three hours later

a feeling of distress, diarrhea, profuse perspiration. Soon vomiting of a green color, mixed with blood. Pale lips, dry tongue, pallid face, temperature 36 (96.8 Fahr.), scarcely perceptible pulse. Complete anuria. With catheter no urine secured from bladder. Delirium, coma, death three days after injection. No autopsy.

Caussade and Regnard's case (*Bull. de la Soc. méd. des Hôpitaux*, February 20th, 1911).

Patient 33 years old. Hard chancre. Later roseola and mucus patches. Mercury very badly borne for which reason patient was irregularly treated. Then considerable edema; albuminuria, 5 grams to the liter. As a result of milk diet declination of the edema; increase of albumin to 9 in 1,000. Patient very weak, emaciated, bedridden. Small urinary excretion—450 or 500 grams a day. Notwithstanding mercurial injections, the oliguria continued. On January 6th, patient was given 0.3 of salvarsan intravenously. Well borne. However, the oliguria increased. On January 9th, the amount of urine excreted was but 50 grams; the percentage of albumin increased to 33 grms per liter. On the eighth day of anuria, patient died in a condition of cachexia but without pain.

Autopsy: Acute diffuse nephritis with granular epithelial and amyloid degeneration of the glomeruli.

If the anuria passes, then recovery takes place, as illustrated by the following case.

George Livermore's case. Anuria after salvarsan (*J. A. M. A.*, 1912, October 5th).

In May, 1911, a nineteen-year-old patient developed a hard chancre, and a month or so later secondaries appeared. For six months he was treated with mercury, as a result of which all manifestations disappeared. The internal organs, especially the kidneys, sound. On July 2nd, the patient, who showed no signs of lues, was given an intravenous injection of 0.55 salvarsan. In one hour vomiting and diarrhea developed, and after a time anuria became evident. On the next day a small quantity of urine was drawn off. This urine contained much albumin. In a short time

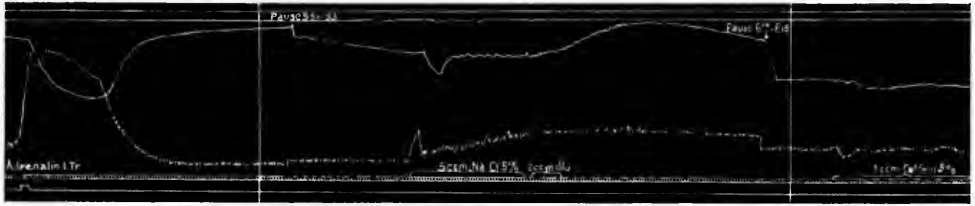

Adrenalin 1 Tr
Sccm Na Cl 5%
1 ccm Coffein 5%

Fig. 2.

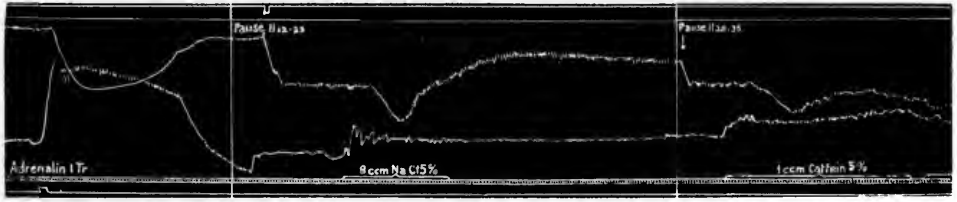

Pause 11 sec. 25
Pause 11 sec. 35
Adrenalin 1 Tr
8 ccm Na Cl 5%
1 ccm Coffein 5%

Fig. 3.

the uremic symptoms moderated, after which full urinary excretion became established.

A similar case is also reported by Wolff and Mulzer.*

A seamstress, 27 years old, received on June 1st, 1912, 0.7 neosalvarsan intravenously, and 1.2 of the same on June 4th, all of which was borne without reaction. On June 8th, 1.4. On the following day temperature was normal, but patient suffered from severe vomiting. This continued until the 15th. On June 13th complete anuria. Signs of interference with function of lower limbs. June 17th, severe cystitis, albumin, casts. June 19th, marked hemorrhagic nephritis; anuria; bedridden. July 2nd, anuria. Extremely small quantity of urine, free from blood. July 17th, condition the same, albumin and casts.

When we come to inquire why such a renal insufficiency should supervene, why an occasional patient of the thousands injected (I have given more than 25,000 injections), should suffer this fate, I am convinced, at least so far as my patient is concerned, that it is not to salvarsan but, on the contrary, to the combined treatment, mercury and salvarsan, the disaster should be attributed. In my case mercurial treatment was carried on for two weeks under my supervision.

Physicians have argued with much warmth as to who was the first to have the idea of the combined treatment. Indeed, there is scarcely a syphilologist who has not made a

*Muenchner Med. Wochenschr., 1912, No. 31.

claim for priority in this matter. It cannot at all be questioned but that the combined treatment has certain advantages, and occasionally I have myself employed it, but looking at the matter with scientific eyes one cannot reach a definite conclusion as to the difference between the action of mercury and salvarsan, nor can one advance unassailable reasons for the use of mercury in one case and salvarsan in another, any more than he can say when the both should be employed. But still more regrettable is the fact that no one has yet answered the question: What harm can be produced through the use of this combination of two different substances?

It is quite inconceivable how we are going to determine the toxic or idiosyncratic action of salvarsan if we combine with it a drug such as quicksilver, which can cause, even in the smallest dosage and in the most mysterious fashion, varied and severe collateral effects and even, at times, a fatal termination. Just today, December 12th, 1912, I have received into my department a woman who from October 5th on rubbed her husband five times with mercurial ointment, and who now suffers from a severe necrotic stomatitis, than which, notwithstanding my wide experience in this field, I have never seen a worse one.

Particularly so far as it relates to the kidneys this observation is of the highest importance. It is now well known that mercury in a large percentage of cases causes an irritation of the kidneys which becomes obvious

through albuminuria and cylindruria. Reiss* has lately pointed out the extraordinary frequency of this phenomenon. By reason of the disproportionate excretion of the mercury, this condition may reach at times, especially during the second week of the treatment, a very severe grade.

Salvarsan irritates the kidneys but little, especially on account of the aromatic character of the arsenic combination. Atoxyl causes much more renal irritation; arsacetin produced according to Spiethoff** a constant and often times a lasting irritation of the kidneys (albumin, hyaline and granular casts) a point other investigators of the drug (Neisser, Milian, Lambkin and Salmon) do not call attention to. Although of the two employed in the combined treatment, as far as the kidneys are concerned quicksilver is by far the most pernicious, yet, however, in view of all the circumstances salvarsan must not be held to be entirely innocuous.

If one would acquire an understanding of the circumstances operating in this matter, then one must quit thinking of the postmortem kidney which the pathological anatomist shows us to be more or less changed, but, on the contrary, one must make use of the living kidney functioning under physiological and pathological conditions. On this question the classic

**Beitrag zur Kenntnis der bei Quecksilberbehandlung vorkommenden Cylindrurie. Archiv. f. Dermatol.*, Bd. III, 2 Heft.

***Compare Borcher's dissertation: Die toxischen Nebenwirkungen des Arsacetins mit besonderer Berücksichtigung der Nierenreizungen.*, Jena, 1910.

experimental work of Schlayer* and his co-workers, on the toxic nephritides and the function of diseased kidneys, casts a welcome beam of light. This work has established that there is a fundamental difference between the action of mercury and arsenic on the kidney; the two drugs act upon entirely different parts of the renal tissue. It has been proven with exactness that mercury belongs to that group of substances which produce a pronounced tubular nephritis; of these chromium may be accepted as the type. Therefore, in the beginning there is a good secretion with completely normal function of the vessels, notwithstanding free excretion of albumin and the presence of large numbers of casts with which the already extensive and fixed defects of the epithelia well coincide. After a rather lengthy existence of the nephritis there gradually comes a diminution in the capacity of the renal vessels to dilate and with it a decrease in diuresis. In sharp contrast to the above there is the other group of toxic nephritides, such as those produced by arsenic or cantharides; these cause a vascular nephritis. In this group there occurs, even after minimum doses, a marked impairment of the renal vessels' power to dilate as well as to contract, with accompanying suppression. In these cases the clinical picture offers fewer characteristics than that of chromium and mercury poisoning; furthermore, the quantity of albu-

Schlayer and Hedinger. Archiv. f. klin. Medizin., Bd. 90-91.

Schlayer and Takayasu, ebenda Bd. 98.

min as well as of casts is for a long time not so large. It is arsenic particularly which always affects the capillaries, characterized, especially after intravenous injection, in a short space of time by a severe impairment of the renal function even increasing in severity to the extreme of complete renal insufficiency. In connection with this clinical picture there is but a slight anatomical change.

Toward the better understanding of these fundamental factors, let me quote several tests made by Schlayer and Hedinger during the course of their "Experimental studies on toxic nephritis" (*l. c.*). In these studies the renal volume was secured with an oncometer (Runne-Heidelberg), and the blood pressure in the carotid recorded with a special instrument. By means of an electric drop counter devised by Prof. Löwi of Vienna, the urinary excretion from both kidneys was accurately gauged. With normal animals the following results were gotten:

After the kidney volume had been determined by means of an accurate level, an appreciable stimulation was employed, whereupon occurred a quickly transitory rise of blood pressure with a quick drop in kidney volume corresponding to the contraction of the splanchnic vessels. Then the kidney again quickly dilated with an approximate return to its original volume.

Then under an injection of adrenalin (1 drop of 1 per cent. solution in 0.5 c.c. 0.9 per cent. salt solution) the kidney volume showed a marked drop with enormous rise in blood pressure. After return to a normal height, 5

per cent. sodium chloride solution (5 c.c. to the kilogram) was injected. This caused dilatation of the renal blood vessels with strong pulsation, and also an immediate diuresis. After cessation of the dilatation and wane of the diuresis, caffeine (2 c.c. 5 per cent. solution *pro* 1½ kg.) was injected, whereupon occurred the same phenomena, viz., dilatation of the renal vessels and diuresis. Finally, frequent injections of phloridzin were given which in normal animals caused moderate diuresis with glycosuria but without increase in kidney volume.

The phenomena attending chromium poisoning are shown by the following experiment and curve:

Rabbit No. 19, weight 1,500 grams, received 1 c.c. chrom. potassium (2.00—15.00) subcutaneously. No diarrhea. The animal is visibly sick. Bladder half full. Urine: enormous quantity of casts, especially granular and epithelial, a few erythrocytes; albumin about 6 per cent. (Esbach).

Upon appreciable stimulation fairly well marked contraction sets in; with adrenalin* somewhat less. With chloride of sodium minimum dilatation of the kidney but however, without diuresis, although the ureters, as shown by tests, are permeable. With caffeine is noted a retarded and very slight dilatation with minimum secretion.

Pathological anatomy: Kidney large; medullary substance moderately hyperemic; cortex pale.

Microscopical: Almost complete necrosis of the

*During this contraction-reflex the secretion was incorrectly gauged. This was caused by the escape of the salt solution with which the bladder was filled, a consequence of contraction of the bladder and ureters due to the adrenalin. This occurred a number of times in the beginning of this work.

entire cortex, only at occasional sites a few remaining tubules, casts in lumen plentiful. Glomeruli large, showing irregular swelling of the capsule. Suggestion of albumin-ring in the fine network between capsule and glomeruli.

These phenomena are associated with sublimate poisoning:

Rabbit No. 11, weight 1,300 grams, received subcutaneously 2½ c.c. of a 1 per cent. solution of sublimate 71 hours before. The animal is yet quite lively, has no diarrhea. The bladder is half full; the urine contains hyaline and granular casts and epithelium in plenty, but very few erythrocytes. Albumen about 5 per cent.

Pathological anatomy: Kidney rather large, cortex pale.

Microscopical: Large quantity of casts in the tubules of the medulla, variously also in the cortex. Large quantity of a spotted, flaky disintegrated substance (lime deposits) in the epithelium of the convoluted tubules; likewise in the ascending loops; many of the tubules are entirely denuded of epithelium.

The glomeruli show a scarcity of nuclei, moderately congested, do not fill out the capsule entirely. Nowhere is there any exudate.

Finally, toward the end, with large doses and after three or four days' duration the following functional phenomena exhibited themselves:

Upon appreciable stimulation and adrenalin contraction of the kidney still occurred, upon which diuretics scarcely produced any impression. The diuresis itself is very slight. Neither diuresis nor glycosuria followed phloridzin. The bladder is still rather well distended. The urine contains many casts of all sorts, and epithelium. Erythrocytes not plentiful. Albumin in large amount.

The pathological findings in this stage reveal

TABLE I.	Time.		Blood-pressure	Renal volume	Drops of urine in five minutes	
	Hour	Min.	Millimetres		Right	Left
Beginning	11	00	72	± 0	4	0
Appreciable stimulation	11	05	116	—45	—	—
Adrenalin	11	09	146	—30	—	—
Salt solution*	11	24	82	+17	1	0
Caffeine	11	36	87	+15	8	4 in 10 min.

*During the period between 11.12 and 11.23 the instrument for taking the blood pressure was removed in order to provide for dilatation of the organ.

TABLE II.	Time		Blood-pressure	Kidney volume	Drops of urine in five min.	
	Hours	Min.	Millimeters		Right	Left
Beginning	11	00	94	± 0	0	0
Appreciable stimulation	11	03	140	—43	—	—
Adrenalin	11	14	120	—35	—	—
Salt solution	11	23	104	+42	5	4
Caffeine	12	20	112	+35	13	10
Induced fatal hemorrhage	12	34	98	—75 in 1 min.	—	—

marked necrosis of the epithelium in the injured tubules and in the pyramids, particularly in the ascending limbs of the loops. In the glomeruli there are now no marked changes, only occasional epithelial swellings in the capsule, no definite exudates, none or only an occasional desquamation of the capsule epithelium.

This stage is illustrated by the following:

Rabbit No. 9, weight 1,550 grams, received 84 hours before 0.8 c.c. of a 1 per cent. solution of sublimate under the skin, then 60 and 36 hours before respectively, 1½ c.c. of the same solution. The animal is somewhat weak. Has no diarrhea. The bladder is full. The urine contains large quantities of casts, principally granular, moderately numerous epithelial cells and erythrocytes. Albumin 4 per cent.

Pathological anatomy: The kidney is very large, the cortex pale and shows fine radiating stripes.

Microscopical: Many casts in the excretory canals, also in the convoluted tubules of the labyrinth and cortex. Occasional hemorrhages in the border regions. The injured uriniferous tubules and particularly the ascending loops exhibit very wide spread flaky necrosis (lime deposits), the still remaining epithelium shows mostly poor nuclear staining and cloudy protoplasm. Many tubules for long distances are denuded of epithelium. The glomeruli are hemorrhagic, rather poor in nuclei, entirely fill the capsules; only here and there can one find a suggestion of swelling of the capsule epithelium.

We see, therefore, that sublimate nephritis in its functional course offers exactly the same picture as chromium nephritis; in the beginning there is good secretion with completely normal function of the vessels notwithstanding an abundant excretion of albumin and the

TABLE III.	Time		Blood-pressure	Kidney volume	Drops of urine in five min.	
	Hours	Min.	Millimeters		Right	Left
Beginning	9	10	74	± 0	0	0
Appreciable stimulation	9	15	106	—40	—	—
Adrenalin	9	20	156	—51	—	—
Salt solution	9	35	66	+30	4	3
Caffeine	9	58	68	+15	6	4
Production of fatal hemorrhage	10	12	60	—45 in 1 min.	—	—

TABLE IV.	Time		Blood-pressure	Kidney volume	Drops of urine in five min.	
	Hours	Min.	Millimeters		Left	Right
Beginning	3	17	48	± 0	0	0
Appreciable stimulation	3	22	76	—19	—	—
Adrenalin	3	31	130	—28	—	—
Salt solution	3	35	58	+ 8	2	1
NO_2SO_4	3	50	56	+11	1	2
Caffeine	4	05	50	+ 7	4	2

presence of many casts with which the already extensive anatomical damage of the epithelium coincides.

Only after a lengthy existence of the nephritis and after high dosage of the causative agent, there occurs, with severe damage of the tubules, a gradual diminution of the renal vessels' capacity to dilate and a decline in diuresis, which both finally become entirely *nil.*

In all stages, however, the contractility of the renal vessels remains constant, except toward the end it is somewhat less than normal.

In regard to the functional phenomena it has been shown that the polyuria of the initial stage is not so marked in chromium poisoning as in poisoning by other drug, and further the sublimate nephritis distinguishes itself from chromium nephritis in two ways as far as the pathological anatomy is concerned: The one is the strikingly slight impairment of the glomeruli as shown in the histological picture; even with almost completely suspended capacity of the vessels to dilate, epithelial swelling of the capsule is found at only a few points. Nowhere is there exudate, etc. The second point of difference is to be found in the deposits of lime after large doses continued for some time.

We shall come back later to the first point. The second makes it clear that there must be a difference in the biochemical course between chromium and sublimate poisoning, but it shows, however, at the same time that notwithstanding this difference in the functional

TABLE V.	Time		Blood-pressure	Kidney volume	Drops of urine in five min.	
	Hours	Min.	Millimeters		Right	Left
Beginning	5	38	60	± 0	0	0
Appreciable stimulation	5	42	82	— 8	—	—
Adrenalin	5	45	136	—25	—	—
Salt solution	5	55	72	+17	0	0
					Improvement in renal pulse.	Improvement in renal pulse.
Caffeine	6	16	62	± 0	0	0

phenomena, the result to the organism, so far as investigated, can be entirely similar.*.

But entirely different are the conditions attaching to cantharides, which point is illustrated by the following:

Rabbit No. 7, weight 1,500 grams, four and one-half hours before the beginning of the experiment, received a subcutaneous injection of ½ c.c. of cantharidin, 1:100 or 0.005. Animal seems quite lively. The bladder contains bloody urine in small quantity. In the urine is an abundance of epithelial cells, large erythrocytes, rather plentiful epithelial casts, little albumin (about 1 per cent.) in filtered urine. Kidney pulsates fairly well.

Rabbit No. 13, weight 1,400 grams, nine and one-half hours before beginning of experiment received a subcutaneous injection of ½ c.c. cantharidin, 1:100 or 0.005. The animal has diarrhea and appears weak. The bladder is nearly empty. In

*Observation. Our investigations show that the supposed capillary thrombosis held by Kaufmann, Silbermann and others to be the cause of the death of the epithelium, is not necessarily present in sublimate nephritis in rabbits or, at least, not to any great degree. We see, notwithstanding extensive and severe lesions of the epithelium, a marked capacity of the renal vessels to dilate and contract as well as prompt reduction of kidney volume following the opening of a vein to produce death. It would be impossible for both to be present with any extensive capillary thrombosis. Even in the final stages the kidney still has good contractility, and its pulsation becomes stronger after the use of diuretics, so that also in this stage no marked capillary thrombosis can be present, as we would necessarily have to accept in explanation of the enormous destruction of the epithelium according to the explanation given by Kaufmann. Our results in this respect confirm the views promulgated by Klemperer, that the condition is reached in some other manner.

