PERSONAL OBSERVATIONS ON THE INTRAVENOUS METHOD OF ADMINISTERING SALVARSAN.*

By J. L. KIRBY-SMITH, M.D.,
Jacksonville, Fla.

From the very beginning of the use of Salvarsan, better known as "606," Prof. Erlich strongly advocated the intravenous method of administration in his communications to the profession. At the time he presented the drug to us for use in the treatment of syphilis, his plea was for this method to be used exclusively, knowing that intravenous injections by those of experience was not entirely free from danger to the patient, not from the drug *per se*, but from faulty technique of the operator. He expressed himself as though he expected the drug to be used by those especially trained for such procedures, thereby minimizing the unpleasant or fatal results.

For a while in this country very few intravenous injections of Salvarsan were given, due mostly to reported dangers of this large dose of an unstable arsenical preparation, and to the complicated details of the original technique as was first given for this mode of administration. As a result the profession as a whole used the method of Alt and Wechsleman (neutral suspension) and the "clear alkaline solution," also the "emulsion in divided doses," though a few workers cautiously used intravenous injections. After a few months of general use, the former methods have proven to be somewhat disappointing in their results, or at least to be very inferior to the intravenous method; especially was this true of the "neutral suspension method," as devised by Alt and Wechsleman. At the present time all of the above methods have been practically superseded by the intravenous injections. From my experience with all three methods and from observing the clinical reports of other workers in the field of venereal disease, I think this change is fully warranted, and I shall try in this paper to bring before

your attention the disadvantages of the subcutaneous and intramuscular methods, also the advantages and contra-indications for the intravenous administration, and try to show why the latter technique is superior to the former.

Those of you who have had occasion to use Salvarsan, and gave the drug by the subcutaneous or intramuscular routes, can testify to the pain and local reaction both at the time of the injection and at a later period; also as to the difficulties in the actual preparation of the drug for injection, especially so in the neutral suspension method for subcutaneous injection. Then, too, no doubt some have seen the unpleasant after-effects at the site of injection, i. e., persistent induration and tumefaction, at times necrosis and suppuration, and the resulting slow repairing ulcer, these sequelae sometimes following even after the most painstaking efforts at asepsis in the preparation of the drug and the patient for the injection, showing to what extent the tissue is irritated by the Salvarsan. I find from my notes on forty injections of Salvarsan by the subcutaneous and intramuscular methods, given in the early part of the past year, that 50 per cent were followed by unpleasant after-effects at the site of the injection, varying from simple induration to necrosis and suppuration. The first twelve cases were reported in a paper read before the Duval County Medical Society in March, 1911. Of these cases three were followed by necrosis and suppuration—two had painful indurated masses at the site of the injection, which later had to be dissected out—one three months after the injection and the other four months. Both of these cases were treated by the Alt and Wechsleman method (the neutral suspension). The encysted mass that was removed when opened was found to

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contain a yellowish like fluid very similar to the emulsion that was injected several months previous, and showed the presence of arsenic and no bacteria. In both of these cases there was primary lesion of syphilis and well developed secondaries, which promptly disappeared a few days after the injection. One of these five months later had recurrences of secondaries and was given another injection, intravenously, at the Johns Hopkins Hospital in Baltimore—the other had recurrences before the indurated mass was removed, with two intravenous injections of Salvarsan in the course of two weeks' time. The patient has now remained free from any recurrences or symptoms of syphilis for a year, and during that time two serological examinations made were negative.

In a November number of the New York Medical Journal, Dr. F. P. Hoover, of Jacksonville, in an article reporting "Ear Troubles Following 606," gives the history of two patients treated by me, with another case, making three in all, which he reports as probable ear conditions due to Salvarsan—two were otitis media, and the other some disturbance of the internal ear, a possible irritation of the auditory nerve. All of these cases had received subcutaneous injections of a neutral suspension. One of these had already been mentioned as having had a painful indurated mass at the site of the injection, which later, on account of the pain and discomfort complained of, was dissected out. In this case after an intravenous injection of Salvarsan the otitis media rapidly subsided and the patient's hearing became normal. The case of otitis media Dr. Hoover reports as slowly improving after a few weeks. This case did not receive a second injection. In the case of the disturbance of the internal ear no appreciable effect has been seen in the patient's hearing even after two intravenous injections. It is now sixteen months since the patient first exhibited hearing disturbances. He is practically deaf in both ears. I might mention at this point that the patient only received a small dose of

