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Original Articles.

REVIEW OF UNTOWARD EFFECTS FOLLOWING ARSPHENAMINE AND ITS DERIVATIVES.

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Now that it is about ten years since salvarsan was first introduced, it would seem that, though it is still too early to say much about how far we have progressed in the cure of syphilis, we should, nevertheless, be able to tell what untoward effects may follow its use.

In the first place, what is the normal reaction following its use? Usually there is nothing or only a slight malaise with nausea for a few hours. Nearly half the patients show a moderate fever on the day of injection with phenomena due to dilatation of the capillaries, a direct action of arsenic, showing flushing of the face, occasionally slight edema of the lids or lips, chilly sensations, more or less marked, often followed by sweating, occasionally profuse; fairly often nausea and slight headache. There may be vomiting once or twice, or even repeated during the night, with severe headache and marked congestion of the conjunctivae. If active le-

sions are present, there is often a temporary exaggeration of these, the Herxheimer reaction. Formerly these general symptoms were regarded as due in large part to impurities in the water, but during the war the water used was frequently not freshly distilled and so long as it was fairly fresh and absolutely sterile, it did not seem to cause a great deal more reaction. As these symptoms are far more common in those having active lesions at the time, it seems that very likely they are a sort of a general Herxheimer reaction and Gobeau¹ thinks that this is so frequently the case that the immediate reaction means considerable as regards present activity of the disease. On the other hand, these are all symptoms described in the pharmacology of arsenic and it would seem that most of the reactions could be ascribed to toxic effects of the latter, in a large number of cases, with the impurities of the water and the generalized Herxheimer reaction as contributory factors. The varying personal idiosyncrasies toward the drug would account for the freedom of some people from the reactions and the affections of others. Then, too, it is quite noticeable that, in some cases, the reactions are increased by inability of the patient to eliminate the drug through disease of the liver and kidneys, especially the latter.

These normal reactions last a few hours, not

more than ten or twelve or at the very most twenty-four. If the fever lasts longer than this it is a sign of intolerance. Another type of fever showing intolerance on the part of the patient is that appearing from the second to the sixth day, usually after the patient has had several previous doses of the drug. It is also seen after mercury and if the patient has had both we distinguish those due to mercury by other signs of mercury poisoning, such as the metallic taste, salivation, fetid odor of breath and soreness of the gums. When due to the arsphenamine, the fever is often accompanied by other signs, such as severe vomiting and headache, urticarial lesions at site of injection or elsewhere on the body, or a general erythematous rash, edema of the face and hands and feet and pains in the bones or joints. This fever generally reaches 102 or 103° F., or even higher, and instead of falling at once as in the normal reaction, remains elevated for three or four days or longer, falling by lysis. This is always a sign of intolerance and the drug should either be suspended for a time or entirely interrupted.

The skin manifestations usually appear eight to ten days after the injection of arsphenamine, though they may appear immediately. The outbreak is usually accompanied by considerable fever, headache and general malaise, with occasional vomiting. Urticarial, scarlatiniform and morbilliform rashes and, occasionally herpes labialis and even herpes zoster have been described. These all last three to six days. Those resembling measles and scarlet fever are followed by desquamation. A more serious skin complication is dermatitis exfoliativa. One case seen lately shows the milder form of this:

Mrs. H., aged 58, housewife. Diagnosis: Tabes. Wassermann reaction on blood and spinal fluid strongly positive. Cell count 75. Globulin positive. Given six doses of diarsenol (0.4 to 0.6) at intervals of one to two weeks. Severe, prolonged reaction following each dose, especially the later ones. No mercury given. Fourteen days after last dose general, intense redness of skin with beginning scaling. In places oozing and crusting, especially where surface has been rubbed. Followed by lamellar desquamation of entire surface, including palms and soles, which was completed about the seventeenth day. Considerable edema of face and of forearms and lower legs at start with marked congestion of conjunctivae. Mucous membranes normal except for some fissuring and scaling of

lips. Urine showed no albumin or sugar at any time.

Following is a case from the skin service at the Boston City Hospital, reported through the kindness of Dr. T. W. Thorndike, with post-mortem findings quoted through the courtesy of the medical examiner, Dr. T. W. Leary.