TABLE VI.	Time.		Blood Pressure	Kidney Vol.	Drops of Urine in 5 Minutes.		Remarks
	Hrs.	Min.	Millimeters.		Right.	Left.	
Begin	11	32	84	±0	5	3	Increase of tension of kidney pule. In urine little albumin, moderate abundance of granular casts and erythrocytes.
Appreciable stimulation	11	37	114	—30	—	—	
Adrenalin	11	44	152	—61	—	—	
Ac. Arsen. intraven. 0.01	11	48-50	50	Kidney sinks 55 mm. in 5 minutes.			
	12	15	42	Lever of instrument unchanged.			
Salt solution	12	16	72	+61			
Acid. Arsen. 0.01 intraven	12	40-44	30	Lever of instrument unchanged.	77	58	
Adrenalin	12	50	81	—25			
Salt solution	1	05	34	±0	2	4	
Closing pressure			28	No reduction of kidney upon hemorrhage.	1	2	

the urine are numerous swollen epithelial cells, few casts, many erythrocytes. Albumin not definite. Curve 4, figure III, illustrates the course.

Thus, the deleterious effect following cantharidin is entirely different from that of chromium and sublimate. All experimental work shows with great clearness that cantharidin has a totally different action on the kidneys from that produced by chromium.

After the shortest time, even after minimum doses, there occurred an enormous impairment of the dilatability as well as contractility of the renal vessels, with coincident failure of diuresis. At the same time the clinical investigation showed much fewer phenomena than with chromium, likewise the quantity of casts as well as albumin was not near so great; the striking feature was the abundance of erythrocytes.

With longer protracted or severer poisonous influence a complete insufficiency of the renal vessels develops, the pulsation of the kidney and urinary excretion cease entirely, but the pathological examination does not disclose a condition that corresponds with the renal disturbance such as one may find in the less pronounced impairment of the urinary function following chromium poisoning.

According to all observations in regard to cantharides nephritis, the clinical picture is that of a marked, very rapidly setting in disease of the renal vessels. If this assumption be correct, then it remains that a poison which spends its force mainly in the capillaries, will produce the same sort of an effect.

We found the same to hold good in regard to arsenic. Boehm* and Schmiedeberg** through their investigations have shown this characteristic, and recently it was demonstrated through the efforts of Magnus† who produced a marked edema through saline infusion following the injection of arsenic. He also holds the opinion that arsenic is to be looked upon as a typical capillary poison.

In our experimental work we subjected animals to arsenic, and even employed arsenous acid in one per cent. solution intravenously as well as subcutaneously. In all, three demonstrations were made in this manner. Two of them, the one treated with an intravenous solution, the other with subcutaneous, are cited here.

Healthy rabbit of 1600 grams. No albumin in urine. Left kidney connected with oncometer. Pathologico-anatomical findings. Kidney large, cortex rather markedly hyperemic.

Microscopical: Occasional hemorrhagic spots, especially in the border strata. But a few casts in the excretory canals. The epithelia of the tubuli contorti involved to a slight extent. Nowhere damage to nuclei. Staining of nuclei good. No fusion of the protoplasm. The glomeruli are very much congested and fill their capsules entirely. They contain nuclei in abundance. With most there is epithelial swelling of the capsule. With some desquamation (?). Nowhere exudate.

Rabbit, weighing 1550 grams, received a subcutaneous injection of 1½ cc. of a 1% sol. arsen. acid. seven hours before beginning of experiment; four hours later another injection (1 cc.) of the

**Arch. f. exp. Pathol. u. Pharm.* Bd. 2 and 16.

**Schmiedeberg, *Grundrisz der Pharmakol. IV Aufl.* p. 406. ff.

†*Arch. f. exp. Path. u. Pharm.*, Bd. 42, p. 267.

same. The bladder is empty. The animal has diarrhea and is somewhat weak.

Pathologico-anatomical findings: Kidney is large, the border regions markedly hyperemic.

Microscopical: Moderately abundant casts in excretory canals; likewise in the border regions; only moderately abundant hemorrhages. The epithelium of the tubuli contorti indicates rather extensive cloudiness of the protoplasm, which in occasional tubules is coagulated in flakes. At the same time damage to the nuclei is not clearly established. The glomeruli are very much congested, and fill the capsules completely; rather rich in nuclear elements; occasional slight desquamation of the capsule, as a rule but moderate swelling, no exudate.

We find therefore, as was expected from the above mentioned observations, an entirely analogous behavior of the renal circulatory system with arsenic as with cantharidin. After a short period, especially with intravenous injection, serious impairment of the organ's power to dilate as well as to contract was noted, with complete cessation of diuresis.

Also in this experiment, there appears in its final stages a phenomenon of the renal blood supply similar to that attending the use of cantharidin. A secondary increase in volume of the kidney following stimulation of the capacity of contraction. Likewise, as with cantharidin, the secretion of urine is relatively less; there are rather more casts and a smaller amount of albumen with complete renal insufficiency. The pathological findings are even less than with cantharidin. It might well be that more marked phenomena, especially of the glomeruli, would appear with a longer duration of the nephritis; for us the essential

TABLE VII.	Time.		Blood Pressure.	Kidney Volume.	Drops of Urine in 5 Minutes.	
	Hours	Minutes.	Millimetres.		Left.	Right.
Begin	8	40	34	±0	1	0
Salt solution	8	43	58	+54	17	11*
Appreciable stimulation	8	54	82	—30	2	0
Adrenalin	9	00	126	—20**		
Caffein	9	10	40	+10	2	1
Na_2SO_4	9	20	46	+8	3	2
Adrenalin	9	28	142	—18†		

Upon suffocation reduction took place within two minutes of 10 mm.

*In urine casts in abundance as also erythrocytes. Albumin in moderate quantity.

**Immediately following the rise of 50 mm. and quick reduction to the state before adrenalin.

†After rise of 45 mm. gradual reduction to previous state.

feature was the determination of a less noticeably marked anatomical change with well proven renal insufficiency.

A difference between arsenic and cantharidin is to be found in the blood pressure, which falls very much faster and deeper after the first than following the use of the latter agent.

In seeking a reason for this difference, we find it could be caused either through the active influence which, as is well known, arsenic exerts upon the vasomotor center, or through the wide extension of the damage inflicted upon the peripheral capillaries.

Perhaps one cannot entirely accept the proposition that salvarsan in the abstract has the same effect as arsenic upon the renal blood supply but it acts in the same sense as the demonstrated reduction of blood pressure (as shown in my patients by Professors Nikolai and Siesskind) proves, especially after intravenous introduction. At times a slight impairment which has existed may become changed into a fatal danger, especially when the function of the renal circulatory system has suffered through the previous administration of another poison.

Practically all fatal cases of salvarsan therapy in the person of healthy, strong patients, show the fatal combination of energetic mercurial treatment and the intravenous injection of salvarsan.

One might well complain that salvarsan fatalities are not sufficiently explained by the above in view of the immense number of recorded cases in which the combined treatment was employed without any evil feature. It

depends wholly upon what period of observation an investigation of the burden thrown by salvarsan upon a kidney already damaged by mercury, is taken up. With moderately severe intoxication with sublimate, it is seen in experiments, that on the first day of the poisoning, with increased intake of salt, polyuria occurs with somewhat augmented excretion of the saline, but that the same increase of intake on the second and following days is responded to by a marked incapacity to eliminate the saline. The excretion of iodide of potassium is also delayed. The excretion of milk sugar from the beginning and thenceforth proceeds well, so much so that from the second day the excretory curves of the saline and the sugar diverge widely. Only on the fourth day as the damage to the capillaries becomes marked does retardation of excretion of lactose set in. Therefore, the kidney can yet eliminate milk sugar when for a long period it has no longer responded to an increase of salt intake. In the case of renal congestion caused by arsenic, the animals, in most instances, die quickly in anuria. Where investigation was possible, retardation of lactose excretion manifested itself. It is not fixed as to which type the salvarsan excretion belongs; however, it may by reason of damage done by mercury to the kidneys, undergo, under all circumstances, a substantial retardation. Concerning the above, one is at once clear, if he observes the circumstances attending mercurial poisoning in cases which do not terminate fatally. Thus, for ex-

ample, Pfeiffer* reports from the clinic of Quincke, a case of a young man who had taken a teaspoonful (?) of sublimate, but who at once drank lukewarm milk and vomited freely. This patient recovered. During his stay in the hospital polyuria took place on the first day, followed by suppression until the eighth day at which time polyuria again occurred. The circumstances are shown most clearly by the following record. (See Table VIII.)

Anuria is a conspicuous symptom of mercurial poisoning. Only those cases in which it is overcome, end favorably. Thus Kolb** reports the case of a sister and brother who took bichloride with suicidal intent. The sister died with total suppression. The brother passed eight days with the excretion of but 31 c.c. of urine; this contained hyaline, granular and epithelial casts and white and red blood cells. There was an immense quantity of albumin for six days, after which the quantity diminished so that on the twelfth day but a slight trace was found with acetic acid-ferrocyanide of potassium. At this period the excretion of urine ran up to 3,500 c.c., then dropped to 2,500-3,000 c.c. (sp. gr. ranging from 1,002 to 1,012) where it remained. Upon admission of the patients blood pressure was normal; on the third day that of the sister 280, that of the brother 230. According to Geisböck† the blood pressure at first rises and then sinks until the end comes; he recorded 125,

Ueber akute Sublimat- und Oxalsäurevergiftung. Archiv f. klin. Med. Nr. 90, S. 591.

**Muench. med. Wochenschrift.* 1904, p. 582.

†*Archiv f. klin. Med.* Vol. 83.

TABLE VIII.

Day of Illness.	Urine in 24 Hours.	Reaction.	Specific Gravity.	Appearance.	Albumin.	Sediment.	Weight.
1/2	300*	alk.	1008	Clear.	Trace.		
	1250*	ac.	1006	Cloudy.	1%**	0	
	500*	alk.	1010	"			
2/3	155	alk.†	1033	"		Casts, hyaline, granular, epithelial.	47.5
3/4	6	ac.	1014	"			
4/5	15	ac.	1014	"	1% to 1¾%		
5/6	41	ac.	1011	"			48.5
6/7	32	ac.	1011	"		"	
7/8	108	ac.	1013	"		"	
8/9	100	ac.	1010	"		"	48.3
9/10	290	ac.	1010	Clear.		"	
10/11	700	ac.	1010	"		"	
11/12	1400	ac.	1010	"	¼%	"	48.5
12/13	2000	ac.	1009	"		"	
13/14	2700	ac.	1010	"		"	
14/15	2200	ac.	1005	"		"	47††
15/16	2500	ac.	1005	"	0	0	

*The excretion of twelve hours only. **According to Esbach. (Albumin and no globulin.) †8.7 cm. of n/10 H_2SO_4 were necessary to neutralize 10 cm. of urine. ††Weight on 16th day 45½, 18th day 46, 24th.

110, 80, 70, 60. In such cases, as mentioned by Hohlweg,* notwithstanding that no evidence of uremic symptoms supervene, there is retention of nitrogenous products. He reports two cases of acute mercurial poisoning.

"Regarding the first patient (a female), who was received into the hospital 24 hours after taking four oxycyanate pastilles of one gram each, there was complete anuria from the beginning of the period of observation until seven days later when death took place. Not one drop of urine was secured through the catheter when introduced into the bladder. Marked diarrhea with bloody passages occurred; edema was not a symptom. The blood pressure oscillated between 105 and 130 mm. Hg. The patient died without any uremic manifestations. Autopsy denied.

"The second patient (also a female) on December 15th, 1910, swallowed half of a sublimate pastille. Nothwithstanding the prompt attendance of a physician who employed the stomach pump, washing out the stomach, there occurred on the following day intense abdominal pain and watery stools which, however, were not bloody. On December 19th, the patient was sent to the hospital. Up to this time patient has not passed any urine. Upon admission into hospital patient was apathetic but not unconscious. During her second day in the hospital patient frequently vomited grayish green, vile smelling masses. On December 20th, blood pressure was 135 mm. Hg. On the same day by means of the catheter 4 c.c. of urine was removed;

*l. c. p. 234.

this contained much albumin, many leucocytes, hyaline and granular casts. On December 21st 15 c.c. of urine secured. On the same day at 11 o'clock a. m. venesection was employed; 12 hours later death took place. No uremic symptoms had set in. Autopsy disclosed eschars on tongue and mucous lining of cheeks, striped hemorrhages of the stomach and colon mucosa. There was about 200 c.c. of urine in the bladder. The kidneys showed extensive necrosis of the epithelium with proliferation of the uriniferous tubules (Geh. Rat. Bostroem).

"In the first case venesection was performed 54 hours before death, in the second case 12 hours.

"The figures for the total rest-nitrogen were respectively 0.204 and 0.298; for the portion precipitated with tannin 0.000 and 0.015; for the portion not precipitated through tannin 0.033 and 0.045; for urea nitrogen 0.071 and 0.238."

This enormous retention of nitrogenous products of the blood is the expression of the incapacity of the kidneys to remove these products from the organism. One can easily understand that this insufficiency for foreign substances, such as salvarsan, must be of a still higher grade and with marked oliguria can be fatal.

There may happen a vascular sensitiveness of the kidneys expressing itself in poly—and oliguria, but without albuminuria, in many patients upon the administration of small doses of mercury. There is even a number of recorded deaths from minimum doses of mer-

cury, for example, from a small quantity of gray ointment applied for the relief of pediculosis. Volk reports the death of a patient who only lay in the same room with other patients who wore small Welander sacks. It was a 21-year-old patient suffering from tuberculosis. In the room in question, which had an air capacity of 750 cubic metres, there were 24 patients of whom 5 or 6 wore the sacks, while with the others the application of mercury was not carried on in this room. In nine days there was swelling of the tongue which, notwithstanding the most careful attention, increased in severity. Although thereafter the patient was placed in a room practically free from mercurial influence, the condition progressed to ulcerative stomatitis which continued without stop until death came. Mercury was found in the urine and kidneys in abundance.* Hitherto, entirely too little consideration has been paid to the excretion of urine in persons manifesting a susceptibility to mercury. Thus, just lately I have observed a young man who exhibited indications of insufficiency of the pulmonary valves, this manifesting itself in weakness of ventricular action, and a maximum blood pressure of 105 with a minimum of 80. On account of a recurring angina he received on the 10th, 18th, 21st and 25th of September, 1912, salvarsan, 0.1 each time. As with each injection the temperature rose to 38 C. (100.5 Fahr.), with diarrhea and headache of a moderate degree, I refrained from further injections. On Oc-

**Dermat. Zeitschrift*, Bd. XV, 606.

tober 14th, 15th and 16th, the patient was rubbed with ungt. ciner., 4 grammes being used each time. On account of diarrhea and general discomfort this treatment was also interrupted. Loss of appetite continued. In the urine there was no albumin or sugar, nor were casts present; the quantity of urine was 950 c.c. on October 19th, 950 on October 20th, 600 on October 21st, 600 on October 22nd, 400 on October 23rd, 400 on October 24th. In spite of the daily administration of 3 grams of diuretin the quantity of urine did not increase, but remained in small quantity. On the 24th of October it was 400, 500 on the 25th, 500 on the 26th, 400 on the 27th, 400 on the 28th, 400 on the 29th, 400 on the 30th, 400 on the 31st, 400 on November 1st, 600 on November 2nd, 600 on November 3rd, 600 on November 4th, 600 on November 5th, 600 on November 6th, 600 on November 7th. On November 5th, epithelial cells were found in sediment; no albumin or casts. In this manner the condition remained until December 7th.

Now, through the investigations of Schlayer and Takayasu, we know that vascular hypersusceptibility in vascular nephritides, may remain unchanged even after a year, as shown by the entirely unchanged character of the disturbed excretory conditions.

It is further known that the elimination of mercury does not take place uniformly, but on the contrary in an irregular manner. Corresponding to the above are the toxic symptoms of these hypersusceptible persons in remissions and exacerbations (*alternatives*

d'ameliorations et de vechutes, Letulle). These may extend through many months, and indeed, years. Furthermore, after these long periods, stomatitis, enteritis and particularly mercurial angina in the Plaut-Vincent form, with exanthemata may recur.

Quite characteristic is the following case which I observed some time ago. Pat. F., on account of syphilitic manifestations, was rubbed January 17th, 18th, 19th and 20th, 1906, with unguentum ciner., 3 grams being employed each time. Directly after the second rubbing fever and universal reddening of the skin appeared. The treatment was suspended and with bathing and powder, the manifestations disappeared. Two weeks later without any further antisyphilitic treatment, there again appeared an extensive reddening of the skin, and with it angina and very high fever. The process impressed one as being scarlet fever. No albumin in the urine. After extensive desquamation the patient was discharged cured on March 7th, 1906. From June 1st to June 27th, the patient was again under our care exhibiting the same serious clinical picture as before. Again there was no albumin. Four days after discharge again the same symptoms supervened, but the patient did not present himself at the hospital until July 2nd, 1906. Upon complete disappearance of the typical mercurial eruption, on account of a persisting papular eruption of the scrotum and a palmar psoriasis, an attempt was made to carefully administer mercury; on August 7th, at 11:30, he received 0.015 hydrar. salicyl.

Immediately thereafter the patient was

seized with headache, chills, and rise in temperature; also, by 2 o'clock an intense exanthem covering the entire body was clearly visible. No albumin or sugar in urine. After recovery, in order to accustom the patient to mercury, he was given a capsule of mergal (divided into two doses) on September 26th, 28th, 30th and 31st. A half hour after the administration of each dose there appeared headache, a sensation of heat, reddening and pruritus over the entire body.

On October 4th, 1906, he was again received by us, and showed, although he had not received any mercury, the same picture of dermatitis universalis and recurring papular eruption. He was treated with Zittmann's decoction.

At this time there was a similar case in my department in which the disturbance of diuresis often seen in these cases, became well established. Karl W., 23 years old, on account of syphilis, received from his physician six injections of salicylate of mercury. Following the fourth injection an eruption made its appearance, for the treatment of which the patient was received into the Virchow Hospital on December 21st. There was found a general dark reddening of the skin, desquamation of the skin in shreds; after desquamation there was slight weeping of the desquamated areas. The urine contained albumin, epithelial cells, leucocytes and granular casts in moderate quantity. Finally toward the end of June the patient, after loss of hair and nails, was fairly well cured, although much reduced. On account of positive Wassermann and al-

terations in the spinal fluid (Nonne ++ Gold +++ Cells ++ W. 500 per cent. 0) he received in July seven injections, one of 0.1, one of 0.3, five of 0.2, all of which he bore without trouble.

Without renewal of the mercurial treatment, he suddenly took sick on the night of October 12th, showing the same picture of a general, slightly weeping mercurial dermatitis. The urine was at this time free from albumin and formed elements. However, upon admission into the hospital the activity of the kidneys was found markedly reduced, and later, coincidently with the drying of the skin and disappearance of the inflammation after desquamation, suddenly developed into polyuria.

October 14-15th, 260 c.c. sp. gr. 1032.
October 15-16th, 550 c.c. sp. gr. 1029.
October 16-17th, 740 c.c. sp. gr. 1021.
October 17-18th, 2150 c.c sp. gr. 1010.
October 18-19th, 2500 c.c. sp. gr. 1012.

In about this way the urinary secretion remained until November 5th, when the patient was completely restored. From November 6th on the urine was normal, and on November 7th, the patient was given ½ gram of iodide of potassium. It was normally eliminated; urine 1500-1700 c.c. with sp. gr. of 1012-1016. On November 13th, 0.1 and on November 16th, 0.4 of salvarsan given and borne without the slightest reaction.

Such exanthemata may take place under different provocations, for example under the introduction of salvarsan in the presence of damaged kidneys. In this manner I understand the case of death reported by Brauer.