Salvarsan, not more than 6 grains. At the time of the injection the needle became plugged, and only about half of the suspension was injected, and the patient now has a hard encysted mass at the site of the injection. However, there was a rapid disappearance of a bilateral iritis and papulo-pustular syphiloderms. In this case, as in all three, the symptoms of ear troubles came on several weeks after the injection and there is ground for discussion in all three cases. Was the condition brought on by the Salvarsan or was it a syphilitic process? Certainly it is impossible to state definitely, but by the rapid improvement in the cases of otitis media after the second injection the evidence is in favor of the latter supposition, while in the case of the disturbance of the internal ear, in which no appreciable improvement followed the two injections, the condition no doubt was due to the Salvarsan either directly or indirectly, or to certain changes that the drug undergoes when given by the subcutaneous or intramuscular methods. At this point I will say a few words about the preparation of the patient for the treatment, and the simplified technique that is used at the present time for the administration of Salvarsan. As the title of this paper shows, I am presenting my own observations in the use of the drug, and such being the case, you will notice an absence of references to the report of other workers in the field of syphilology. I trust, though, that some of you present will be able to bear out with me from your own experiences with Salvarsan the remarks that I will make.

In every case before giving an intravenous injection of salvarsan, it is necessary to make a thorough physical examination of the patient, especially to ascertain if there is an existing nephritis or organic disease of the heart. If such should be found, the injection should only be given at the patient's own risk. Certainly there is a decided danger of fatal complications, even with the most skilled administration of the drug. Nevertheless, in some cases in which the presumptive evidence of

the diseased condition of the heart or kidneys is due to syphilis, the case will warrant the risk. During the past year I have had only three syphilitic patients whom I thought best not to treat by intravenous injections owing to organic diseases of the heart or kidney. One was an advanced case of Bright's disease, which originated before the luetic infection—the other two had valvular lesions of the heart. One of these cases was a man of 64 years with an initial lesion. All three of these patients did not care to take the risk of the treatment, so reliance had to be placed in mercurial treatment. I am in the habit of having patients report to my office for the injection without having had anything to eat for several hours, also having ordered a cathartic beforehand. I have found that by this there will be less immediate unpleasant after-effects from the Salvarsan.

When first using the intravenous method of injections a number of difficulties were met, both as to the working of the apparatus, and the preparation of the drug for injection, but more particularly so in the actual administration of the drug. Like everything else in medicine and surgery, one has to learn from experience, more particularly so from one's own experience. Certainly this applies to my own case. For a while I used an apparatus devised by Thessico, which consisted of a rather complicated pumping arrangement. After two injections, I found this affair to be very unnecessary. The next procedure was the using of two infusion bottles, one for the salt and the other for the Salvarsan solution tubes from these connected to a three-way cock, and the fluid allowed to flow through the needle by gravity. This proved to be very unsatisfactory. At the present time I use only one bottle, and instead of allowing for gravity, use a rubber hand bulb attached to the mouth of the bottle to increase the pressure so that the fluid will flow in more rapidly. The question of dissecting up the vein for injection after four trials was given up as being entirely unnecessary. In the preparation of

the solution for injection too much care cannot be taken. I am sure that success in the giving of Salvarsan intravenously has been due to the careful preparation of the solution, using only distilled sterile water for the salt solution, in every case making a fresh salt solution at the time of the injection, always filtering and boiling. By so doing you will always be able to get the Salvarsan into a clear solution, 6 per cent salt solution used. Then, too, you must have a hot solution for the dissolving of the Salvarsan. This is very essential. Having a five-foot rubber tube connected with the infusion bottle and the needle, I have found that the solution should be 110-115 F.: with the room temperature at about 75 F., the temperature for the solution as it enters the vein will be around 100 F. Should the thermometer at the needle register below this, hot salt solution should be added to the infusion bottle. Any solution below 100 F. temperature increases the unpleasant immediate after-effect, vomiting, chill and fever. Another essential to the proper preparation of Salvarsan solution for intravenous injection is the sodium hydroxide solution. Always have this freshly prepared 15 per cent solution, distilled water used for the solution filtered and boiled.

I have not kept a record of the number of doses of Salvarsan I have had to throw aside through some error in the making of the solution, or to some peculiar characteristic of the drug itself. Certainly the number will reach twenty-five, mostly happening in the first few months of using the drug, but with careful attention to the details of the preparation of the solution, I rarely now meet with any difficulties in making a clear solution. The technique of introducing the needle into the vein is a very simple one, but in doing so, even with considerable experience, one often meets with difficulties. First of all it is absolutely essential to have a sharp needle, one that is free from any rust or corrosion. If such is not the case, the chances are that you will have trouble penetrating the vein.