G. S. Male. Aged 36. Blacksmith. Admitted to hospital July 8, 1919. History of chancre three months previously with positive Wassermann reaction. Treated by private physician with mercury pills and five doses of arsphenamine (dose and variety of drug not ascertained) during a period of four weeks. Last dose eight days before entrance to hospital. Present condition started five days after last injection. On entrance showed general erythema with profuse scaling, oozing and crusting in places. Edema of face and extremities. Process soon involved mouth, with swollen and bleeding gums and inability to take nourishment. Rather rapid loss of strength and emaciation. Urine showed slightest possible trace of albumin at entrance, which soon disappeared. Temperature normal for first few days. Slight watery discharge from both ears at entrance, which persisted. Malnutrition increased. Septic temperature and cough developed and patient died four weeks after onset of rash. Postmortem showed double otitis media, broncho-pneumonia and practically nothing else.

Another skin condition which has been described is melanosis. Generally after the last of a course of injections the patient has had an erythematous rash followed by desquamation which latter persisted for some time and was accompanied by a general bronzing of the skin of the entire surface. In several cases reported there was also a keratosis of the palms and soles, in one of them markedly warty, such as seen in chronic arsenic poisoning. One case of this observed in my practice was a woman, Mrs. J. P., aged 38, who had had a gumma of the liver removed some seven years previously and had lately developed lichen planus, for which she had received considerable arsenic in the form of Fowler's solution. Shortly after receiving salvarsan, 0.6 g., without rash or symptoms of malaise, the skin gradually turned dark, especially about the folds of the axillae and on the buttocks until the skin was generally of a dark brown tint. Like the cases mentioned in the literature, there was no pigmentation of the mucous membranes such as is found in Addison's disease and, like most of them, the color, after a matter of three or four years,

has gradually returned to normal. This case never showed the keratoses of the palms and soles. These cases have been noted in all stages of syphilis under treatment with salvarsan. After the milder scarlatiniform and morbilliform rashes the arsphenamine may be resumed in a few weeks without much fear of a recurrence of the rash, though a few cases of recurrence have been reported. It seems better, as suggested by Gutmann,² to change the preparation in these cases. After the dermatitis exfoliativa, or melanosis, it would seem better to avoid further use of arsphenamine preparations, or at any rate to wait at least for several months and then proceed with very small doses and at long intervals. All these are undoubtedly due to arsenic poisoning as they have all been noted in chronic arsenic poisoning cases. Possibly an idiosyncrasy makes the patient more susceptible, but it is arsenic poisoning just the same.

Outside of the neuralgic pains often seen after arsphenamine, little has been seen or written on the bad after effects of the drug on the peripheral nervous system. Variot and Bouquier,³ however, report one case of peripheral neuritis in the legs, going on to paralysis and reaction of degeneration in the nerve trunks in a congenital case who had received three courses of six or eight injections each at three-week intervals. Pains in the legs were complained of during the last course. Pierre Marie⁴ reports a transverse myelitis in another congenital case following an intensive course of treatment with arsenobenzol. Bory⁵ reports a case of a primary lesion treated with three doses of arsphenamine who developed meningitis and myelitis commencing three days after the last dose and which left the patient with a spastic paraplegia. Closely allied to the peripheral nervous system is a polyarthritis described both by Chabonier, and Bleton⁶ and also by Kutznitzky.⁷ This seems to appear more frequently in women and especially in those who have received a good deal of arsphenamine. It appears about two weeks after the last dose of the drug, with pains, especially in the morning, but wearing off somewhat during the day. The joints appear normal on examination and the trouble seems to be in the bursae and muscular attachments around the joints. Any joints may be affected, often several of the larger ones at one time. The trouble clears up spontaneously in a few weeks. It is

not materially affected as a rule by salicylates or mercury or arsphenamine. As this condition has been observed in cases other than syphilis who were treated with arsenic preparations, I think that there can be no question but that this is a case of poisonous effect of the drug. In speaking of the after effects of arsphenamine on the nervous system, I have purposely omitted speaking of the affection of the optic and auditory nerves, as I think that these have been shown to be unquestionably due to a recidive from too little and not too much treatment and, therefore, are due to syphilis and not to arsphenamine.