In general, the course of this case did not resemble the other fatal cases, but, on the contrary, in a striking manner (nephritis with granular casts, bloody diarrhea, no convulsions) the descriptions of those fatal cases following the use of insoluble preparations of mercury.

S., 34 years old, gardener, well nourished, well muscled, internal organs without pathological changes, denied any former illness. The time of infection could not be determined. Chancre on the glans since January 14th, 1912. Condition on January 22nd, 1912: Lesion on glans, disseminated maculo-papular exanthem, papules on the margins of the tongue and upon the tonsils. Wassermann positive. Under the direction of his private physician had undergone twelve inunctions with ungt. cinereum of 4 grams each, the last of which was on February 2nd, 1912. From February 6th to February 23rd, patient received one calomel injection of 0.03, five calomel injections of 0.05. On account of stomatitis treatment was interrupted. Urine free from albumin. On February 28th given one injection of salvarsan, 0.4. In the afternoon vomiting and diarrhea. March 6th, second injection of salvarsan 0.4 with diarrhea following in the afternoon. On the same day third injection of salvarsan given (0.4) with increase of diarrhea and vomiting. On March 7th diffuse, in places confluent, macular eruption of erythematous nature. Albumin present (marked opalescence), a few hyaline and granular casts. March 9th exanthem faded, but yet recognizable. Today fourth injection of salvarsan, 0.4 given. March 10th, exanthem has grown more marked reminding one of the Jarisch-Herxheimer reaction occurring in syphilitic exanthemata treated with salvarsan. Albumin positive (marked opalescence). Few hyaline and granular casts. March 12th, exanthem extended. Efflorescences confluent, urticarial in character. Desquamation of the hands. March 16th, exanthem barely perceptible;

flaky desquamation of the body, that of the hands in larger pieces as in scarlet fever. Urinary condition as above. March 18th, eruption completely gone. Desquamation of the hands still going on. Wassermann negative. March 23rd, for two days a recent disseminated, and confluent urticarial, erythematous exanthem. Falling of the hair. Temperature 38.5 C. (101.4 F.). Bloody diarrhea, abdominal pains, urinary condition unchanged. March 25th the eruption has become universal. March 26th the dermatitis of the scrotum and anus is "weeping." Urine as above. Temperature 39.3 C. (102.7 F.). March 27th universal serofibrinous dermatitis, rhagades over joints. Continuous fever. March 30th, rhagades on other sites. Desquamation of the skin over large part of the body, disclosing weeping surface beneath, especially on abdomen and back. Blisters on the mucosa of tongue. Diarrhea and marked prostration. Temperature 38.7 C. (101.6 F.), pulse 120. On April 4th, with increasing somnolence and increase of temperature to 40 C. (104 F.), death took place. The skin of the entire body resembled a very severe burn of the second degree. Postmortem (pathological institute): Extensive dermatitis, covering entire body. Severe parenchymatous nephritis. Slight degeneration of the heart muscle and liver. Small hemorrhages in the mucous membrane of the sigmoid and rectum. Hyperemia of the lower lobes of the edematous lung. Enlargement of the spleen. Marked chronic meningitis. Very marked edema of the brain and moderate edema of the meninges. The bladder contains about 700 cc. of urine. Albumin positive (opalescence); occasional erythrocytes and leucocytes, granular and hyaline casts.

With its serofibrinous, general character, and merging borders, which give it a resemblance to scarlet fever, the exanthem is absolutely like a mercury-dermatitis. The salvarsan dermatoses are always lightly spotted or are universal erythemata, which do not proceed to

serous infiltration of the skin and to a characteristic desquamation. Furthermore, they do not have the long duration.

Just recently I saw an exanthem of similar character attributed to salvarsan. A young woman, on October 23rd, 1912, received at the hands of a dermatologist a salvarsan injection which was well borne. Following this, she was rubbed with six capsules of gray ointment. After this course an eruption of small water-filled blisters appeared. On December 4th, 1912, she came to my department with universal reddening of the skin and large-flaked desquamation, that from the feet and hands taking the form of a glove.

An examination of the desquamated epidermis on December 8th, that is six weeks after the exhibition of the mercury, showed the same to have a rich mercury content, while arsenic was not present. The urine also contained mercury.

On the whole, one must wonder at the confusion of many physicians in regard to salvarsan, for so many of them attribute to salvarsan an effect which is clearly that of mercury. Thus the following item is to be found in the *Presse Médicale,* No. 100, December 4, 1912:

"Au non die M. Boulliard, M. Paul Guillon présente un malade atteint de syphilis en Aôut dernier pui a suivi d'abord un traitement mercuriel, puis un traitement par l'arséno-benzol, quinze jours après la troizieme injection d'arseno-benzol, la malade accusa une dermatite exfoliante généralisée ainsi qu'une gengivostomatitie ulcéreuse aiguë et persistante.

Dans deux autres cas, l'auteur a pu constater semblables lésions; il rapproche celle-ci des cas de gangrène de la bouche signalés par M. Dritsky et recommande, dans le traitement par l'arséno-benzol comme dans le traitement mercuriel, de surveiller attentivement la bouche des malades."

These occurrences, according to the description of the salvarsan reactions of Neisser and Hoffmann, are very much like the reactions of mercurial stomatitis.

Zimmermann who describes this salvarsan reaction on the teeth from the Herxheimer clinic, says:

"For a long time we have been able to observe this salvarsan reaction on the teeth, and determined that it usually took place in patients who had a more or less severe stomatitis. It is a matter frequently concerning prostitutes who have decayed teeth, and in whom, notwithstanding the most careful attention to the mouth, a severe stomatitis occurs even after small doses of mercury.

"The pain begins suddenly, often just after the patient has left the operating table. In some cases, in fact, it takes place before the injection is finished. The pain is partly localized in certain sites (it is immaterial whether especially marked stomatitic changes are present or not) and partly as a boring and drawing, like that of a burn. It may be seated at one angle of the jaw and then suddenly change to the other. In one or two hours the pain entirely ceases.

"We believe these phenomena may be traced, perhaps, to a sudden destruction of spiro-

chaetes in the teeth and mouth and the liberation of toxins under the spirillocidal influence of the salvarsan. Since a stomatitis is highly favorable to the above process, we are able to understand why we never see the same sort of a reaction in cases of syphilis treated solely with salvarsan. We have never been able to establish a diminution of motility of spirochaetes from the teeth in the dark field, after an injection of salvarsan."

In my department where pure salvarsan therapy is employed such reaction never present themselves. Quite convincing that these stomatitides are of a mercurial nature is the circumstance that in my department, to which, at my request a dentist was appointed to take care of the mouth of patients undergoing mercurial treatment, since the year 1910, that is, since the inauguration of my policy of employing salvarsan alone, mouth disorders have been very infrequent and the dentist is the same as being without any duties.

These observations seem to indicate that following salvarsan injections reactions may take place in other parts of the body, especially in the renal arteries or other small vessels which have been damaged by mercury or where mercury still remains but is not securely anchored in the tissues.

One must consider that, as the excellently conducted investigations of Möller and Blomquist* show, the capacity of the kidney to eliminate mercury from the system is rather

**Dermatol. Zeitschr. Bd. XVII, H. II Ueber die Quecksilberausscheidung durch die Nieren.*

limited and marked individual deviations may be noted. According to the various investigations of Almkvist* mercury is retained in the renal cells and even in the epithelial cells of the collecting tubules, in which degeneration is brought about.

How such foci react to a blood current impregnated with salvarsan we do not know. Some accounts in the literature speak, with a certain plausibility, of an occasional explosive effect. I am inclined, in general, to explain the great difference in opinion of various authors in writing of the collateral effects of salvarsan, as being based upon different modes of treatment, i. e., the pure use of salvarsan or the combined treatment.

Concerning this I cannot add anything of special import; the description of a so careful investigator as Gennerisch does not correspond in its various features with the picture of the consequences of salvarsan injections, as we usually see it.

But it is easy to understand that it is only in certain moments that the employment of salvarsan is dangerous, especially when through mercury a vascular oliguria is brought about and the eliminative function interfered with.

For example, my assistant, Dr. Pakuscher, in a case of moderate mercurial nephritis, was not able to demonstrate iodide of potash which had been given, in the urine until twelve days had elapsed.

Very recently a case of sublimate poisoning

*Dermatol. Zeitschr, Bd. XIX, H. II.

was subjected by Conzen to the newer methods of determining renal function. Concerning this Conzen wrote the following:

"The glomeruli are fully intact; the tubuli are the site of attack. The experimental investigations of Schlayer prove functionally that there are isolated areas of tubular defects. Only with a quite severe damage is there a later impairment of the function of the glomeruli. Consequently this case is particularly well adapted to serve in measuring the value of the renal tests.

"CASE 12.—F. M., 31 years old, attempted suicide on January 7th, 1912, by drinking a glassful of water containing one gram of sublimate. Immediately red colored material was vomited; in the evening repeated attacks of dizziness, spots before the eyes, further wretching and vomiting of bloody masses. During the night and on the next day there was diarrhea. Received into hospital on January 8th. At this time strong flow of saliva, burning in mouth, difficulty in swallowing.

"On the evening of the 7th, after evacuation of a small quantity of urine from the bladder, complete suppression set in. Not until January 14th was any urine found in bladder and then but 50 cc. It was light in color, with one per cent. of albumin and containing an abundance of epithelial cells, some leucocytes and fragments of hyaline casts. On the 15th and 16th there were further diarrheal passages with the simultaneous discharge of an extremely small quantity of urine, so small in quantity as to prevent successful analysis. On the 17th about 250 cc. Albumin present showing a distinct cloudiness. Microscopical examination as on the 14th, except many granular casts.

"From January 18th until March 8th, and then from this date until April 1st, the renal powers were uninterruptedly under observation.

"The quantity of albumin still small, perceptible to slight clouding; the above named formed elements gradually diminished. The blood pressure always remained at from 150 to 90 (the high

blood pressure described as occurring on the first day of sublimate poisoning was not noted in this case). The condition of the heart and retina remained normal.

"From January 22nd on, the urinary secretion corresponded to the fluid intake; from February 1st to February 10th somewhat of a polyuria existed, then normal diuresis. From the beginning the sp. gr. was 1007 to 1014. Just once it reached 1014. During a right-sided pneumonia, upper lobe, lasting from January 23rd to January 29th, and during a consequent miscarriage (in the fifth month), with a temperature which lasted until February 3rd, the sp. gr. never reached above 1010.

"The further discussion will concern itself chiefly with the period between January 18th and January 29th.

"With an average intake of 5 to 8 grams of salt, the elimination was 0.1 to 0.3 per cent. with an absolute quantity of 1.5 to 4.8 grams; it was thus too low. The addition of 10 grams of salt was not attempted, it not being thought wise. In view of the above, it seems undoubtedly that the case was that of tubular impairment. On January 23rd and 27th 0.5 of iodide of potassium was given. With the Sandow test I was unable to produce a measurably red coloring of the chloroform. Severe damage of the tubuli therefore evident. On January 25th 2 grams of lactose intravenously. Only after 24 hours was elimination finished. At the time of injection the pneumonia had existed for two days, yet the urine did not contain more albumin than previously. Also the sediment was free from blood, there being only a few leucocytes, hyaline and granular casts and epithelial cells.

"Whether, therefore, a glomerular defect caused by the pulmonary infection was the reason for the delayed lactose elimination is somewhat doubtful, yet this should not be dismissed as being unworthy further consideration. That blockage of the tubules with detached epithelium paralyzed the filtration power of the otherwise normally functionating glomeruli, with interference with the elimination of the lactose, is, in view of the re-

storation of diuresis in a week's time, scarcely to be accepted.

"From February 2nd on, the absolute and percentage quantities of salt elimination in comparison with the intake reached a normal figure, so that only through the low and fixed sp. gr. did the tubular hyposthenuria remain in evidence. An additional intake of 10 grams of salt which was given on February 8th was almost entirely retained. The elimination of about 3 grams took place not in an increase of concentration but, on the contrary, through a slight polyuria extending over several days. This polyuria had already been noticed in a slight degree since February 4th, which was the first day on which the patient was free from fever. Here would be the second point which might possibly indicate a slight functional damage of the glomeruli, a hypersusceptibility.

"February 9th 0.5 iodide of potassium. Elimination in 53 hours, therefore occurring in the normal variation period. How this prompt iodide elimination, at a time of existing tubular concentration-defect, is to be explained, I am not able to say.

"February 11th 2 grams of lactose. Elimination in 10 hours, therefore a retardation which, however, did not correspond to a glomerular nephritis due to the pneumonia or miscarriage.

"February 14th, increase in water intake; eliminated in 24 hours.

"February 25th, 10 grams of salt added to usual salt intake. Eliminated in 48 hours and through increase in concentration.

"March 21st and 31st, again 10 grams of salt. Although not eliminated in entire quantity (5.5 and 7 grams) yet excretion secured through increase in concentration.

"March 19th, 0.5 iodide of potassium eliminated in 49 hours.

"March 23rd, 2 grams of lactose eliminated in 6 hours.

"March 25th, increase in water intake. Eliminated in 24 hours. A fixed and low sp. gr., but no polyuria. Trace of albumin in urine. Since March

7th no casts and leucocytes, only abundant epithelial cells.

"Regarding the reaction of the urine; from January 18th to February 3rd that is, to the end of the fever, it was slightly acid, from then the acid values grew somewhat.

"With the salt addition on February 25th and on March 21st and 31st, an increase in albumin was noted each time, but without change in the diuresis or general condition of the patient.

"Since the elimination of albumin takes place through the glomeruli, then of course it is here we would look for disease when albumin is noted.

"In a case of poisoning with sublimate there is a pronounced and severe damage done to the tubuli (tubular hyposthenuria; iodide elimination rather markedly retarded) which is demonstrable only until about the middle of the 4th week after the ingestion of the poison. This shows itself in a reduction of concentration-power but not in retardation of iodide elimination; the functional impairment of the tubuli exists for several months, at least, after poisoning.

"A retardation of lactose elimination manifested itself as long as 11 weeks after the infliction of the damage done by the sublimate. At the beginning this was marked and associated with mild polyuria. It was not shown that the pneumonia or miscarriage (as mentioned in the above case), could have given rise to the acute glomerular nephritis.

"Taken together with the excretion of albumin upon the increase of salt intake, the results of the functional tests indicate that in sublimate poisoning in humans besides the anatomical damage done to the tubuli, a functional impairment of the glomeruli is also to be assumed."

To what extent only a temporary insufficiency influences the accidents which are attributed to salvarsan may be seen in the fact that frequently the same accidents, that is to say the epileptiform attacks and even coma

itself, may be overcome and then later salvarsan again administered without evil result. A case in point is that reported by Milian: A young officer received 0.6 of salvarsan, four days after which coma supervened and for a week amnesia existed. However, later the patient tolerated injections of salvarsan, respectively, 0.2, 0.3 and 0.4 without reaction. Quite recently Bettmenn* has published a similar case. A 24-year-old carpenter received on May 29th and June 4th, each, a dose of 0.75 neosalvarsan. On June 7th, without warning the patient fell to the ground senseless. Pupils without reaction, vomiting, irregular pulse. The condition lasted for several hours; recovery then followed. Albumin in urine. Patient had been under mercury. On July 6th, 0.45 neosalvarsan was given without reaction.

A similar case occurred in the practice of Dreyfuss, which was reported by Ehrlich.**

To this category belong those cases which are cured after lumbar puncture. This measure operates very frequently, as reported in gynecological publications, as a life-saving procedure in eclampsia and uremia, that is clinically similar conditions.†

Walter Frey†† has also recently written from

*_Müncher med. Wochen._ 1912, No. 43.

**_Abhandlungen zur Salvarsantherapie_, Bd. II, XXX S. 583.

†_Korrespondenzblatt f. Schweizer Aerzte_, 1912, No. 17.

††_Compare Parades, due coma et de la ponction lombaire. Thèse Montpellier_, 1912. Further, in _Gesammelte Abhandlungen zur Salvarsantherapie_, Bd. II, S. 600, the cases of Meirowsky and Spielhoff.

the Basle clinic concerning lumbar puncture in the presence of the cerebral type of uremia.

According to all experience up to the present time, one is warranted in accepting the conclusion that a normal kidney is never functionally damaged by salvarsan, but that, on the contrary, disturbances of salvarsan elimination take place only with already diseased kidneys.

It is also becoming clear why the acute and subacute inflammations of the kidney, for example those due to mercury, in general are more dangerous, even though the pathological changes are less, than the chronic nephritides. In these toxic renal inflammations the entire kidney is concerned, glomeruli and tubuli suffering a certain damage in common, whereas in the chronic nephritides the disease is focal or patchy alongside of completely functionating areas, which even take on a compensatory activity.

One must remember that while such kidneys may the first time successfully carry on salvarsan elimination, yet through the burden so extensive a functional impairment may be inflicted upon the vessels that with the second injection of salvarsan its elimination and also that of the urinary substances is seriously disturbed. Dreser injected animals with acid fuchsin following which the urine became red colored, while, at the same time, the renal cells remained uncolored. With the second injection of this character the cells of the uriniferous tubules became colored. The cells become wearied and damaged. Likewise, as a

result of a temporary ligature of the renal artery, renal cells retain the color. Heidenhain, Nussbaum and Graetzer have shown the same to hold good with indigo-sodium sulphate (Martin Fischer, Nephritis).

We have already pointed out that the clinical and pathological picture of salvarsan fatalities does not agree with that of arsenical poisoning. Even less so does it resemble the picture of a fatal case of uremia; it is much more likely caused by salvarsan retained in the blood or in the tissues in consequence of the renal insufficiency. A clear conception of the process is given by the investigations of Andrews who showed at Ehrlich's institute that mice, to which salvarsan, arsenophenylglycin, sublimate, akridinsal and salicylarsenmethylester, are given and which are then injected with sulphorhodamin, a rose red coloring material, do not eliminate the coloring material in case the poison has caused renal insufficiency, and they die within 24 hours.

Several factors indicate that the exanthemata of salvarsan as well as those of mercury, play a part, in the presence of temporary cessation of the renal function, in the vicarious elimination of the remedial agent by means of the skin.

Following every injection of salvarsan the substance circulates in the blood, and the question arises, how is it that the usually innocent material may suddenly take on a poisonous nature? Ostwald has compared salvarsan to a snapping dog carrying a muzzle. The question is, under what circumstances does salvarsan slip its muzzle? If we observe the

type of innocuous arsenic combinations—Bunsen's cacodyl—then we see that this, as pointed out by Schulz, becomes poisonous so soon as the cacodyl combination remains for a longer period than usual in the body. Müller, Schoeller and Schrauth consider that the (chronic) poisonous action of the organic mercury products is the resultant of the quickness of elimination and the ease with which the complex preparations are broken up; they understand thereby mercury's power to disassociate itself from its combination and to affect the body. Now we know that in the majority of instances, salvarsan is quickly eliminated from the organism, while arsenic remains somewhat longer in the body, especially in the liver and the musculature. If a decomposable substance goes quickly through the body then it can easily be innocuous; but on the other hand, let it go through slowly, then chemical changes consequent upon the longer duration of elimination become inevitable, and under certain circumstances the agent may become poisonous. Through Heffter's investigations of the retention of cacodylic acid in the organism, it is established that a number of animal organs (liver, stomach and bowel) contain substances which are endowed with an energetic power of reduction and are able to reduce cacodylic acid with the formation of cacodyloxid. It is therefore probable that salvarsan with a long retention in the body also undergoes such reduction. In the case of the more easily decomposed neosalvarsan this probably occurs more often than with old salvarsan.