As to the amount of Salvarsan for each

injection the dose was varied from 4 to 15 grains, depending on the age, sex and severity of the infection: as an average in the 300 injections 10 grains were used. The amount of Salvarsan solution used in the injection varied from 300 to 100 cc, depending on the condition of the patient's heart and circulation. I am in the habit of ascertaining the blood pressure of the patient before treatment. Should this be below 100 or above 140 the amount of salt solution would be increased or reduced accordingly.

No mention has as yet been made of the constitutional reactions following an intravenous injection of Salvarsan. This furnishes one with material for considerable reflection. First might be considered the immediate symptoms, those that follow from a few minutes to several hours after the treatment, the most prominent of which are the chill, usually preceded by nausea or vomiting, headache, occasionally intestinal cramps with diarrhoea and in most cases elevation of temperature, often as much as 104 degrees. The later symptoms that occur after the first day are slight vertigo, headache, at times constipation, a general malaise, which occasionally persists for several days. Too much attention cannot be given to daily examination of the patient's urine for albumin, as it is on the kidneys that the work of excretion of this arsenical preparation is placed. In all cases the urine becomes high colored and very frequently an albuminuria is noticed, which may persist for weeks. It is very important to have the patient on very light diet for several days following the injection: the frequent drinking of water and saline laxatives add to the rapidity of elimination. Arsenic is present in the urine a few hours after the injection and continues present for several days.

In respect to the constitutional reactions taken as a whole, I have found that they largely depend on the severity of the infection. A patient with well developed secondaries will in every case show marked reactions, i. e.,

chill, nausea, at times vomiting, while another with no active symptoms of the disease, will possibly escape any unpleasant after-effects. This I have observed from the very first in the use of Salvarsan.

For months hardly an issue of a medical journal has been free from reports on Salvarsan; hundreds, even thousands, of monographs have appeared dealing with all phases of this wonderful drug. Since Salvarsan has been used by the profession for over a year, one can now note more balanced or absence of hysterical reports on the effects of Salvarsan. In fact, the remedy is an accepted specific for syphilis, and by the gradual perfection of the technique of administration one hears very little of the dangers of the use of the drug. To some extent this is due to the fact that in every community there is some one who has given more or less study to the administration of the drug, and accordingly has reached a certain degree of perfection in that line of work, thereby reducing to the minimum the supposed to be dangers of the drug. This is, as I mentioned at the beginning of this report, what Prof. Ehrlich desired. At the present day intravenous injections of Salvarsan are given in one's office, the patient allowed to go home, and within twenty-four to thirty-six hours permitted to return to his work, this, though, depending on the severity of the infection. During the past sixteen months I have given 300 intravenous injections of Salvarsan to 133 syphilitic patients, as follows: Sixty-seven given two injections, 50 three injections, and 16 one injection each. Of this number 13 had primary lesions only, 60 with secondary, 20 tertiary or late secondary syphiloderms, 4 lesions of the nervous system, 30 with no active symptom but positive Wasserman, 4 no active symptoms and negative serological report though positive history of former infection and vigorous treatment with mercury for several years, 2 hereditary syphilis. Of the 133 syphilitic patients treated with Salvarsan, 85 were given mercury between injections and 28 had

already been under mercurial treatment for periods varying from 2 to 6 or more years; the remaining 20 received only Salvarsan injections; of these 12 were given three intravenous injections in three months, 8 two injections in two weeks' time. Those of you who have had much experience with venereal patients, especially syphilitics, appreciate the difficulties in keeping up with your patient; particularly is this true when you have relieved him of the immediate discomfort of his disease and you may have been so unwise as to have allowed him some credit. By these irregularities it has made it impossible to follow the results in forty patients. In all I have had only six patients to return with recurrences; all of these cases had only received one injection and had had no mercurial treatment, five had been given treatment in the primary stages of the infection and the other had well developed secondaries. In late secondary or tertiary ulcerations I have not had a single recurrence of the condition after two intravenous injections; true, most of the patients were given a vigorous mercurial treatment as well. Three cases of locomotor ataxia are included under syphilis of the nervous system; two were given two intravenous injections without any appreciable effect on the disease, both showing marked improvement in their general health. Both of these cases were well advanced. The third case of tabes treated was markedly improved by Salvarsan; the disease was of only a few months' duration.