When we consider the action of arsphenamine on the brain, we come to one of the most serious aspects of the accidents following its use. The common pathological findings in these cases which have terminated fatally are an edema of the brain, frequently with minute hemorrhages, especially in the floor of the lateral ventricles. There has also been seen a true hemorrhagic encephalitis with multiple hemorrhages all over the surface of the brain. Many of the cases in the literature described as the latter or edema of the brain are, probably, too rapidly fatal or recover too rapidly for either condition to have developed, but there are a certain number of them, as shown by autopsy. Either directly after the injection or a few hours or even days later, the patient feels weak or has an epileptiform seizure, sometimes with fever of 102° F. or so, and then becomes unconscious. Sometimes the latter appears with very few premonitory signs. The pupils are dilated, sometimes react, and at others do not. Knee jerks are absent. Babinski present. Often tonic contractures of limbs and face muscles (trismus). Urinary incontinence, stertorous breathing, deepening of coma and death. Some of these cases have apparently been saved by venesection, lumbar puncture, salt solution infusions, adrenalin subcutaneously and intravenously and cardiac stimulation.

Another interesting and important accident following arsphenamine is the so-called anaphylactoid reaction. In some of these cases nothing is found at autopsy. In others edema of the lungs, frequently associated with an acute or chronic renal condition. Jackson & Smith⁸ have shown that on dogs toxic symptoms are produced by increasing the concentration of the drug and at the same time increas-

ing the rapidity of injection. Partly owing to the action of the arsenic in paralyzing the capillaries and partly, possibly, to multiple microscopic pulmonary emboli from precipitation caused by the drug, there is an immediate and progressive increase of pulmonary blood pressure, sometimes to 100% above normal. This increase was shown to be also due in part to the alkalinity of the solution. At the same time there is a fall in the systemic blood pressure, though not so marked (25-50%). The right heart is dilated and the kidney contracted. A number of the intermediary by-products formed in the manufacture of arsphenamine were tested and found to be non-toxic. It would seem that this increase in pressure on one side of the heart with decrease on the other would be likely to cause a delirium cordis, which has been noted clinically. Moreover, it would seem that this might be the cause of death in some of these cases where nothing has been found pathologically. It would also account for the edema of the lungs in some cases where no lesion of the kidney or cardio-vascular system is present. Clinically, these cases occur frequently after several injections of the drug, more rarely after the first. More often in the cases reported, the doses given were larger than those in general use today. Many of the cases had shown so-called intoxication symptoms after previous doses. In others there is an old valvular trouble or a previous kidney lesion. It has occurred in all the stages of the syphilitic infection.

The following case is related to me by Dr. H. M. Clute:

Male. Age 38. No organic lesions. Early latent syphilis. Had received two courses of neosalvarsan (a French preparation) without serious reactions. Given 0.9 g. neoarsenobenzol (French) in 20 c.c. of freshly distilled water. Patient all right for about three minutes. He then stated that something was wrong and gripped his chest. Face became red and edema of eyelids followed. Neck veins swollen. Choking sensation. Projectile vomiting. Then marked pallor, rapid, noisy and severe dyspnea and bulging of eyes. Given camphor in oil gr. 3, and atropin gr. 1/50 s.c. Pupils dilated, but reactions were normal. Reflexes normal. In about ten minutes entirely recovered except for marked weakness and slight swelling about the eyes. Next day no ill effects except that he felt as if he had been on a spree the night before.

Many of these cases terminate fatally at once or following a few days of coma with

anuria, convulsions and pulmonary edema. In the latter form there is, usually, a cardio-vascular lesion which existed previously or a kidney lesion.

In the treatment of such cases, cardiac stimulants, artificial respiration, adrenalin and tyramine have been used with some success and some failures. Many of them could be avoided by using smaller doses as a routine and watching for prolonged and late fever after previous injections and for other signs showing intoxication, more especially in the cardio-vascular and renal cases.

Another danger in cardio-vascular cases is seen in cases of cerebral endarteritis. I had an unfortunate result a few years ago in the case of a physician who had just suffered a hemiplegia due to cerebral endarteritis. I gave him one small dose of salvarsan which was well borne and seemed to improve the general condition considerably. A week later, following a second dose of 0.6 g. the patient went into coma and died in 48 hours. I feel sure that this large dose caused an increased congestion or a fresh hemorrhage which proved fatal.