In his memorable address on October 31st, 1909, before the German Chemical Society, Ehrlich offered information on the toxicity of products in the organism originating in the reduction of arsanil.

It is a well known fact that in the compound Arsanil, the oxygen carrying complex of arsenic attached to the benzene ring (or benzol ring) is pentavalent, hence Arsanil is to be considered as an aromatic acid of arsenic. Now it became necessary to convert this substance into the products obtained by reduction in which arsenic appears as a trivalent element (analogous to arsenous acid, $As_2 O_3$ also called arsenic trioxide).

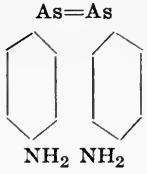
Following a new line of procedure Professor Bertheim and myself have succeeded in obtaining two distinct products according to the relative strengths of the various reducing agents employed, which correspond to those produced and ascribed by Michaelis to the graded stages of reduction of phenylarsenious acid, namely:

1. The monomolecular As O—product, white in color and soluble in acids and alkalis, the p-aminophenylarsenous oxid,

and

2. The product obtained by further reduc-

tion, whereby through condensation of two molecules of the first described compound an entirely new compound of arsenic is produced, the yellow diaminoarsenobenzene, soluble only in acids;



The toxicological character of the substances is radically changed through the above described process of reduction. It has been shown that the highest toxicity is always obtained in compounds in which the element arsenic in union with oxygen occurs trivalent (As O—). To become considered as important is the relative nontoxic character of the arseno compounds of glycine.

Relative Toxicity of the products of reduction. (Lethal dose.)

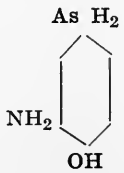
	(Sodium salts of) Arsinacid.	As O— compounds.	Arseno compounds.
1. NH_2	1:200	1:15,000	1:7000
2. OH.	1:75	1:13,000	1:1000
3. NH. CH_2 .COOH.	1:20	1:1000	1:70

The above indicates the degree of dilution of which exactly 1 c.cm. is capable of killing a mouse weighing 20 grams.

His Excellency Professor Ehrlich has kindly placed at my disposal his views relative to the theory as to the changes which may take place in the composition of salvarsan.

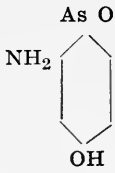
Through chemical influences three distinct compounds may be obtained from salvarsan, in which the substance occurs as an arseno-compound:

1st. Through further reduction a compound is formed which Ehrlich calls Phenylarsin, which is analogous to Arsin also called arsenuretted hydrogen (AsH_3)



We have tested this compound known as Phenylarsin, the dose of which is 0.1, and have found the same more *toxic* but also more *active* than salvarsan. The formation of a compound as Phenylarsin in the animal body is practically an impossibility as the substance is only formed under the most powerful reducing influences.

2nd. On the other hand there is a possibility of the formation of a compound which Ehrlich calls "Arsenoxide," through the oxidation of salvarsan, which is a substance far more toxic in character than the previously described product, Phenylarsin.



(Arsenoxide)

" 'Arsenoxide' is readily formed by exposing the alkaline solution to the air, and in my personal opinion this 'Arsenoxide' is the chief cause of the serious reactions so often complained of. In support of this statement I am relying upon the experiences which were extensively described and related in the first experiments and observations with arsenophenylglycin disturbances occurred in the beginning; one case resulted fatally. The disagreeable manifestations were probably caused by my first method in preserving the arsenophenylglycin in which at least ten per cent. of cases of serious disturbances occurred in the beginning; glycin in ordinary stoppered bottles instead of, as now, *in vacuo.*"

"It is my belief," says Prof. Ehrlich, further, "that the interference with the renal function which you presume exists, is occasioned by the retention of salvarsan in the organism or blood, which favors the formation of the more dangerous arsenoxide. At least it seems almost proven that certain easily oxydizable substances which under ordinary conditions do *not color* animals, cause a distinct *bluish coloration* of the body of animals which receive too large a dose of the substance which consequently causes an inhibition of proper

elimination of the drug. There occurred then a biological oxydation, and this I prefer to accept in explanation of the unhappy effects following salvarsan."

3. "The Arsenoxide can be still further oxidized, to phenylarsin acid. I believe, however, that this is but rarely the case; at any rate such an extensize oxydation cannot be drawn upon to furnish an explanation of death since the p-Oxymetamidophenylarsinacid is much less toxic than salvarsan and in the employed dosage must be considered as without danger."

Salvarsan which has undergone decomposition causes renal damage and anuria. Thus Eitner saw an anuria lasting two or three days in a patient in whose case the salvarsan powder, employed for injection, had been exposed for two weeks to the air. Malinowski saw an anuria lasting for ten days following an injection of salvarsan which had been exposed for five days to the air. Jakimoff demonstrated experimentally the increased toxicity of oxydized salvarsan for the kidneys. Concerning this point we shall later by means of exact investigations secure an explanation of fatal poisoning. As the picture of this poisoning does not correspond to the poisoning by arsenic, then it must be determined whether the groups which are related to arsenic do not cause the poisoning following decomposition. Sabbattini,* in this connection, has made many

**Physikalische Betrachtungen über toxische Hg. Wirkungen. Biochem. Zeitschrift,* 1908, 337, *Festschrift für Hamburger.*

striking experiments relating to the complex mercury combinations and their division..

As must always be emphasized, salvarsan fatalities do not resemble arsenical fatalities. But they do have a close resemblance to deaths caused by carbon monoxide. Here we find the same clinical picture, headache, convulsions, vomiting, unconsciousness, coma, involuntary passages of urine and feces, etc.*

The old investigations of Klebs** particularly show a close analogy; from three cases coming to autopsy he pictured the last stage as presenting deep coma, marked dyspnea and cyanosis, which are so frequently mentioned in descriptions of salvarsan fatalities, added there to, in the first and third case, tetanic muscular rigidity and muscular twitchings with fully accelerated pulse. Especially striking was the extraordinary abundance of blood in all regions. He particularly mentions the fine capillary congestion of the brain, especially of the gray matter; and in the kidneys and liver an injection of so marked a character as to be comparable only to an artificial injection of the vessels. It is not encephalitis hemorrhagica but, on the contrary, the enormous distension of the vessels which is the constant finding in death from salvarsan.

The cyanosis and dyspnea in salvarsan fatalities, which occurred in a particularly characteristic manner in the case of Busse and Merian and which were effectively combated with inhalations of oxygen, show plainly that

*Kunkel. *Toxikologie*, s. 336.

**Wirkungen des Kohlenoxydes auf tierschen Organismus. Virchow's Arch.* Bd. 32, s. 450.

one should not lose sight of the possibility of disturbance of respiratory innervation. One is also reminded somewhat of the "red asphyxia" of Claude Bernard. Through this then also the cerebral irritation (convulsions, paralysis, coma) could easily be explained. It is generally known how violently the central nervous system reacts to interferences with its supply of oxygen. In carbon dioxide poisoning the most conspicuous findings are the capillary hemorrhages in the brain, and foci of softening. It must again be emphasized that purpura of the brain and encephalitis hemorrhagica are not characteristics of arsenical poisoning. These do not depend upon capillary thrombi, as could occur in arsenic poisoning, but upon diapedesis through damaged blood vessels.* In conjunction with Dr. Pakuscher I have examined several cases of encephalitis hemorrhagica after salvarsan with the greatest exactness, reaching my former conclusion that this could depend upon emboli, yet at the same time I did not omit careful attention to the possibility of thrombi but with negative results.

An exception to this view occurs in the case of Marschalko and Veszprém.**

*Martin B. Schmidt (*l. c.*) cites a case: Jerome Schneider, 21 years of age, was treated for 11 days in the skin clinic at Heidelburg with chrysarobin and arsenic. Just as he was about to be discharged he was suddenly seized with headache and unconsciousness, dying in 36 hours. Autopsy: Ecchymoses in brain and endocardium. Hyperemia of the kidneys and other abdominal organs. One could scarcely attribute this mysterious death to arsenic poisoning.

**_Deutsche med. Wochen._ 1912, 26.

A 38-year-old state's official received at the hands of his physician on November 10th, 1911, an intravenous injection of 0.53 salvarsan which was made up with distilled water that was not fresh. In two hours the patient became ill with vomiting, but this soon passed away. On the next morning there occurred chills, temperature of 40 C. (104 Fahr.), and vomiting; on the 14th unconsciousness, temperature 36.5 C. (97.7 Fahr.), epileptiform attack, etc. Death five days after injection.

Encephalitis hemorrhagica without purulent infiltration. The capillaries partly distended with uniform, hyaline thrombi, and also in some of the largest vessels pronounced thrombi of the vessel-walls were found.

Unfortunately the functional power of the kidneys and the condition of the chorioidal plexus was not observed. But it is fair to assume that damage occurred in the kidney through toxic action of the drug permitting an abnormal permeability of the capillary walls. (*Magnus, Bildung der Lymph, in Oppenheimer, Biochemie,* II, 2.)

But the resemblance extends still further, in that in carbonic acid gas poisoning and focal softening, these hemorrhages are most frequently to be found in the larger basal ganglia especially in the lenticular nucleus, therefore exactly as in salvarsan poisoning.

Pölchen aptly explained this peculiarity of carbon dioxide poisoning. "The carbon dioxide circulating in the blood impairs the nourishment of the vessels and thereupon follows necrobiosis." So we see fatty or hyaline (salvarsan) changes of the same, but no thrombi.

"Especially the vessels of the *regio innominata* and of both the inner limbs of the lenticular nucleus become diseased, because these vessels at their origin are extraordinarily small, and very long, 5 to 5 cm. without anastomosis and without vasa vasorum, and thus solely dependent upon the blood circulating through their lumina for sustenance. The narrower the vessels become, the more deleterious, naturally, becomes the poisoned blood; thus we found the vessel walls close by to the broad trunk of the middle cerebral artery, still intact."*

It struck Klebs as strange that in carbon dioxide poisoning the trunks of the cerebral vessels are strikingly tortuous, especially the finer branches, and he gives a convincing description of the microscopical appearance. He explains the lengthened and tortuous condition of the vessels through an atony of the vessels caused by the poison, in which, however, by reason of the strong systolic force of the heart, an abundance of blood is circulated. He explains this phenomenon, especially as it occurs in the meningeal artery, thus: "While in elastic tissues, such as the lungs or spleen, an increase of arterial contents causes an increase in size of the entire organ without dislocation or change of position of the vessels, and in more solid tissues, renal for instance, on account of the intimate connection of vessel wall and parenchyma in general no dislocation of either part takes place, the wall of the men-

**Zur Aetiologie der Gehirnerweichungen nach Kohlendunstvergiftung. Virchow's Archiv*, Bd. s. 26.

ingeal artery with its adventitia lies as if in a canal, in the dura mater, the rigid walls of which do not give before the impact of the pulsation."

In the future, therefore, in cases of salvarsan poisoning, one must direct his view more than formerly to the state of the blood current, especially as concerns its oxygen content; for salvarsan is an exceptionally potent reducing agent, as shown histologically by Tryb* through the delicate methods of Unna and Golodetz.

According to what has been said, in the future one will have to employ, when administering intravenous injections of salvarsan, the utmost care in estimating the renal function. Our observations relating to this matter with pure salvarsan therapy, show that in general in such cases diuresis is of a normal type; only now and then does it reach a stage of polyuria and but seldom does the quantity of urine sink to as low as 600-800 c.cm. In later cases we have frequently seen the injection of salvarsan responded to with headache, vomiting and exhaustion, and therefore we exercise the greatest care concerning the dosage and frequency of injection. With the combined treatment still greater care must be shown.

After the first injection of salvarsan, which for the purpose of testing the idiosyncrasy of the patient should not be in excess of 0.1 or 0.2, one must always pay strict attention to diuresis. In our department even a minimum reaction or slight increase in temperature oc-

Monatshefte f. prakt. Dermat. Bd. 52, s. 406.

Name:
Albumen 0
500/026
500/026
400/030
300/032
3×Lagilch
0·5 Urotropin
Albumen 0·3‰
Albumen 0·2‰
900/024
900/022
1200/018
1200/016
900/020
600/022
Alb. 0·2‰
Alb. 0·2‰
Alb. 0·2‰
Alb. 0·2‰
120 g
42
41
40
39
38
37
36
35

Chart III.

curs with great rarity; even following the first injection such phenomena seldom occur. We carefully investigate every reaction, even the slightest, and extraordinarily frequently we find a dependence of the reaction upon impairment of renal function. As a paradigm let me cite the following case:

A 33-year-old woman, suffering with a luetic stricture of the rectum, who had been frequently treated with mercury, urine free from albumin, received 0.1 salvarsan on November 14th, 1912. Temperature at this time 37.6 C. (99.6 Fahr.). November 15th 37.6 C. (99.6 Fahr.).

See chart III.*

We have observed the same in hypoplasia of the heart with oliguria.

It is also to be noted that long continuing infectious diseases, diphtheria and scarlet fever above all, can leave in their wake a vascular hyposthenuria.

Just recently we saw a young girl with occult syphilis, who showed a positive Wassermann and who had never been treated, following an injection of 0.1 salvarsan on November 15th, develop a temperature of 39.6 C. (103.2 Fahr.). Then oliguria without albumin occurred. On November 16th, amount of urine passed 700 c.cm., sp. gr. 1024; November 17th, 200 c.cm. (!) sp. gr. 1028, November 18th, 400 c.cm. sp. gr. 1030, November 19th, 500 c.cm. sp. gr. 1030. Presumably

*Also the next injection of 0.1 of salvarsan was responded to with exactly the same reaction. One can very easily believe that such a patient, if receiving two or three injections of 0.4-0.6 salvarsan might not eliminate the drug.

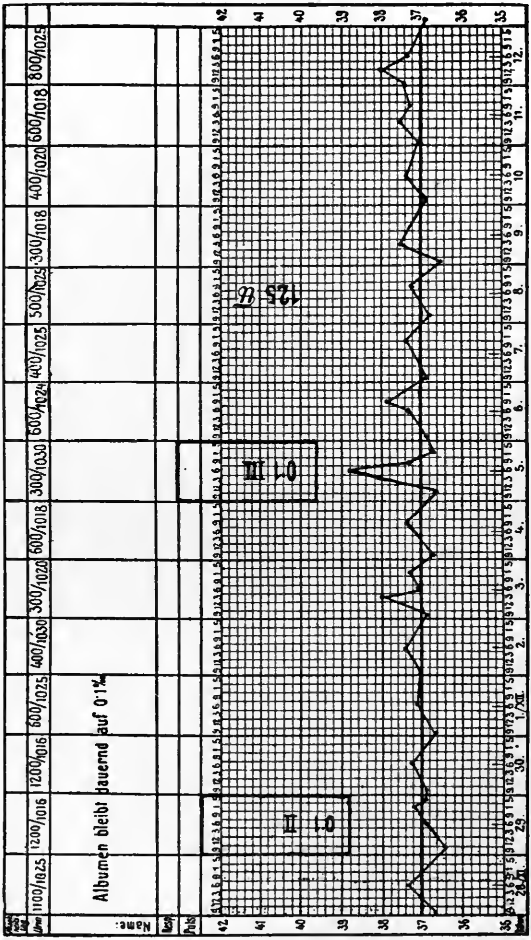

Albumen bleibt dauernd auf 0·1‰
1100/1025
1200/1016
1200/1016
600/1025
400/1030
300/1020
600/1018
300/1030
600/1024
400/1025
500/1025
300/1018
400/1020
600/1018
800/1025

Chart IV.

the cause for the drop in the functional curve was a diphtheritic attack suffered in 1911.

It is clear that the damage to renal vessels which produces polyuria is of a moderate grade, while that which is associated with oliguria represents a severer grade. It is probable—further proof on this point must be worked out—that only with severe damage to the kidney is there sufficient interference with the elimination of salvarsan to produce a menacing state. Practically speaking, then it is only oliguria which is to be considered in the question when confronted by a death after salvarsan. Whether the lighter grades of damage to the renal vessels, they can manifest themselves in an increase or even a (pseudo) normal quantity of urine, have a practical significance can only be determined by further observations. If no absolute standard of the functional power of the renal vessels can be determined through observation of diuresis, then we must look to the premonitory symptoms which in such cases usually occur after the administration of salvarsan, these being coated tongue, prostration, vomiting, headache, a general discomfort due to disturbance of the renal function, and which point to the need for a more exact investigation of such symptoms according to the method of Schlayer and Takayasu, and then we must avoid further burdening the kidneys.

Generally speaking a determination of the quantity of urine and its specific gravity, secured over several days, suffices, and it is only seldom that one will be required to employ the more refined functional tests. It appears to

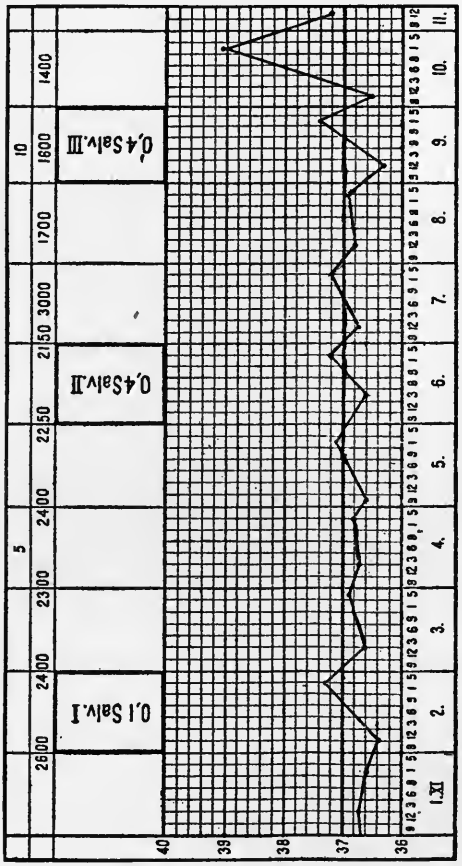


Chart V.

be of large importance not to reach conclusions based upon examinations made directly after injection but rather to postpone judgment until the second or third day, especially if there be a moderate temperature.

Chart V shows how a patient who had received five injections of salicylate of mercury, presenting a polyuria thereafter, had no change in urinary secretion following an injection of 0.1 salvarsan, but who after the second injection of 0.4 salvarsan presented a polyuria of 3000 c.cm. The next day this dropped to a normal quantity, 1700 c.cm. The third injection was responded to, not on the same day but on the following day, with a temperature of 39 C. (102.2 Fahr.); in contradistinction to this rise of temperature the urinary secretion was about normal, 1400 c.cm. The next day the temperature dropped to normal. However, on the fourth day after the injection the blood contained, according to Prof. Loeb's estimation, a strikingly large quantity of arsenic; the exact quantitative amount was not ascertained.

Isolated cases of a similar character have been reported where death took place even with normal diuresis. The type is as follows. Case of Balzer and Candat.*

Male, 34 years of age, two chancres on chin. Calomel ointment 30 per cent. One week later mucous patches on right tonsil with abundant spirochaetes. No roseola. Urine normal. November 24th 0.3 salvarsan intravenously. Four hours later chills, temperature 39.2 C. (102.6 Fahr.). December 1st urine free from albumin.

*Bulletin de la société de dermat. 1912, No. 1.