Before passing on to a general summary of the subject of Salvarsan, a few words as to reported dangers, or reported accidents following the use of the drug: Deafness, blindness, Bright's disease and even death are some of the important sequelae that a few practitioners tell their patients will follow treatment by "606." I know of only one death reported in Florida from the use of Salvarsan, and in this case I would be willing to wager my license that the death was not due to the drug *per se*, as I understand the patient had a cerebral

tumor of probably syphilitic origin, and no doubt there were other complications which made the treatment contraindicated. I have had one case of nephritis following an attempted intravenous injection; the patient in question was referred to me for treatment for tertiary syphilis. At the time I had given two intravenous injections, and the technique used was very crude, the apparatus used being the "pumping arrangement." Hardly two grains of Salvarsan were given. As the physician referring the patient vouched for the physical condition, no urinalysis was made before the injection was given, hence it is more than probable that the kidneys were already involved. Be it as it may, immediately after the treatment, or within twenty-four hours, the patient exhibited symptoms of nephritis, the urinalysis showed a paraneuritic nephritis.

The advantages from treatment of syphilis by intravenous injections of Salvarsan are many. Certainly the wonderful results that we get completely overshadow that from the old treatment. The patient feels the effect of the medicine within twenty-four hours, active lesions disappear in a few days, danger of transmission of the infection to others that he might come in contact with is promptly overcome. True, you can get this by mercurial treatment, but at the expense of time and great inconvenience to the patient, and no matter how carefully you may watch your patient, there is a constant danger of producing mercurialism. From my observation in the treatment of luetic patients there is not the slightest room for comparison of the two drugs in the cure of syphilis, and there is not the slightest doubt in my mind that Salvarsan is the specific for the infection, the result not obtained by one or two injections, but several during the first year of the infection. At the present day the accepted plan of treatment is to follow out the above, with the additional mercurial treatment between injections of Salvarsan, either giving injection of mercury or using inunctions. Too much stress cannot be laid on the

importance of serological examination after the completion of the treatment, and at intervals of six months for two years.

Before closing, I wish to express my ap-

preciation to the physicians throughout the State, and more especially of Duval County, for the courtesy of referring to me syphilitic patients, which has made this report possible.

PAIN IN THE ABDOMEN AND ITS SIGNIFICANCE.*

By P. C. PERRY, M.D.,
Jacksonville, Fla.

It is impossible for the writer to take up all of the diagnostic points in connection with this subject, due to the length of same. To clearly understand why pain is present in the abdomen, it is but right that we should consider the nerve supply of the abdomen and its viscera, as of the first consideration. The principal nerve supplies are the epigastric or solar plexus, the hypogastric plexus, and the pelvic or sacral plexus.

The epigastric or solar plexus supplies all the viscera in the abdominal cavity. It consists of a great network of nerves and ganglia, situated behind the pancreas and the lesser peritoneal cavity and in front of the aorta and crura of the diaphragm. It surrounds the coeliac axis and root of the mesenteric artery, extending downward as low as the pancreas and outward to the supra renal capsules. This plexus and the ganglia connected with it, receive the great, the small and the least splanchnic nerves of both sides, and some filaments from the right pneumogastric nerve. It distributes filaments which accompany, under the use of plexuses, all the branches from the front of the abdominal aorta.

Of the ganglia of which the solar plexus is partly composed, the principal are the two semilunar ganglia, which are situated one on each side of the plexus and are the largest ganglia in the body.

From the epigastric or solar plexus, are derived the following: the phrenic; the suprarenal, the renal, the spermatic, the superior mes-

enteric, the aortic, and the coeliac. The coeliac plexus has three divisions; the gastric, the splenic and the hepatic.

The hypogastric plexus supplies the viscera of the pelvic cavity. It is situated in front of the promontory of the sacrum, between the two common iliac arteries, and is formed by the union of numerous filaments, which descend on each side from the abdominal aortic plexus and from the lumbar ganglia. This plexus contains no evident ganglia. It bifurcates below into two lateral portions, which form the pelvic plexuses.

The pelvic plexus, or sacral plexus, sometimes called the inferior hypogastric, supplies the viscera of the pelvic cavity and is situated at the side of the rectum in the male and at the side of the rectum and vagina in the female. It is formed by a continuation of the hypogastric plexus, by branches from the second, third and fourth sacral nerves, and by a few filaments from the first two sacral ganglia. At the point of junction of these nerves small ganglia are found. From this plexus numerous branches are distributed to all the viscera of the pelvis. They accompany the branches of the internal iliac artery.

I will first consider the pathological conditions that are present in the abdomen and that are the cause for 80 per cent or more, of the pain within the abdomen. Of these, ulcers of the stomach; ulcers of the abdomen or the pyloric end; inflammation of the gall bladder and of the duct of the liver; together with

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