In aneurisms there may be softening of the coverings and rupture following arsphenamine, as in one case reported by Dever and Boles.⁹

I have already mentioned the danger of giving arsphenamine in cases of kidney disease. On the other hand, in advanced nephritis the drug may be used with caution and without deleterious effects. We have at the present time in the Out-Patient Department of the Boston City Hospital two cases of advanced chronic nephritis who have received repeated injections of arsphenamine without the least disturbance of the kidney, as shown by careful functional tests by Dr. W. R. Ohler in the hospital laboratory.

In regard to the digestive system, vomiting and diarrhea are so common that they need only to be mentioned. However, if either is prolonged and serious, it is a sign of intolerance and should be taken into account with the next dose and the future intervals.

In regard to the liver, the important complication is jaundice. Some cases of immediate jaundice have been reported, the earliest occurring about two hours after the injection, but, though some of these are due to the immediate toxic action of the arsphenamine, probably a large number of them are really due to syphilis. On the other hand, there is an increasing

number of reports of jaundice following from one to five months after the last injection of arsphenamine. These have been reported in cases where no mercury has been used, so that element can be eliminated. Many run a mild course and some are quite severe and several have terminated fatally with acute yellow atrophy. The jaundice lasts, in those cases which recover, from three to thirteen weeks. It can occur in any stage of syphilis, including tabes. It has been reported after all makes and derivatives of arsphenamine and after one or many doses. Some cases follow an erythematous rash with desquamation, but more often not. About a half have no symptoms. Many have a prodromal period of digestive disturbance with vomiting or diarrhea. Many complain of a pressure sensation over the liver region, but rarely of real pain. The liver is often enlarged, but often not. The spleen is occasionally enlarged. The urine contains bile and sometimes shows signs of irritation. The stool frequently is clay colored, but is occasionally bile stained. Those cases developing acute yellow atrophy usually run an acute stormy course with severe vomiting, rapidly developing coma and death in a few days, as the following case which I treated at the Carney Hospital:

Female. Age 28. Secondary syphilis, with rash, sore throat and headache. Three doses of neosalvarsan, each 0.9 g., at weekly intervals, followed by two injections of mercury and mercury pills. Slightly less than three months after last dose of neosalvarsan she showed slight jaundice, which was very marked a week later. Vomiting severe. Coma developed and death occurred fifteen days after onset of jaundice. Postmortem at the Boston City Hospital (record given me through the kindness of Dr. F. B. Mallory) showed acute yellow atrophy of liver, fatty degeneration of the heart, early bronchopneumonia, slight ascites, extensive general ecchymotic hemorrhage into mesentery and in one island of Langerhans of pancreas.

Without going into details, it seems fairly well established that the arsphenamine has a part in the etiology of these cases of late jaundice. Scott and Pearson claim¹⁰ that the preceding syphilis has caused some damage to the liver cells, which gives a predisposition to later damage. Pulvermacher¹¹ and Zimmern,¹² after a very exhaustive discussion, think that the arsenic deposited in the liver is the main factor, but that it is made active by other conditions, such as catarrh of the stomach or duodenum or an achylia gastrica, or more com-

monly through the disturbances of liver function due to the low diet which the patients have had during the war. This question of low diet during the war is hardly applicable in this country, however. It has been pretty definitely shown that syphilis is not a cause in the sense of a monorecitive. The question of the benzol radical of the arsphenamine as a cause is discussed by Pulvermacher, but there is little ground for assuming that this plays any part in the etiology.

In regard to the treatment, most authors agree that salvarsan should be used again in these cases only after a long interval. Rest, diet, and alkaline salts seem to be preferred by most men.

In conclusion, we have in arsphenamine a very powerful drug for the treatment of syphilis, but one which may cause most serious lesions, especially of the skin, gastro-enteric, nervous, and cardiovascular systems, sometimes leading to death. Although some of these disturbances are unavoidable, it would seem that many of them might be averted by care in the administration and careful judgment in regard to the dosage, the intervals between the doses and the total amount given.

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ARGYROL.

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ARGYROL was introduced in 1902. It was originally made by extracting gliadin from wheat and treating it under pressure in an autoclave, obtaining thereby a white granular precipitate, which is said to be of the nature of a vitellin. When this is combined with silver, the resulting product is a dark brown powder containing 30% of metal.¹ Commercially the so-called vitellin is obtained from serum albumen by hydrolysis.² According to Marshall and Neave,³ argyrol contains 20% of silver, not 30%.