Salvarsan 0.3. Temperature 37.6 C. (99.7 Fahr.). December 2nd anorexia. December 3rd unrest, delirium, semi-consciousness, twitchings, rigidity. Reflexes retained. Unequally dilated pupils. Urine clear, in good quantity, without albumin or sugar. Coma. Cerebrospinal fluid showed high pressure and clear, few cells, marked quantity of albumin, positive Wassermann. December 4th cyanosis. December 5th some albumin in urine. Second lumbar puncture, abundant polynuclear cells. Epileptic attack. Death. No autopsy.

On the same day eight other patients were given the same dose in the same manner but without reaction. Therefore, it cannot be said that the preparation was in the least poisonous.

Arsenic in the spinal fluid. A noticeable quantity of arsenic in blood taken from a vein. This blood was drawn on December 4th. It is thus shown that in this instance there was a retention of arsenic. Since the elimination of fluids was normal but an abundance of arsenic could be demonstrated in the blood even after several days, there then could be present an interstitial nephritis, as a result of which the capacity for the elimination of fluids was not interfered with, while the power to eliminate substances circulating in the blood and the power of concentration were impaired. One must give heed to these circumstances in judging the individual salvarsan fatalities, in which it may be alleged that only salvarsan was employed. In all vascular nephritides following cessation of oliguria there comes a stage of polyuria in which lactose elimination is more or less interfered with; often there will be almost complete retention (Schlayer and Takayasu, *l. c.*, page 383). Neither an increased

nor a normal urinary secretion permits a definite conclusion to be reached of an intact or specially good function of the kidneys. Generally speaking, both represent a milder grade of damage to the renal vessels than the marked oliguria, yet either may exist in the presence of a high grade damage of the renal vessels (*l. c.* p. 389). This polyuria has for a cause a hypersensitiveness of the renal circulatory system in consequence of morbid irritations; these may be lasting or transitory. The same sort of condition can be caused by syphilis. Hirsch* directed attention to the frequency of contracted kidneys of an insidious character in syphilitics. Löhlein pointed out the possible connection of primary syphilitic disease of the blood vessels with this form. It is quite noteworthy that the cases of contracted kidney without arteriosclerosis collected by Roth** (under Jorl's guidance) mostly concerned young individuals.

Hirsch also emphasizes how in such cases which are unable by reason of renal insufficiency to eliminate mercury, severe poisoning takes place. This also holds good with salvarsan. In a case of Dr. Gey's (for this I am indebted to a private communication from his Excellency, Ehrlich, in which death took place two days after one injection, there was found a marked interstitial nephritis with extensive alterations in the glomeruli and fatty degeneration of the uriniferous tubules together with beginning cirrhosis of the liver.

**Virchow's Archiv.* Bd. 77.
***Med. Klinik*, 1912, No. 23.

In general, as shown by complications, alterations in the internal organs referable to the abuse of alcohol, are strikingly frequently found at autopsy; particularly chronic leptomeningitis is frequently found. In this connection the old French proverb, *"La Syphilis et l'Alcool font mauvais mariage,"* may pertinently be quoted.

It is clear that insufficiency of the kidneys does not sufficiently explain all cases of salvarsan fatalities. But for the most of these cases which are not to be included in this type, arsenic poisoning offers no explanation, on the contrary observation shows that here the various clinical pictures and death-causes are to be considered together. Almost always these patients are individuals with definite insufficiency of various organs, demonstrable before injection of the agent and demanding great caution in every sort of surgical interference. Those cases in which our present methods of examination do not disclose the cause of death, are but rarely met with. That extra-renal conditions could influence a retardation of salvarsan elimination is evident. To be drawn into consideration are certain cardiac disorders.

Apparently salvarsan does not have a bad influence on the heart, in fact in heart diseases, especially in arteriosclerosis, it is usually well borne. As a rule it has a splendid effect on circulatory troubles due to syphilis. On the contrary, however, salvarsan is always a burden for an overworked, poorly balanced heart. This is demonstrated by the cases described by Martius* in which autopsy disclosed

**Abhandlungen über Salvarsan.* Bd. II, s. 473.

valvular insufficiency, sclerosis of the coronary arteries and myocarditis. In this connection retarded elimination often plays a considerable part. Also hypoplasia of the heart or kidneys may also cause the same. The same holds good in the employment of salvarsan in the presence of febrile disorders and at the conclusion of infectious diseases (influenza, diphtheria, scarlet fever), in which, under certain conditions, extensive functional disturbances, mayhap demonstrable only with the most exact methods, may be present.

Then the fever caused by contaminated water might also lead to the retention of salvarsan; the recent investigations of Schwenkebecher, v. Hösslin and others, show that in fever there is salt retention in the blood. It is to be mentioned, however, that patients who have been given intravenous injections of lactose and who had fever, 40 C. (104 Fahr.), and chills, normally excreted the sugar. Likewise extra-renal circumstances have no essential bearing on the elimination of iodide of potassium. While, therefore, foreign substances are eliminated according to rather uniform rules, the elimination of bodily substances (water, NaCl) is variable and influenced by numerous conditions, both renal and extrarenal.

Generally speaking the diseased brain tolerates salvarsan well. That in quite exceptional instances patients with extensive changes or with diseased foci in vital centers, do not tolerate the treatment, particularly when they receive rather large doses, is not difficult to understand; it should be emphasized, however,

that oftentimes in such cases the injection is borne without reaction, and then frequently enough one experiences sudden deaths with mercury injections or even without any therapy whatsoever. Latent meningeal tuberculosis appears to offer a certain danger as several fatal cases of Finger's show. It is our habit in tuberculosis with headache always to examine the spinal fluid before the employment of salvarsan that it may be clearly determined whether it is lues or tuberculosis.

There yet remain to be considered occasional fatal cases due to acute yellow atrophy of the liver. Such cases are frequently observed in consequence of syphilis and the employment of mercury as treatment, so one cannot attribute them to the salvarsan, particularly since they as a rule occur at a considerable period after the injection; and the less so since just here the most surprising results of salvarsan (Umber*) have been described even after failure of the most active mercury preparations (Duhot**). Therefore, it is to be considered that acute yellow atrophy of the liver due to florid syphilis may associate itself with a severe epithelial necrosis of the kidney which is not recognized clinically, and offering great difficulties in the way of elimination of every drug agent, as described by Janssen in his Dissertation (Berlin, January 14th, 1911). Therefore, the conclusion is that the condition which we have been in the habit of describing as acute yellow atrophy of the liver,

Abhandlungen zur Salvarsantherapie, Bd. II, s. 365.

**Ebenda*, s. 352.

is only the acute terminal process of a clinically latent but clearly demonstrable, chronic condition.

In this connection the excellent, searching investigations of Severin and Heinrichsdorf* concerning these circumstances, are to be remembered. One case especially of these authors, in which icterus followed immediately the third injection of salvarsan, can according to my opinion, best be explained on the assumption that the last injection of the hitherto well borne salvarsan, offered the broken link of a chain for the causative factor.

If one takes into consideration the previously reported salvarsan fatalities, then may one entertain the hope that in the future similar cases can be avoided almost without exception, and that but a few not sufficiently explained, remain to be dealt with. Future investigations will discover the genesis of these, and it must be endeavored to explain whether insufficiency of other organs plays a part in connection with these cases. One must now think especially of the choroidal plexus. Our case shows, as does that of Balzer, that with retention of salvarsan in the blood the choroid plexus may be so badly damaged that the previously albumin-free liquor will contain an abundance of albumin, in fact, even to the point of spontaneous coagulation. With the normal choroid plexus, injections of salvarsan cause no increase in albumin.** As to this point it must be carefully determined if the

*Zeitschr. f. klin. Med., Bd. 76, s. 138.

**Wechselmann: *Die Wirkung des Salvarsans auf den Liquor cerebrospinalis. Berl. klin. Wochenschr.*, 1912.

plexus in the case of salvarsan fatalities undergoes pathological changes. We know that with tuberculosis the permeability of the same to certain substances is increased, and the same might occasionally hold good with syphilis.

Schmorl,* for instance, reported that a quantity of substances, which are dissolved in the blood, pass into the spinal fluid but not into the ventricular fluid, and conversely; that in both of these fluids there may be differences in the content of biliary pigment, albumin, sugar and those substances which cause the Wassermann reaction. The normal interchange of these substances could also be hindered if more or less severe changes are present in the plexus. In this case of Schmorl's there was a gummatous condition apparent in an anterior section of the corpus callosum. Syphilitic granulation tissue, taking the place of nervous tissue, had encroached upon the superior choroidal horns and in the tissue of the plexus there were extensive small-cell infiltrations; the epithelium, in great part, was missing. The blood and ventricular fluid gave a positive Wassermann, the spinal fluid a negative.

A recently published paper by Langbein and Oeller, a clinico-pathological contribution to the question of acute hemorrhagic encephalitis (from the Leipziger Institute of von Strümpell and Marchand), seems to me to possess a distinct bearing on our question. A 35 year old woman, free from signs of lues

*Verhandlungen der pathologischen Gesellschaft, 1910, B. 288.

and without demonstrable infection, died with clinical phenomena of hemorrhagic encephalitis, which was confirmed at autopsy. Moreover, there were found primary and secondary inflammatory processes in the meninges of the base and convexity of the cerebrum. "In this case it seems justifiable to conclude that the other existing changes in veins and brain were consequent upon the inflammatory processes in the horns of the third ventricle and the choroid plexus of the lateral ventricle and of the third ventricle, but which, however, one had to designate as primary processes, as in other organs, and in the cranial cavity no inflammatory focus could be found from which a metastatic involvement could have taken place. Always hereafter, with similar cases, it would be advisable to take into consideration the possibility of tuberculosis, and while the latter might be only in the initial stage, yet in a very short time it could lead to a tuberculous meningitis with resulting thrombosis."

After all this we are justified in saying that salvarsan *per se* employed in normal persons in the customary dosage is nontoxic. Any evil consequence observed is always due to some organic insufficiency, especially of the kidneys. For this insufficiency the responsible factors are frequently mercury, perhaps exceptionally rare salvarsan, and also other weakening factors, such as the influence of syphilis on the blood vessels as well as other infections and intoxications. If the most effective results are to be secured from salvarsan it is of the greatest importance to care-

fully heed the foregoing points during the drug's administration.

It is quite conceivable and, in fact, justifiable, that some physicians, following the early experience with the other arsenic compounds, were distrustful of salvarsan from the very beginning, and friends of salvarsan, even though they had seen its elegant healing effect, feared that the not too well understood collateral effects might operate to deprive us of the advantage of this agent. But this stage is now passed. One should not forget that the same opposition arose against mercury at the time of its introduction as now against salvarsan. Physicians have been too prone to minimize its good effects, and to place in the foreground the evil effects caused through improper employment. Let us now remember that from 1580 to 1655 every teacher at Heidelberg had to take an oath that he would never use mercury! It is this divided condition of opinion among physicians which permits, even to the present, the quack to thrive so well! But the standpoint of those physicians who recognized the value of mercury even in early days and who through the greatest care, reduced its evil effects to the lowest possible point, at last prevailed. Rightly, exclaims the great Botallius: *"Quis criminabitur ignem, unde pro servorum negligentia basilica domini consumpta est!"* The same holds good for salvarsan. My entire experience with more than 25,000 injections forces me to the inevitable conclusion that salvarsan is much less toxic than mercury. My department in which salvarsan is used almost exclusively has given

me much less care and trouble during the past three years than in the previous period when mercury was employed; it is certain that the undesirable effects of salvarsan with us have become much rarer and of less importance as we have better learned to master the technique of its use, and to employ a dosage adapted to the individual case. The clinician always has to deal with ununiform clinical material, and in that lies the main difficulty of properly employing a remedial agent which has been experimentally tested in a laboratory. The hope of a cure for infections binds the experimental worker and the clinician, but the material upon which they work is radically different; there the healthy animal with sound organs, here the patient exhibiting the most varied deviations from normal. Therefore, without the systematic, definitely planned aid of the clinician the introduction of a chemotherapeutic preparation is impossible.

In conclusion, I wish to present a list of salvarsan fatalities which have become known to me. Should I omit certain cases it is because they possess no value for this table, as it is my purpose here to offer not a statistical presentation of cases, but rather to deal with their genesis. It is somewhat difficult to bring these observations from chaos to order, particularly so since the greater number of these observations have been imperfectly described. These observations will serve for the establishment of certain principles which may be employed in future anomalous cases of salvarsan therapy; in this way it will be easier to find an explanation of the question involved. I am

taking into consideration only those cases of adults, for luetic infants die under such varied circumstances that one can scarcely pick out any special cause.

In the beginning, let it be emphasized that with subcutaneous and intramuscular injections of salvarsan the cerebral type of fatalities has not been observed. In these methods of administration apparently there is never so severe a burden thrown on the kidney as tc occasion renal failure.

Fatalities Following Subcutaneous Injections.

Below are given the cases of death which have been reported as following the use of salvarsan subcutaneously. In all there are six. It will be seen that a direct connection between death and the use of salvarsan can hardly be established, as the patients concerned suffered from the severest involvements of vital organs, and salvarsan was employed as a last resort in a bare hope of saving the patient's life. Schiele's case (No. 3) which is given below, shows an intractable, malignant syphilis in the person of a young girl, who, after a temporary improvement, died two and a half months after the injection. One case reported by Marcus I am not considering at all, as the patient threw himself out of a window a month after the injection. Therefore, the subcutaneous method, as I have always maintained, has not with certainty been the cause of a death. The cases show different types.

1. Case of Ehlers and Jörgenson (*Münch. med. Wochenschr.* No. 42, 1911, p. 2183). A 40-year-old paralytic. Infection eleven years previous. Since 1908 symptoms of paralysis. In June, 1910, apopletic attack. Since then decrease in bodily weight. On Aug. 25th, 1910, injection of 0.5 "606" subcutaneously. Thereafter gradually increasing indications of poisoning of the nervous system. Tremor, outbreaks of perspiration, etc. Rapid decline in strength. Five days after the injection death took place with symptoms of progressive paralysis of the heart.

Autopsy: Fatty degeneration of the heart, kidneys and liver.

2. Case of Martius. (*Münch med. Wochenschr.* No. 20, 1911.) 56-year-old woman with cardiac attacks. Aortitis luetica, with insufficiency of the aortic valve, established clinically. A radiogram showed a diffused thickening of the aorta but no aneurism. In spite of inunctions the cardiac attacks increased, for which reason 0.5 gram of salvarsan in neutral suspension was given subcutaneously. At first these attacks ceased, but two weeks later again began, and on the 17th day death took place in an anginal attack.

Autopsy: Hypertrophy of the left ventricle, aortic insufficiency, aortitis luetica, hydropericardium, hydrothorax, moderate interstitial nephritis.

3. Case of Schiele. (*St. Petersburger med. Wochenschr.*, No. 33, 1911.) 29-year-old girl with congenital syphilis. In spite of every treatment the disease processes made progress. Poorly developed, infantile appearance, completely deaf. Palate perforated. Both apices of lungs infiltrated, liver and spleen enlarged. Abdominal pain upon pressure, finally hallucinations, etc. A trepanation wound of the mastoid process suppurated for nine months. On Oct. 10th a subcutaneous injection of salvarsan, 0.3 was given. Temporary improvement. Death Dec. 26th.

4. Case of Schiele. (*St. Petersburger med. Wochenschr.* No. 33, 1911.) 28-year-old patient infected eight years before. Since then irregularly treated with mercury. Suffered from paralysis of

the left side of the body, with disturbances of swallowing and speech. Injection of 0.4 salvarsan subcutaneously. Death in five days.

Autopsy: Large soft focus in cerebellum. Chronic leptomeningitis. Arteriosclerosis of the basal arteries.

5. Case of Spiethoff. (*Münch med. Wochenschr.*, No. 4, 1911.) In a patient suffering from gastric crises of an indeterminate nature, there was found a well compensated, moderate aortic insufficiency. Wassermann positive. A careful x-ray examination disclosed nothing. Injection of 0.3 salvarsan subcutaneously. At first well borne. After a few days the heart became weaker and weaker, and on the 11th day following injection, caused death.

Autopsy: Aortic insufficiency, aortitis luetica, myocardial degeneration, marked sclerosis of the coronary arteries.

6. Case of Hans Willige. (*Muench. med. Wochenschr.* No. 46, 1911, page 2403.) Patient 44 years old, infected with syphilis in 1892; became a diabetic ten years later. Since 1908 had disturbances of vision. Wassermann strongly positive. Somewhat emaciated. Pupillary reaction sluggish. Vision, right, ⅓; left, 1/10. Liver enlarged with nodular thickening. Urine, daily quantity 2 to 2½ litres with 2.5 to 3.5 grams albumin. Patient shows a changeable disposition, now excitable now depressed. On Sept. 9th, 1910, injection of 0.35 gram of salvarsan given subcutaneously between the shoulder blades. The following day patient could sleep, yet showed a deep, painful infiltration at the site of injection. The next day there came vomiting, abdominal pain, constant distress with marked thirst. At the same time an eruption appeared on the arms. On Sept. 12th condition the same. On the 13th coma, pulse 110, irregular. From the afternoon on patient's condition grew steadily worse. Death on the 15th.

Autopsy: Cerebral edema, myocardial degeneration, light parenchymatous inflammation of the intestinal tract, the liver and the kidneys. Trace of arsenic in the urine and in the liver.

Deaths Following Intramuscular Injections.

Fifteen deaths have been reported following intramuscular injections. Besides these there are two other cases cited by Jadassohn, in which it could not be clearly determined whether the injection had been given intramuscularly or subcutaneously. Also in these cases there could not be shown any connection between the salvarsan and death, that is, in the sense of a poisoning. In a few cases death follows a month or more later from septicemia or hemorrhage. Comparatively speaking emboli often follow this method, in contradistinction to their non-occurrence in the subcutaneous method.

1. Case of Dr. A. in K. (Martius). (*Muench. med. Wochenschr.*, No. 20, 1911.) Patient 47 years old, tabetic, suffering with aortitis and aneurism of the arch. Wassermann positive. Upon expressed wish of patient 0.6 gram of salvarsan injected intragluteally. Following this with entire loss of appetite patient became weaker and weaker. Fifteen days after injection there appeared a painful, hemorrhagic pemphigus. Death on the 21st day.

Autopsy: Hypertrophy and dilatation of the left ventricle, and moderate dilatation of the arch of the aorta. Atrophic liver showing fatty degeneration. Marked parenchymatous degeneration of the kidneys.

2. Case of Finger (Mucha). (*Wiener klin. Wochenschr.*, No. 27, 1911, page 963, and No. 28, 1911, page 1012.) Child, seven years old, well developed, with mucous patches on lips and papules on the genitals. Eyes normal. Chronic middle ear trouble (suppuration). Light bronchitis; no albumin. Jan. 17th intramuscular injection of 0.2 gram salvarsan. Following day, headache and

Herxheimer reaction. Papules showing improvement; on following day cured. On Feb. 18th involuntary movements of the head and eyes. On Mar 18th, notwithstanding that the involuntary movements have ceased, patient is fully apathetic. Vomiting and headache. Lumbar puncture shows high pressure, a clear liquid containing mono- and polynuclear leucocytes. The previously strongly positive Wassermann now became weakly positive. On March 26th, coma with purulent discharge from the ear, which makes one suspect an abscess of the brain. March 31st, trepanation was tried but without results. April 3rd, patient died.

Autopsy: Purulent leptomeningitis of the base. Increase of ventricular fluid. Tuberculosis, calculous nodules of the spleen.

3. Case of Herxheimer and Altmann. (*Deutsche med. Wochenschr.*, No. 10, 1911.) Male, 25 years old, with symptoms of a progressive paralysis. Several years ago apical tuberculosis. Intragluteal injection of 0.5 gram salvarsan in neutral solution Sept. 15th, 1910. On the 20th one can see a marked infiltration at the site of injection. Patient complains of sharp cough with slimy material from bronchi. Died suddenly on Oct. 5th of pulmonary embolism following a thrombus from the femoral vein, which was due to a streptococcus infection at the point of injection.

Autopsy: Old fibrous deposit in both apices, and encysted caseous foci. Peural adhesions.

4. Case of Hrdliczka. (*Wiener klin. Wochenschr.*, No. 21, 1911.) Officer, 33 years old, infected 1903. From then to 1908 well treated with mercury. Since 1909 increase of symptoms. Oct. 24th, 1910, intramuscular injection of 0.6 gram of salvarsan in neutral suspension. At the time there was a periostitis of the tibia. With January came stomach disturbances, vomiting, attacks of dizziness, and disturbances of vision. On February 6th, noticed weakness of memory. Wassermann negative. Clinically there is nothing to be seen, neither of nervous nor organic ailments. February 28th came stiffness of jaws, facial paralysis, disturbances of speech, fever and unconsciousness. Patient died March 8th.

5. Case of Jacquet. (*Gazette des Hôp.*, No. 120, 1911.) Patient 42 years old, alcoholic, with ulcerated syphilide the size of a dollar on thigh. For years patient has complained of vomiting and bowel disturbances, due presumably to dilatation of the stomach. Sept. 17th intramuscular injection of 0.5 gram salvarsan. Pronounced pain and moderate fever. The syphilide cleared up and healed over. On the seventh day following the injection patient vomited dark masses. The anemia and weakness increased. Death Sept. 29th.

Autopsy: Ulcus ventriculi with rough edges, pyloric stenosis, dilatation of the stomach.

6. Case of Lane. (*Bri. Med. Jour.*, Sept. 23rd, 1911, page 673.) Patient 27 years old, infected six months previously. At the time of injection phagedenic ulcer on penis, ulcerations upon the inner side of the thigh and palate. Six calomel injections without any result. Sept. 24th intramuscular injection of 0.5 gram salvarsan. Notwithstanding the injection the palate perforated; the completely necrotic jaw-bone had to be removed. Death occurred Dec. 2nd from septicemia.

7. Case of Martius. (*Muench. med. Wochenschr.*, No. 20, 1911.) Patient with tabes. Clinical examination of the heart discloses an accentuated second aortic sound. Intramuscular injection of 0.6 gram salvarsan in 8 c.cm. olive oil. Well borne. Girdle pains disappeared. On the sixth day following injection death suddenly occurred.

Autopsy: Syphilitic aortitis. Moderate sclerosis of the aorta and the peripheral arteries. Moderate dilatation and hypertrophy of the left ventricle. Fresh foci of degeneration in the heart muscle, particularly in the left ventricle.

8. Case of Martius. (*Muench. med. Wochenschr.*, No. 20, 1911.) Paralytic, 47 years old, with lung tuberculosis. Intragluteal injection of 0.5 gram salvarsan in neutral suspension. Two weeks later death occurred from pulmonary emboli following necrosis at site of injection.

Autopsy: Confirmation of clinical findings.

9. Case of Schiele. (*St. Petersburger med. Wochenschr.*, No. 33, 1911.) Twelve year old scholar. Malignant syphilis. Great damage to

bony parts of nasal passages; almost all of the soft palate is destroyed. The hard palate covered with deep ulcerations. Intramuscular injection of 0.3 gram salvarsan. Following injection patient is very restless. Temperature rises to between 38 and 40 C. (100.5—104). Ulcerations respond slowly. For this reason mercurial course is given. After six weeks an injection of 0.5 gram. salvarsan is given; necrosis at the site of the injection gives rise to a fatal hemorrhage.

10. Case of Spiethoff. (*Muench. med. Wochenschr.*, No. 4, 1911.) Female, 28 years of age, markedly cachetic, tertiary lues of the palate. Treated without results with atoxyl for three years. An intramuscular injection of 0.5 gram salvarsan given on the afternoon of June 20th. At ten o'clock in the evening no visible changes; slight pain at sight of injection required morphine. At five o'clock next morning the woman was found dead in bed.

Autopsy: Tertiary syphilis of the palate, cicatricial stricture of the pharynx, gummatous scar in liver, hyperplasia of the heart and of the aorta. No trace of arsenical poisoning.

11. Case of Werther. (*Muench. med. Wochenschr.*, No. 10, 1911, page 505.) Sixty-year-old man, very anemic, suffering from cerebral syphilis and hemiplegia. Intramuscular injection of 0.5 gram. salvarsan. Death following day.

Autopsy: Large soft focus in brain. Endarteritis of the cerebral arteries, syphilitic aortitis, myocardial degeneration.

12. Case of Westphal. (*Berliner klin. Wochenschr.*, No. 22, 1911, page 973.) Woman 33 years old, alleges no infection yet three miscarriages have occurred. (At an earlier period the husband had had a chancre.) Never treated for syphilis. Complained of lancinating pains, dizzy spells, difficulty of hearing, vomiting and double vision. Gradually locomotion became disturbed; after six months complete loss of locomotion. Then paralysis of arms. Clinical examination on June 22, 1911, discloses loss of pupillary and patellar reflexes. July 14th received an intragluteal injection of 0.2 gram salvarsan in neutral sus-

pension. At first well borne. Shortly afterwards complains of dyspnea, which in spite of artificial respiration quickly progresses to apnea. Death 36 hours later.

Autopsy: Syphilitic aortitis. Degeneration of the posterior columns, and acute specific spinal meningitis.

13. Case of Willige. (*Muench. med. Wochenschr.*, No. 46, 1910, page 2403.) Following intramuscular injection of 0.8 gram salvarsan appeared rather severe phenomena. At the site of injection there was visible a dark, hemorrhagic eruption, which quickly spread to the buttocks and thighs, and only cleared up after five days and then with scar formation. Wassermann became negative after four weeks. Appearance of an eruption resembling acne. At the site of injection one could note a painless infiltration. Death seven weeks after injection in consequence of a fresh paralytic attack.

14. Case of Jadassohn. (*Deutsche med. Wochenschr.*, No. 51, 1910.) Forty-year-old patient in bad general condition. No history of syphilis. Aortic aneurism with much pain. Injection of 0.4 gram salvarsan. At first mild rise in temperature, then drop to normal. On the ninth day after injection death took place.

Autopsy: Aortic aneurysm, spleen and kidney infarcts, pneumonia, left lower lobe.

15. Case of Jadassohn. (*Deutsche med. Wochenschr.*, No. 51, 1910.) Forty-year-old patient with severe cerebral syphilis, marked myocarditis, weakness of heart. At request of the mother of patient, an injection of 0.1 of salvarsan was given notwithstanding that patient was already *in extremis*. Death on following day.

Death After Intravenous Injections.

And now will be reported these fatalities taking place after intravenous injections of salvarsan, which occurred shortly after the injection, and in which plain technical errors or

organic changes might be held responsible for the death. It is evident that doses far in excess of what the patient's condition warranted, were employed.

Generally speaking it is highly probable that fatalities which occur in a short time, even within a few hours, after the injection can take place as a result of unnoticed errors. Pointing to this is the circumstance that they are rarely reported, and practically never by physicians who have given many injections. To forget to render the salvarsan solution alkaline is especially dangerous if the solution is not very much diluted. Another dangerous factor is the non-detection of the so-called "anaphylactic" state, for the introduction of a large quantity of salvarsan, during such a state, could easily be the cause of death. It is noteworthy that these cases, once all too frequently reported, now, since the employment of the intravenous method of administration, are but rarely recorded. Either these cases have been preventable cases or the fatalities have been due to lesions which were very severe within themselves.

1. Case of Paul Bar. (*Bull. de l'Acad. de Méd.*, No. 55, 1911.) Nineteen days after receiving an intravenous injection of 0.5 gram of salvarsan, dissolved in 100 c.cm., a pregnant woman showed a marked albuminuria. Shortly thereafter an angina. The patient was delivered of a dead child. Died five days later of a double-sided pneumonia.

2. Case of Dind. An old man, addicted to tobacco and alcohol, in poorly nourished condition, circulatory disturbances, markedly tuberculous. Died three days after the injection with pulmonary symptoms and renal suppuration. (Dose and skill unknown.)

3. Case of Dind. An old syphilitic. Reached hospital in coma and was given an injection of 0.1 gram salvarsan as a last resort. Died during afternoon.

Autopsy: Tuberculous meningitis, pulmonary tuberculosis.

4. Case of De Favente. (*Giorn. ital. delle mal. ven. e delle pelle*, 1912.) Patient 31 years old; infected ten years before. Patient received three calomel injections. Wassermann still positive. Patient complained especially of severe headache at night. Intravenous injection of 0.48 gram salvarsan. Two hours after injection unconscious, epileptic attack lasting an hour and a half, with collapse. Death ten hours after the injection.

Autopsy: Syphilitic basal meningitis, diffuse gummata of the liver, cerebral hemorrhage.

5. Case of Finger (Mucha). (*Wiener klin. Wochenschr.*, Nos. 27-28, 1911.) Male, 33 years old, with secondary syphilis. (Iritis and neuritis optica.) Ears and internal organs healthy. Jan 3rd, 0.4 gram salvarsan intravenously. Wassermann ++. On following day Herxheimer reaction. On the 14th gone. Wassermann +. Second injection of 0.4 gram well borne. Jan. 31st Wassermann ++. March 9th recurrence with neuritis optica hemorrhagica. March 13th no particular nervous symptoms. On the following day patient complained of severe pain in the ears; headache, and indisposition. March 15th another intravenous injection of 0.4 gram. The following day patient suffered from headache and vomiting, but on the 17th entirely well. March 18th patient had a double-sided paralysis of the lower extremities with a Babinski. March 23rd right-sided paralysis of the face. On the 25th left-sided hemiplegia. On the following day, clonic convulsions and fever. March 28th, death.

Autopsy: Acute tuberculosis of base of brain, kidneys and intestines. Chronic tuberculosis of the bronchial and cervical glands.

6. Case of Finger (Mucha). (*Wiener klin. Wochenschr.*, Nos. 27 and 28, 1911.) Woman, 22 years old, poorly developed. Infected ten weeks before. Has eruption on buttocks, neck and the

extremities. Wassermann ++. No albumin. Internal organs sound. On March 29th given 0.4 gram "606," following which patient had headache and light fever. Notwithstanding headache which persisted patient received another injection of 0.4 gram on April 11th. Wassermann +. The following day patient complained of general indisposition, diarrhea and increased headache. On the 14th temperature 39 C. (102 Fahr.). A week later patient fell into a coma. Lumbar puncture, high pressure of fluid which contained many lymphocytes, few polynuclear leucocytes and few bacteria. Stiffness of neck together with eye and fascial paralysis. April 27th, death.

Autopsy: Acute miliary tuberculosis of the base of the brain and left lung. Caseated bronchial glands. Cerebral edema, parenchymatous degeneration of the heart, the liver and kidneys. Acute endometritis.

7. Case of Finger (Mucha). (*Wiener klin. Wochenschr.*, Nos. 27 and 28, 1911.) Male, 33 years old, infected three months previously. At first treated with injections of mercury. Jan. 2, 1911, reseola on buttocks and the extremities. Wassermann +++. Eyes, ears and internal organs sound. No albuminuria. Jan. 7th, intravenous injection of 0.4 gram salvarsan. Well borne. Temperature 39.2 C. (102 Fahr.). Jan. 2nd, second injection of 0.4 gram. Also well borne. Wassermann +++. On Feb. 25th, patient presented himself with severe iridocyclitis of the right eye. Wassermann +. On March 3rd, neuritis of the vestibular nerve. On March 7th,—45 days after the injection—the urine still contained a trace of arsenic. On March 9th patient received third injection of 0.4 gram. Wassermann negative. Only headache. The vestibular neuritis showed improvement, yet the general condition of the patient steadily grew worse. Dizzy spells and headache until May 15th. On the night of this day an apoplectic attack with right-sided paralysis and bilateral neuritis optica. Lumbar puncture, no force, supplied about 25 c.cm. of a clear fluid which contained many mono- and polynuclear leucocytes,

but no bacteria. Patient died on the same day in the evening, five weeks after last injection.

Autopsy: Fresh softening of the cerebral cortex. Leptomeningitis of the base of the brain. Thrombosis of the vessels on the convexity. Meninigitis and endarteritis luetica. Cicatrization of right lung with caseous foci in apices.

8. Case of Fraenkel. (*Muench. med. Wochenschr.*, No. 34, 1910, page 1771.) Man, 25 years old, confused speech, deafness. Infected several years before. Aug. 5th, injection of 0.4 gram salvarsan intravenously in 115 c.cm. of water. Fifteen minutes later symptoms of arsenical poisoning. Death in three hours.

Autopsy: Chronic leptomeningitis, heart weakness, hypoplasia of the kidneys, hyperemia of the liver, arsenic in large quantities in the spleen, lungs and liver.

9. Case of Hoffman. (*Muench. med. Wochenschr.*, No. 4, 1912.) Man, 42 years old, infected five and one-half years before, since then three courses of mercury and iodide of potassium. At this time patient suffered from loss of sensibility in left leg, loss of locomotion, and difficulty of urination. Urine free of morbid elements. Lumbar puncture shows a cloudy, bloody-tinged liquor, with considerable force. March 3rd, 1911, intravenous injection of 0.6 gram salvarsan. After injection chills, vomiting, and rise of temperature to 39.7 C. (103.5 Fahr.). Next day left-sided fascial paralysis. The condition remained without noteworthy change until March 12th, when with slowly rising temperature and symptoms of increasing heart weakness death took place, nine days after the injection.

Autopsy: Sclerosis of the basilar artery. Brown atrophy of the heart and liver. Gumma of the spinal cord with degeneration of the posterior columns. Chronic luetic leptomeningitis.

10. Case of Klingmueller. (*Muench. med. Wochenschr.*, No. 20, 1911.) Woman, 26 years old, in good health, complained of an occasional sticking pain in region of the heart. Careful clinical examination together with X-ray inspection disclosed nothing. Patient knew nothing of luetic

infection yet had two miscarriages. Wassermann +++. Injection intravenously of 0.3 gram salvarsan. At first well borne. Despite physician's advice, the woman worked in garden on the same day she received injection. She died three days later with evidences of increasing heart weakness.

Autopsy: Embolus in pulmonary artery, luetic aortitis, myocardial degeneration.

11. Case of Kobler. (*Gesellschaft fuer Innere Medizin und Kinderheilkunde in Wien*, Nov. 3rd, 1910.) Death as a consequence of rupture of an aortic aneurysm not previously known.

12. Case of Dr. v. K. in S. (Martius). (*Muench. med. Wochenschr.*, No. 20, 1911.) A case of aortitis syphilitica which died during the administration of salvarsan. Autopsy disclosed an extensive aortitis luetica, and a ruptured aneurysm of the thoracic aorta just above the diaphragm.

13. Case of Lane. (*British Medical Journal*, Sept. 23, 1911.) Male, 30 years of age, apparently in good health. Infected in 1909. At the time of examination without manifestations. Wassermann +. Treated with mercury. Since patient contemplated marriage, he requested that an injection of salvarsan be given him. He received 0.6 gram intravenously. Immediately after the injection prostration, in the afternoon pain in breast, dyspnea and cyanosis. Pulse and temperature good. Through employment of stimulants patient restored. During night died suddenly.

14. Case from Mainz. (*Ehrlich's Discussion of Salvarsan*, 11 vol., page 576.) Strong man. Infected in 1910. In Sept., 1910, received an intramuscular injection of salvarsan. In August, 1912, on account of small papular syphilitic eruption patient received 0.5 gram salvarsan intravenously. In a short time fever of 38.6 C. (101.5 Fahr.), vomiting, liquid stools; three hours and a half after the injection death occurred.

Autopsy: Nothing to account for the sudden death.

15. Case of Markus. (*Muench. med. Wochenschr.*, Jan. 10th, 1911.) Paralytic, infected 20 years before. Aug. 26, 1910, received intravenous injection of 0.4 gram salvarsan. At first there was

improvement, then new attacks and finally death by cerebral apoplexy two months after the injection.

16. Case of Martius. (*Muench. med. Wochenschr.*, No. 20, 1911.) Male, 39 years of age, with cerebral syphilis. Heart trouble since 1910. Clinically, an aortic insufficiency with compensation could be established. Intravenous injection of 0.5 gram salvarsan. Immediately thereafter indisposition and vomiting. Death five hours later in coma.

Autopsy: Marked hypertrophy of both ventricles, high-grade aortic insufficiency, aortitis syphilitica, diffuse myocarditis. Degeneration and necrosis of urinary tubules of both kidneys.

17. Case of Milian. (*Soc. med. des Hôp.* Meeting, Nov. 24, 1911.) Male, 60 years of age, obese, with unilateral paralysis and mitral insufficiency. Upon the express wish of the patient he was given an injection of 0.3 gram salvarsan. Thirty minutes after injection patient fell into coma, with rise of temperature. Death 36 hours later.

Autopsy: Acute edema of the brain. Dilatation of both ventricles.

18. Case of Dr. B. in B. (Martius). (*Muench. med. Wochenschr.*, No. 20, 1911.) Male, 35, strong, with pronounced paralysis. One-half hour after injection, while still in the physician's office, patient suffered from a severe attack of heart failure. With caffeine and ether patient was restored. Four hours after the injection—in the meanwhile the patient had been carried to his hotel—death came with symptoms of increasing weakness of the heart muscle.

Autopsy: Hypertrophy of the heart, nephritis, cirrhosis of the liver, cerebral hemorrhage, arteriosclerosis.

19. Case of Plehn. (*Deutsche med. Wochenschr.*, No. 2, 1911.) Male, 49 years of age, afflicted with cerebro-spinal syphilis since July, 1910. Previous treatment given elsewhere. Oct. 1st, symptoms of a paralysis of the legs, bladder and bowels. Disturbances of speech and mentality. Cystitis, convulsions. In spite of cachexia, bed-sores, and weak

pulse an injection of 0.5 gram salvarsan was given on Oct. 3rd. Death occurred next day.

Autopsy: Almost complete destruction of both kidneys by purulent processes.

20. Case of Ravaut. (*Soc. de Dermatolog. et Syphil.*, June 1st, 1911.) Male, 45 years of age. At time of examination had cancer of tongue. Presents picture of a very weak man. March 13th, 1911, patient received intravenous injection of 0.6 gram salvarsan. Well borne. On the 20th, a like dose. Fifteen days later patient died with symptoms of progressive cachexia.

Autopsy: Extensive cancer of the tongue. Nothing to show arsenical poisoning.

21. Case of Schottmueller. (*Muench. med. Wochenschr.*, No. 51, 1910.) Patient complained of severe painful tumor in the right upper abdominal quadrant. Upon exploratory laparotomy it was determined that the condition was due to syphilis of the liver. Wassermann +. Patient received 0.8 gram salvarsan in 100 c.cm. acid solution intravenously. At first well borne. The next day, 18 hours following injection, the patient died suddenly with symptoms of dyspnea and pulmonary edema.

Autopsy: Gummata of the liver. Slight interstitial nephritis.

22. Case of Stern. This case reported by Stern to the Congress of German Physicians in Karlsruhe, Sept., 1911, as following the use of a hyperalkaline solution of salvarsan.

23. Case of Treupel. (*Deutsche med. Wochenschr.*, No. 23, 1911.) Inveterate smoker, treated with mercury and iodide of potash without any results. Patient received two injections intravenously of 0.4 gram each. Two days after the last injection patient manifested great cerebral excitement, dying shortly after.

Autopsy: Well advanced degeneration of the posterior columns. Diffuse hemorrhagic pachymeningitis, with fresh hemorrhages and punctiform hemorrhages in the medulla. Aortitis syphilitica.

24. Case of Voerner. (*Monatshefte fuer prakt. Dermatolog.*, Bd. 53, No. 2, 1911.) Poorly nourished

smoker. Infected twenty years before. Internal organs without demonstrable lesions. Following request of patient given intravenous injection of 0.6 gram salvarsan. After the injection patient suffered from chills, headache, and vomiting. The next week the patient was again sick with vomiting. In urine, one percent. of albumin. Six weeks later, after a temporary improvement, patient again in bad condition. Again prostrated, with diarrhea and complete apathy. Spleen and liver swollen. Death.

Autopsy: Tuberculous foci throughout peritoneum. Also in spleen, liver and bowels. Swollen tuberculous glands in mediastinum. Adhesions in both pleural cavities.

25. Case of Queyrat. (*Bull. de la Soc. franc. de Dermatolog. et de Syphil.*, No. 1, 1912.) Male, 24 years of age, chancre for ten days. Oct. 21st, 0.6 gram of salvarsan injected intravenously. Urine free. Internal organs without abnormal findings. Injection caused no trouble. No headache. However, one-half hour later patient suddenly seized with prostration. Unconscious and stertorous breathing. In spite of ether injections and artificial respiration patient died in five minutes.

Autopsy: In the right kidney, on the forward inner surface is a broad effusion of blood, of the size of a fifty-cent piece. The entire organ has sustained severe hemorrhages. Microscopically in the glomerulus, between the straight and convoluted tubules, are to be seen widely dilated vessels. The epithelium of the convoluted tubules is detached; the lumen of the tubules in places entirely obliterated. The damage seems to be a diffuse, acute nephritis.

In the following cases, by reason of organs damaged by chronic alcoholism, syphilis or mercury, the system was unable to normally eliminate the administered salvarsan. The greater number of these cases were given the combined treatment. In Almkuist's case (No. 1) there was, indeed, an interval of four

months between the last employment of mercury and the salvarsan injection, yet we know through Moeller's observations (*) that renal damage following the administration of mercury may be weeks in manifesting itself, yes, even months. A point to be observed is the frequency with which chronic leptomeningitis is to be seen in connection with other latent degenerations of an alcoholic nature.

1. Case of Almkuist. (*Muench. med. Wochenschr.*, No. 34, 1911.) Male, 32 years of age, infected in 1905. Treated during a period of three years with eight courses of mercury (inunctions) and six or eight injections of grey oil. Since 1908 increase of difficulties. March 29th, 1910, fresh recurrences. Until Oct. 3, 1910, treated with salicylate of mercury injection and grey oil injections. Since the Wassermann reaction was still positive, Feb. 16, 1911, received an injection of 0.6 gram of salvarsan. Severe vomiting during the night. On the 18th, patient complained of headache and light chills. Three days after injection vomiting started in anew. In the evening patient lay in his room indifferent to surroundings. Face markedly cyanotic. Notwithstanding camphor injections patient remained unconscious, but, however, with slight improvement. On the fourth day pulse became irregular. Albumin and hyaline casts in urine. Difficult breathing. Stiffness and paralysis of the left arm. Coma. This state lasted for five days following the injection, then came a profuse perspiratory outbreak, loss of the corneal reflexes, tonic and clonic twitchings of the legs and arms, convulsions. Death on the sixth day.

Autopsy: Acute hemorrhagic encephalitis, chronic fibrous splenitis, chronic interstitial nephritis, swelling of the liver.

(*)On Mercurial Poisoning and Angina, particularly Stomatitis Ulcero-gangrenosa, together with the indications for and dose of grey oil. *Dermatol. Zeitschrift*, xviii, Nos. 2 and 3.

2. Case of Fischer. (*Muench. med. Wochenschr.*, No. 34, 1911.) Male, 40 years of age, with beginning maculo-papular eruption. For several days patient complained of headache, weariness and fever. Intravenous injection of 0.4 gram salvarsan; subsequent light vomiting and chills. On the following day there was a noticeable Herxheimer reaction, which, however, quickly disappeared. In conjunction with the above, patient given a course of 30 inunctions. Iodide of potassium not well borne. (*) Forty days after the first injection a second was given. Same dose. Again vomiting. On the morning of the third day following the injection, patient began suddenly to feel bad, became apathetic, refused to answer questions, soon out of his head. Then there followed a period of great excitement during which it was difficult to keep him in bed. Tonic convulsions and coma. The pulse became poor, temperature rose to 40 C. (104 Fahr.). On the fourth day after injection, death.

Autopsy: Parenchymatous degeneration of the liver and kidneys. Chronic leptomeningitis and acute encephalitis. Edema and swelling of the brain.

3. Case of Hammer. (*Muench. med. Wochenschr.*, No. 30, 1912.) Jan., 1911, patient showed a primary lesion on the prepuce. Wassermann +++. For this reason patient received on Jan. 17th, 0.6 gram salvarsan intravenously. Temperature rose to 39 C. (102 Fahr.). June 20th, roseolar rash appeared. Another injection of 0.6 gram salvarsan. Temperature to 38.4 C. (101 Fahr.). Patient then took a course of inunctions. In Nov., 1911, on account of an "eruption" patient took another course of 30 inunctions. In February, by reason of "hoarseness" took 12 more inunctions. March 23rd, 1912, papules on tonsils, leucoderma, laryngitis, papules on the laryngeal borders. On the 25th, 0.6 gram salvarsan borne without reaction. Then 18

(*) Frequently here is to be observed an idiosyncrasy against iodide of potash, together with interference with its elimination. The patient reacts with marked swelling of the lining membrane of the pharynx and larynx, which leads to difficulty of breathing.

inunctions. Then again 0.6 gram of salvarsan which at first was well borne, but two days later peculiar sensations in the ears were noticed. Temperature 38.1 C. (100.5 Fahr.). In the evening marked twitching with outbreak of perspiration. The following night vomiting, sleeplessness, three pronounced epileptiform attacks. In urine, albumin, hyaline casts, epithelial cells and blood corpuscles. April 15th, death.

Autopsy: Chronic leptomeningitis. Punctiform hemorrhages in brain. Chronic endarteritis. Cardiac hyperplasia.

4. Case of Kannengiezer. (*Muench. med. Wochenschr.*, No. 34, 1912.) Male, 29 years of age, infected in 1910. Treated with salicylate of mercury and one subcutaneous injection of salvarsan. April 6th, 1911, specific angina. Attacks of dizziness, paralysis of the lower fascial branches, difficulty of hearing. April 28th, intravenous injection of 0.5 gram of salvarsan. Immediately following a course of inunctions. May 10th, no phenomena except headache. May 11th, another injection of 0.5 gram. Well borne, but on following day headache. No albumin in urine. On the third day following injection patient seized with convulsions, together with clonic and tonic convulsive movements. Bloody foam appeared on lips, then loss of consciousness. Shortly following the attack patient became very restless; only with difficulty could he be kept in bed. Constantly he attempted to put his hand to his head. Failed to respond to external irritations. Profuse outbreak of perspiration. Venesection failed to give any relief. Patient fell in coma. On the 4th day temperature 38.8 C. (101.8 Fahr.). Stiffness of neck and cramps in arms. Evening temperature 39.3 C. (102.7 Fahr.). Clonic-tonic movements. Death on the fifth day following injection. (*)

(*) It is noteworthy that on the day of the injection, the inunctions had to be stopped on account of a severe stomatitis which is always accompanied by an insufficiency of the renal function, and therefore, is to be seen in uremia. The appearance of the tubular epithelium also points to damage by mercury.

Autopsy: Chronic leptomeningitis. Punctiform hemorrhages in the brain. Double pneumonia. Brown atrophy and degeneration of the heart and kidneys. Granular condition of the tubular epithelium.

5. Resembling the above is the case of Oltramare. (*Ann. des mal. vén.*, Vol. 6, page 881.) Generally speaking, the elimination of salvarsan may be interfered with by aortic stenosis. Male, 48 years of age, very corpulent, infected 15 years previously. Previously treated with injections of mercury. At the time without manifestations of syphilis. Heart and kidneys without change. Upon the expressed wish of the patient, 0.6 gram salvarsan was injected intravenously. Well borne. The following two days patient went about his duties. On the third day complained of light headache. On the fourth day he lay upon the floor like a dead man. On the fifth day in a state resembling coma, covered with perspiration, cyanotic face, slow pulse, accelerated breathing, always in a convulsive seizure. Temperature 40 C. (104 Fahr.). Death during the night.

Autopsy: Chronic leptomeningitis, stenosis of the ascending aorta, fatty degeneration of the heart, and chronic purulent bronchitis.

6. Case from Plojesti. (*Ehrlich's Discussions on Salvarsan*, vol. II, page 584.) Male, 35 years of ago, old syphilitic. One year previously an intravenous injection of 0.6 gram salvarsan has been well borne. Heavy drinker. Even on the day before the second injection indulged heavily in alcohol. Patient should have received 0.6 gram, but scarcely half the amount had been injected when he collapsed and died.

Autopsy: Pronounced heart, liver and renal changes of an alcoholic character.

7. Case of Dr. St. in D. (*Ehrlich's Discussions on Salvarsan*, Vol. II, page 587.) Male, aged 17, roseola and papules of the scrotum and tonsils. Treated with inunctions up to 4 grams each. On June 19th, received 0.3 gram salvarsan; fever and headache followed. July 3rd, 0.05 calomel injected. July 5th, sulphur bath. July 10th, 0.01 gram of calomel. July 14th, after the twenty-

seventh inunction received the second injection of 0.3 gram salvarsan. Following this patient suffered vomiting, chills, headache. On the following day also vomiting and headache. July 16th, status unchanged. At noon-time fainting spell. In the afternoon, stiffness of neck, noticeable trismus. Pulse 60. In the evening patient became confused. Died during the night.

Autopsy: Subpericardial hemorrhages. Hyperemia of the brain and coverings. Beginning fatty degeneration of the heart muscle. Sclerosis of the aorta. Hydrocephalus internus.

8. Case of Trembur. (*Ibid.*) Patient became infected Nov. 1st, 1911. Chancre appeared on shaft of penis on the 18th. One week later 0.6 gram salvarsan intravenously injected. Some vomiting, no fever. On the 26th, patient began a course of inunctions, 5.0 grams *per diem*. On Dec. 6th, mild gingivitis. Inunctions stopped. Dec. 8th, macular eruption on the buttocks. Dec. 9th, second intravenous injection of salvarsan administered. No reaction. Three days later patient became completely unconscious with tonic-clonic convulsions. Pulse regular. Stiffness of the neck. Picking at bed-clothes. Temperature 38 C. (100.5 Fahr.). Dec. 13th. Again loss of consciousness and clonic movements. Pronounced outbreak of perspiration. Picking at bed-clothes more marked. In the evening beginning edema of the lungs, cyanosis. On Dec. 14th, in the morning, death took place. Before death pulse dropped to 32 per minute.

Diagnosis: Meningitis, inferior poliocephalitis.

9. Case of Portner. (See text.)

10. Case of Lesser. (*Berliner klin. Wochenschr.*, No. 13, 1912, page 593.) Male, 39 years old, infected fifteen years before. Present symptoms point to a beginning tabes dorsalis. On Nov. 10th, 1911, received 0.5 gram salvarsan intravenously. Following this injection, vomiting and fever. Nov. 16th, 0.6 gram salvarsan injected. Also after this injection, fever, vomiting and diarrhea. On Nov. 21st, that is, five days after the last injection, epileptiform attack, coma in which patient died.

Autopsy: Leptomeningitis.

The following cases concern themselves with nephritis, in some instances of a toxic (mercurial) character, in others of a syphilitic nature. In some instances nitrogenous retention or uremic symptoms were noticed; in some anuria occurred (see cases cited in text); in others still the renal damage seemed to be of a mild character, or severe renal changes were found at autopsy, which were unsuspected during life because the urine was not examined with care.

1. Case from Berlin. (*Ehrlich's Discussions on Salvarsan*, Vol. II, page 576.) Male, 26 years of age, infected in August. On Sept. 28th, a typical roseola appeared on breast and back. Hypodermic injections of salicylate of mercury (0.5 gram). Stopped on disappearance of lesions about Oct. 28th. Nov. 10th, appearance of new lesions. Albumin in urine, strikingly large spleen. The albumin pointed to the character of renal lesion. Adopting the opinion that the splenic enlargement was of a syphilitic character, 0.6 gram salvarsan was intravenously injected Nov. 25th. Vomiting after injection. On the evening of Dec. 6th—11 days after the injection—complaints of headache. On the morning of the 7th, clonic convulsions with loss of consciousness. Deep unconsciousness, pronounced trismus. Temperature 39.5 C. (103 Fahr.). Death took place at noon.

Autopsy: Subacute parenchymatous nephritis. Acute encephalitis. Malignant granuloma of the lymph glands of the entire lower aorta and spleen.

2. Case of Caussade and Regnard. (*Bull. de la Soc. méd. des Hôp.* Session of Feb. 10th, 1911.) Male, 33 years of age, with nephritis and uremia. Emaciated and cachectic. Bedridden for three years. Despite various modes of treatment albumin remained at 9 grams *pro* litre; 5 grams nitrogenous retention in blood. Quantity of urine, 450 c.cm. *per diem*. One injection of 0.3 gram salvarsan had no influence on the course of the

disease. On the ninth day after injection the patient died of anuria.

Autopsy: Acute general, diffuse nephritis. Amyloid degeneration of the glomeruli.

3. Case of Ravaut and Bith. (*Journal méd. franc.*, No. 10, 1911.) Male, 40 years of age, infected in April, 1910. Two months later roseola and patches in mouth. In October papular eruption on buttocks and legs. At the same time mild albuminuria, which disappeared with milk diet. Soon, however, albumin newly makes its appearance, 15 to 18 grams *per diem*. General condition good. Passes between 2 and 2½ litres of urine daily. Notwithstanding energetic treatment with mercury, albuminuria remains unchanged. Jan. 5th, 1911, patient received 0.4 gram salvarsan which was well borne. It had no influence on quantity of urine or albumin. On the contrary, a slight edema of the ankles became noticeable. Jan. 9th, patient received 0.7 gram salvarsan intramuscularly. Immediately thereafter uremic delirium. The next day quantity of urine reduced to one litre which contained 5 grams NaCl and 8 grams nitrogen. Rapid increase of edema until it reached scrotum. Then followed headache, roaring noise in the ears, dyspnea, delirium, convulsions, uremia and death on Jan. 28th, under almost complete anuria.

4. Case of Wechselmann. (See text.)

5. Case of Gennerich. (*Praxis der Salvarsanbehandlung*, page 20, case 602.) Infected Jan., 1912. Chancre and secondaries disappear about the same time. From May 9th to June 7th, 1912, seven injections of calomel. After the fifth injection a stomatitis occurred, by reason of which the injections were stopped from May 25th to June 6th. At the same time some albumin in urine. June 3rd, 0.5 gram salvarsan intravenously. June 5th, 0.9 gram neosalvarsan, and on June 7th, 1.08 neosalvarsan. Seven hours after the third injection came fever, 38.5 C. (101.3 Fahr.), clearly a delayed reaction. Temperature normal next morning, and general condition somewhat improved. At four o'clock in the afternoon convulsions and loss of consciousness. Venesection, salt infusion

every three hours. Mental condition improved. On following morning repetition of the convulsions, cyanosis. Artificial breathing, etc. Death.

Autopsy: Pulmonary embolism. No essential changes in brain. High-grade parenchymatous degeneration of the renal epithelium in the convoluted tubules with extensive, far progressed nuclear necrosis. Gennerich classifies the case as one of toxic retention in consequence of renal insufficiency.

6. Case of Lugue Morata. (*Revista de Med. y Cirujica Practicas.* Feb. 28th, 1911.) Male, 21 years of age, infected two years before. Treated one year with mercury. At the time of examination patches in mouth and pharynx. Weight 43 kilograms. Internal organs without change. Urine normal. Jan. 31st, intravenous injection of 0.4 gram salvarsan. Three hours later vomiting, diarrhea, outbreak of perspiration. Pallid face. Dry mouth. Cyanotic lips. Pulse scarcely perceptible. Complete anuria. Catheter secures no urine from bladder. Delirium, coma, and on the third day following injection patient died.

7. Case of Busse-Merian. (*Muench. med. Wochenschr.*, No. 43, 1112.) Woman.) Condylomata and dirty ulcerations on the labia majora. As early as Oct., 1911, there was an ulcer on the genitals. Now followed a thirty-day course of inunctions, five grams each. Urine normal. The ulcers were now healing slowly. After quitting hospital patient began to suffer from pain in throat. Gargles of no avail. Genital ulceration again making its appearance. Marked reddening of the palate, the uvula and back portion of the mouth. Urine clear and free from albumin. Sp. Gr. 1014. On Aug. 19th, intravenous injection of 0.6 gram neosalvarsan. Well borne. On Aug. 27th, another injection of 0.6 gram neosalvarsan. On the 29th, light tremor, increased patellar reflex. On the 30th, tonic-clonic convulsive movements, loss of consciousness and cyanosis. On the 31st, coma and marked cyanosis. Died in the evening.

Autopsy: Extensive swelling of the epithelium of the convoluted tubules. The epithelium of the

glomerular capsule is partially swollen, thickened and dequamating.

8. Case Levi. (*Arch. d'Ophthalm.*, No. 1, 1911.) Weak male, inveterate smoker, with pyelonephritis. Intravenous injection of salvarsan. Death in three weeks. At autopsy nothing found to account for arsenical poisoning.

9. Case of Marcus. (*Muench. med. Wochenschr.*, No. 2, 1911.) Old, inveterate user of tobacco, with chronic diarrhea, cystitis and pyelonephritis. Death in three weeks following the injection.

10. Case of Neuhaus. (*Muench. med. Wochenschr.*, No. 18, 1911, page 955.) Poorly nourished, much reduced paralytic, with pyelonephritis; died of heart failure five days after an injection of 0.8 gram salvarsan.

11. Case Ravaut and Cain. (*Journal méd. franc.*, No. 10, 1911.) Male, 32 years of age, with pronounced tabes, and paralysis of both motor oculi, infected ten years before. Patient, who is weak, was formerly an alcoholic. Albumin in urine. Heart and lungs without change. Mercury employed without results. Upon patient's particular wish he received 0.6 gram salvarsan on March 13th. Well borne. Slight improvement of the paralysis of the motor oculi. Seven days later received another injection of 0.6 gram salvarsan. Four days later, the patient suddenly was seized with general convulsions; coma which lasted 13 hours. Death on the fifth day.

Autopsy: Acute edema and congestion of the lungs. Sclerotic gummatous changes in the liver, and marked changes in the liver cells. Sclerosis of the connective tissue and vessels of the kidneys. Hemorrhagic foci in the suprarenals. Hyperemia of the thyroid and pineal glands.

12. Case of Sciele. (*St. Petersburger med. Wochenschr.*, No. 33, 1911.) Patient with severe pyelitis died shortly after injection of salvarsan.

13. Case of Schlasberg. (*Dermatol. Zeitschrift.*, Oct., 1912.) Male, 47 years of age, with tertiary syphilis, chronic nephritis and pulmonary tuberculosis. In April, 1908, he was treated with seven injections of grey oil, each containing 0.1 gram

of mercury. Albumin and casts in urine. Sept. 12th, 1911, received an injection of 0.4 gram salvarsan intravenously. Following the injection patient experienced prostration, headache, temperature of 40 C. (104 Fahr.). Edema increasing daily. On the 20th day after injection the patient died.

Autopsy: Both kidneys enlarged. Chronic nephritis.

[This list contains twelve other cases but they are of similar character to those already given, and it is not thought necessary to publish them in this translation.—*Translator.*]

In the next four cases a combined treatment was employed. It is not clear just what deductions we are to draw from the deaths which took place after a second or later injection.

1. Case of Hallopeau. (*Bull de l'Acad. Méd.*, No. 61, 1911.) Male, 35 years of age, infected in 1902 with lues. First chancre, then roseola, mucous patches and now psoriasis palmaris and plantaris. Mercury and hektin without result. Injection of 0.3 gram salvarsan; five days later 0.4 gram. Soon after the second injection patient complained of dryness in the throat as well as an angina and congestion of the face. During the second night continued vomiting. On the third day patient suffered from oppression and had convulsions. Pulse good and regular, urine clear and abundant. The condition of the patient grow steadily worse. Several convulsive attacks, rolling of head and eyes, tonic and clonic twitching of the upper extremities. Temperature 40 C. (104 Fahr.). Death in deep coma.

2. Le Duigou. (*Bull et Mém. de la Soc. Méd. des Hôp.* Nov. 17th, 1911.) Male, 20 years of age, with secondary lues. Internal organs sound. Previously received 20 injections of hektargyr, also iodine pills. Manifestations again appeared four weeks after cessation of treatment. Patient then received three injections of 8 drops each of grey oil. Two weeks later injection of 0.4 gram

salvarsan. After the injection mild fever and vomiting, after which condition was good. A week later the second injection of 0.4 gram salvarsan. On the following two days patient complained of weariness and general feeling of distress. At the same time, diarrhea and palid face. On the third day following injection delirium and convulsiform attacks, vomiting of dark masses, and finally death occurred.

Autopsy: Pronounced congestion of all internal organs, especially the intestinal tract, the lungs, spleen and brain. In the brain in many places, punctiform hemorrhages.

3. Case of Klieneberger. (*Deutsche med. Wochenschr.*, No. 36, 1912, page 1691.) Waitress, 25 years of age. Six months pregnant. Maculo-papular eruption, large condylomata on vagina and anus. Wassermann positive. Inunction course, four grams daily; every seventh day an injection (0.1) of salicylate of mercury. On March 29th, 0.2 gram salvarsan intramuscularly; on April 3rd, 1.2 grams intravenously. Rapidly disappearing urticaria followed injection. A stomatitis recurred during the mercurial course. May 22nd, 0. 6 gram salvarsan intravenously. On the following day moderate indifference to surroundings and apyrexia. May 24th, tonic-clonic movements. Unconsciousness. Treatment for eclampsia according Stroganoff. On the 25th, deep coma, sterterous breathing. Lumbar puncture gave a clear fluid with low pressure. Lymphocytes and albumin. Death at midnight.

Autopsy: Extensive fresh soft areas on both sides in brain, also small hemorrhages in abundance. Hypostatic congestion in lungs just beginning.

4. Case of Dr. M. in C. (*Ehrlich's Discussion of Salvarsan*, Vol. II, page 588.) Male, 38 years of age, tertiary syphilis. Treated for a long period with mercury without results. Dec. 27th, 0.5 gram salvarsan intravenously. Eight days later 0.5 gram salvarsan again injected. Well borne. On the evening of the following day loss of consciousness. Lumbar puncture, salt infusion, camphor, etc. During the night epileptiform attacks, death.

1. Cases in which mercury was not given at the same time with the salvarsan and in which the urine remained free from albumin, and which, however, die after one or two injections of salvarsan, are but rarely encountered. In the text of this work I have analyzed the case of Balzer-Condat. In Pinkus' case the *status lymphaticus* could be considered as underlying the failure of elimination. In Ravaut's case oliguria seems to have been exhibited. In F. Lesser's case, leptomeningitis (see above).

1. Case of Pinkus. (*Dermatol. Zeitschrift*, Aug., 1912.) Girl, 19 years of age, infected when 14. At that time had a course of inunctions. Repeated in 1910. Nov. 29th, 1911, papules at vaginal entrance. Cervical gonorrhea. On the morning of Dec. 1st, she received 0.3 gram salvarsan intravenously. Headache followed injection. On the 6th, received second injection of 0.5 gram. Vomiting followed this injection. On the 7th, complained of abdominal pains (diseased adnexa). No albumin. On the evening of the 8th, she was seized with an acute delirious attack, with shrieking and manifestations of fear. Staring eyes, pupils respond promptly. Unconscious. Pulse strong, rapid. On the 9th, deep coma, convulsions, stringy pulse, camphorated oil. Temperature 41.5 C. (106.7 Fahr.). Heart attack. Camphorated oil again. Temperature 42 C. (107.6 Fahr.). Cheyne-Stokes breathing. Death.

Autopsy: Hyperemia of lungs. Internal organs without change. Many punctiform hemorrhages in the lenticular nucleus.

2. Case of Marschalks-Vesprzémy. Given in text.

The case of Spiethoff stands entirely by itself. The urine showed a marked sugar content in the presence of encephalitis hemorrhagica. The renal condition was not given.

Case of Spiethoff. (*Muench. med. Wochenschr.*, No. 21, 1912.) Male, 19 years of age, in primary stage. Wassermann negative. On Oct. 3rd, 1911, patient received an intravenous injection of 0.5 gram salvarsan in a weakly acid solution. On Oct. 10th, another injection of 0.5 gram. Both injections well borne, aside from moderate fever. Oct. 11th, patient felt well enough to leave the hospital. In the afternoon headache. On next day loss of consciousness, convulsions, poor pulse. In the evening patient returned to hospital. Tracheal breathing with the mouth open. Temperature 39.3 C. (102.7 Fahr.). Urine free from albumin, but Nylander strongly positive. Stiffness of neck, clonic movements. Foam appeared at lips. Lumbar puncture shows; pressure 180, no cellular increase, Nonne ++++. One-half hour after entrance of patient into hospital death occurred.

Autopsy: Edema of the spinal cord, especially in upper part. Nothing else of a pathological nature to be found either macro- or microscopically.

3. Now comes cases dying of acute yellow atrophy of the liver, in which the dependence of death upon salvarsan is highly suspicious. (See text.)

1. Case of Hirsch. (*Muench. med. Wochenschr.*, No. 33, 1911.) Woman, 23 years of age, broad condylomata of the labia majora, erosions, within vagina, inguinal adenitis, leucoderma colli. Dec. 29th, injection of 0.3 gram salvarsan; well borne. Then six injections each of 0.1 salicylate of mercury, and on Feb. 3rd, 1912, patient was given another injection of the mercurial salicylate. After two months, April 19th, the patient suddenly became unconscious, rigid, widely open pupils, convulsiveform twitchings of the entire musculature, slow tense pulse, considerable icterus. Death on April 20th, in coma.

Case of Hoffman. (*Muench. med. Wochenschr.*, No. 33, 1911.) Male, 15 years of age, with syphilitic iritis of the right eye. Wassermann and Stern

positive. Therefore a course of inunctions. During these inunctions there appeared an iritis of the left eye. No results from treatment with mercury; on the contrary, hot applications effected some good. On Feb. 21st, 1911, patient was given an injection of 0.3 gram salvarsan which was well borne. On Feb. 27th, given an intramuscular injection of 0.3 gram; also well borne. On April 8th, upon dismissal, a gastro-intestinal catarrh was discovered, on account of which patient was reentered. April 13th, an icterus developed with frequent vomiting, prostration and headache. These phenomena increased daily. Pulse 55; loss of consciousness; death on June 5th.

Autopsy: Acute yellow atrophy of the liver with moderate ascites.

3. Case of Lane. (*Bri. Med. Jour.*, Sept. 23rd, 1911.) Male, 29 years of age, malignant syphilis since 1909. Once during mercurial treatment did patient show improvement. Recurrences February, 1910 (ulcerations of both cheeks, lips and palate). February 22nd, received an injection of 0.5 salvarsan; shortly thereafter vomiting and coma. Two days later a pronounced icterus appeared, the patient taking on a brownish black color from head to foot. March 1st, delirious; died the following day.

4. Case of Rille. (*Muench. med. Wochenschr.*, No. 11, 1911.) Male, 23 years of age, secondary and tertiary syphilis on account of which received on Sept. 7th, 0.7 gram salvarsan. In November icterus and severe hemorrhages from the nose took place. Nov. 5th, death occurred, just as patient was about to be sent to hospital.

Autopsy: Acute cirrhosis, interstitial nephritis, fatty degeneration of the liver. Arsenic demonstrable in liver.

5. Case of Severin and Heinrischsdorff. (*Zeitschrift fuer klin. Med.*, Vol. 76, page 138.) Male, 30 years of age, acrobat. May, 1911, chancre, pigmentation, adenitis, angina. Wassermann +. One injection of mercury in olive oil, 15% (0.05 gram mercury). June 10th, intravenous injection of 0.6 gram salvarsan. Chills, diarrhea and vomiting. On the 14th, another injection of salvarsan.

Headache. August 11th, 0.6 gram salvarsan. Wassermann +. In evening mild icterus; next morning entire body yellow. Headache, loss of appetite, vomiting. In the urine, hyaline, granular casts, epithelial cells, no leucin or tyrosin. Liver enlarged, sensitive to pressure. Death on Sept. 6th.

Autopsy: Arsenic in liver; less so in spleen. Chronic yellow atrophy of the liver. Hemorrhages in endo- and pericardium. Hemorrhages in both lower lobes. Hyperemia and edema in both under and right upper lobes. Hemorrhages in stomach and bowels. Pronounced icterus of the kidneys. Chronic enlargement of the spleen.

6. Case of Severin and Heinrichsdorff. (*Ibid.*) Female, 29 years of age. Infected in 1909. Arsan, Iod. June, 1910, 72 grams of mercurial ointment. In Sept., 1910, the same. On account of persistence of luetic manifestations patient received 0.35 gram salvarsan intravenously on Dec. 1st. Headache, diarrhea, disappearance of the manifestations. Dec. 6th, 1910, 0.6 gram salvarsan and 1.5 indipin intramuscularly. Dec. 16th, 0.4 gram. Wassermann negative. Jan. 21st, 0.6 gram salvarsan intravenously. Beginning March 13th, and until May 2nd, four injections of mercury. June, 1911, pregnant. Swelling of the limbs, coughing. Instrumental abortion produced Sept. 10th, 1911. Vomiting, diarrhea, bloody mucous discharges from bowels. Icterus. Sept. 21st, received in the hospital with a high-grade icterus, ascites, etc. Urine: Albumin, bilirubin, abundant deeply yellow hyaline and granular casts, epithelial cells, but no tyrosin or leucin. Death Sept. 28th. In the liver only slightest traces of arsenic could be demontrated.

4. We now come to salvarsan fatalities which by reason of inexact observation possess no scientific worth. As a rule these patients had organic lesions.

1. Case of Bloch. (*Korrespondenzheit fuer Schweizer Aerzte*, No. 3, 1911.) Patient with advanced cirrhosis of the liver and severe circulatory

disturbances, died shortly after an intramuscular injection of salvarsan in neutral suspension.

2. Case from London. Male, 47 years old, inveterate smoker, markedly cachetic. Intramuscular injection of 0.5 gram salvarsan. Condition grew worse until death. Nothing of exactness determined.

3. Case of E. Frank. (*Berliner klin. Wochenschr.*, No. 31, 1911.) Male, infected fifteen years previously, suffered for two years from mental weakness. At times excited, at times depressed. Wassermann of blood and cerebro-spinal fluid positive. Oct. 15th, injection of 0.3 gram salvarsan. Memory for certain things rapidly improved. Ten days later another injection of 0.3 gram. Wassermann negative. Five weeks later patient died suddenly in coma. Wassermann had again become positive.

Autopsy: Several indistinct lesions adjacent to the vessels of the cortex.

4. Case of Gaucher. (Mentioned by Lesser, *Berliner klin. Wochenschr.*, No. 13, 1912, page 593.) Male, 48 years old, infected for fifteen years. Aug. 17th, 1911, received an intravenous injection of 0.6 gram salvarsan. On Aug. 21st, after preceding vomiting and prostration, occurrence of convulsions and loss of consciousness. Coma. Death on the 22nd, five days after the injection.

Autopsy: Leptomeningitis.

5. Case of Gaucher. (*Bull. de l'Acad. méd.*, Feb. 6, 1912.) Male, 24 years of age, treated with mercurial pills. Infected two years previously. Following professional advice patient received in Paris in a period of thirteen days, three injections of salvarsan, each 0.3 gram. After each injection vomiting and fever. On the sixth day after the last injection became seized with convulsive attacks which followed severe headache. These repeated themselves. Patient fell into coma and on the seventh day after the last injection, immediately after a transitory improvement, death occurred.

6. Case of Guilain and Ravant. (*Bull. de la Soc. Méd. des Hôp.*, Nov. 4th, 1910.) Woman, 28 years of age, secondary syphilis and hemiplegia.

Injection of 0.45 gram salvarsan without any result. Death in seven days.

Autopsy: Small, soft foci in brain.

7. Case of Dr. H. in B. (Martius). (*Muench. med. Wochenschr.*, No. 20, 1911.) Male, 41 years of age, infected 13 years before. Since April, 1910, pronounced paralysis. In obedience to the afflicted man's wish, he was given an injection of salvarsan. Thereafter slight improvement. Oct. 19th, 1910, further complicated by a pneumonia. Death the next day in consequence of heart weakness.

Autopsy: Hypertrophy of the heart, croupous pneumonia (lower lobes).

8 to 10. Cases of Hamel. (*Verein deutscher Naturforscher und Aerzte*, Koenigsberg.

8. Aortitis syphilitica and aortic aneurysm. Death in three weeks.

9. Severe myelitis ascending. Death in six days.

10. Luetic meningitis. Death shortly after injection.

[Since it is not believed that the inclusion here of the remaining 27 cases of this group would serve any distinct purpose, they are omitted.—*Translator.*]

The following are cases of very severe infections or of serious chronic illnesses. It is not possible to charge salvarsan with being the cause of death in these instances.

1. Case of Dind. (*Revue Méd. de la Suisse K romande*, No. 1, 1912.) Patient had large lymphosarcoma. Death fifteen days after injection of 0.4 gram salvarsan with edema of the tongue and larnyx.

2. Case of Iverson. (Iverson, *Discussion on Salvarsan*, page 342.) Woman, alcoholic, hysterical, suffering from recurring fever, treated fifteen years previously with mercury. She received 0.3 gram salvarsan intramuscularly. Fourteen hours later the spirochetes which at first were found in the blood in abundance, had disappeared. On the fourth day the temperature, hitherto nor-

mal, rose to 38 C. (100.4 Fahr.). At the same time patient appeared to have a double-sided broncho-pneumonia. On the head there was a hemorrhagic eruption which at first resembled that of scarlet fever. Later there appeared acute nephritis, edema of the upper part of the body, swelling of the liver and hemorrhages into the skin, which the reporter looked upon as a condition of idiosyncrasy.

Autopsy: Marked, well advanced general arteriosclerosis, myocarditis, fatty liver, and other pronounced changes of the vital ograns.

3. Case of Leede. (*Muench. med. Wochenschr.*, No. 22, 1911, page 1185.) Patient showed 40% hemoglobin, red blood corpuscles 1,400,000. Patient had worked up to within a short time of admission. He received an intragluteal injection of 0.4 gram salvarsan. Minimal rise of temperature. During the next two weeks became worse—hemoglobin 25%, red blood corpuscles 900,000. With this came dizziness, buzzing in ears, vomiting and rapid decline. Treated with iron-arsenical combinations and fresh air with result that in three months hemoglobin reached 80%. He was thereupon dismissed. In four months recidives, hemoglobin 50%. At this juncture patient received 0.5 gram salvarsan. Thereafter followed striking declension with death in 20 oays.

No autopsy.

4. Case of Moutot. (*Thèse de Chevalier-Seyvet*, page 42, Lyons; 1911.) Woman with epithelioma of the tongue. Operated on Feb. 2nd, 1910. Recurrence. On Feb. 11th, intravenous injection of 0.6 gram salvarsan in alkaline solution. The next day patient complained of dryness in throat. The 17th, hemorrhage and death.

5. 6. Cases seen by Schreyer in Tien Tsin, China. Suffering from tuberculosis, both quickly died following the injection. The reporter attributed death in a measure as due to the drug.

7. Case of von Tordey. (Dreyfus, page 11.) Female with severe, hopeless anemia and tumor of the spleen, received an injection of 0.3 gram subscapularly. After slight improvement patient

became worse and died on the ninth day following injection. Patient was very cachetic.

Autopsy: Splenomegaly.

8. Case of Treupel and Levi. (*Muench. med. Wochenschr.*, No. 5, 1911.) Girl, 15 years of age, tumor of the brain and hydrocephalus internus. No symptoms of lues. Wassermann negative. In deference to the wishes of the parents and the physician in charge, she was given an intramuscular injection of 0.5 gram. At first well borne. After three weeks died suddenly as a consequence of paralysis of respiration.

Autopsy: Glioma cerebelli; hydrocephalus internus.

9. Case of Tscherne-Schwartz and Halpern. (*Roussky Vratsch*, Mar., 1912.) Death took place three hours after intravenous injection of 0.35 gram. Patient had typhoid fever. Death resulted from heart failure following transitory convulsions.

10. Case of Tuchinsky. (*Roussky Vratsch*, March, 1911.) Death occurred six hours after an intravenous injection of 0.5 gram salvarsan in the case of a malarial patient. Death due to heart paralysis. At autopsy, acute nephritis.

From the literature of reported cases of deaths, one can see that such fatalities form a variegated group without showing a distinct type. In only the smallest number of these cases can death be attributed directly to salvarsan. The marked differences in the clinical pictures of fatal cases, among which encephalitis hemorrhagica is a frequent type, show that salvarsan, insofar as the greater number of cases are concerned, is but an indeterminate factor and not a distinct cause of death. Thus no uniform explanation fitting all cases can be given. A glance at the reports of fatalities is sufficient to show how recklessly salvarsan

was employed at first, and it is certain that many of the fatalities could have been avoided.

I am well aware of the fact that this presentation is not without defects, and that I had to use a wide variety of conclusions and deductions. But in view of the eminently practical lessons taught by the fatal cases, and in spite of obvious defects, I consider it my duty to offer these observations in order to impress upon those using salvarsan the need for greater precautions.

These precautions are:

1. The most exact technique.
2. A dose of the drug carefully adapted to the individual case.
3. Careful observation of the urinary secretion when employing salvarsan; resorting to the most exact chemical and microscopical examination of the urine. *This holds good particularly when the combined treatment is employed.*
4. The conjoint use of salvarsan with heavy mercurial treatment is dangerous! If one will use the combined treatment, then give mercury very carefully many days after the last salvarsan injection, but never reverse this rule!
5. Take into careful consideration every general reaction or rise of temperature, following the use of salvarsan, and make a full investigation of the causes of such effect.

Only by close obedience to the above will it be possible to begin the more refined, scientific investigation of apparently so simple, but in reality highly complicated, an occurrence as a salvarsan fatality.