THE EFFECT OF SALVARSAN UPON THE HEART
IN DOGS.*

By J. AUER.

(From the Department of Physiology and Pharmacology of the Rockefeller Institute for Medical Research, New York.)

PLATE 28.

During an investigation on the tolerance of salvarsan by rabbits, it was noticed that the blood pressure sometimes sank profoundly and abruptly during the intravenous injection of the drug, and the impression was produced that this was caused by a sudden weakening of the heart.1 As there is, however, practically no experimental evidence that this drug does affect the heart, and as Nicolai2 states definitely, on the basis of electrocardiograms, that salvarsan does not affect this organ, it seemed desirable to study this aspect of the problem more directly. For this reason the following series of experiments were carried out.

METHOD.

For reasons of convenience, dogs only were employed. Their weight varied from four to seven kilos. They were anesthetized by ether and kept under the influence of the anesthetic by means of intratracheal insufflation.3 As a rule, curarin was given. A cannula was then introduced into the external jugular vein, the sternum split transversely and the heart fully exposed. After the pericardium was opened the ventricles were placed in an oncometer.

This oncometer was made from a bottle whose bottom had been cut away and replaced by a thick rubber dam. In this rubber dam an oval aperture was burned and the ventricles were pushed into the cavity of the glass chamber.

* Received for publication, June 20, 1911.
2 Nicolai, Kongress für innere Medizin, Wiesbaden, 1911, Deutsch. med. Wchnschr., 1911, xxxvii, 859.
The junction between dam and auriculo-ventricular groove on the inside of the chamber was lined with cotton soaked in vaselin. The oncometer was then retained in position by a clamp fixed to a stand, and the chamber itself was connected with a Marey tambour.

In this fashion, the volume change of the ventricles was recorded. In addition, as a rule, the carotid blood pressure was written by means of a Hürlhle membrane or spring manometer, the connecting tubing being filled with a 10 per cent. solution of sodium citrate.

The solutions of salvarsan were prepared in two ways, either alkaline or acid. When the alkaline solution was employed, one cubic centimeter of a normal solution of sodium hydrate was added for every 0.1 gram of the drug, which had previously been ground into solution in a mortar with a quantity of 0.9 per cent. saline solution. A perfectly clear yellowish green liquid resulted, which was then diluted with physiological salt solution to the desired concentration. For the acid solution the drug was merely ground in a mortar with gradually increasing quantities of 0.9 per cent. saline solution; this produced a clear yellow solution which was then diluted.

The concentration of the drug employed most often in this work was 0.5 per cent.

RESULTS.

Alkaline Solution.—The animals stood the infusion of salvarsan in 0.2 per cent. or 0.5 per cent. alkaline solution very well, even with the enormous doses infused (twenty to forty milligrams per kilo. of body weight). Text-figures 1 and 2 show this very well, and no marked changes of either heart volume, blood pressure, or heart rate are recorded. On the basis of this, it might be assumed that the heart had suffered very little, if at all. This impression, however, would be erroneous, as the following observations will show.

In the animal which furnished the curves for text-figure 1, thirty-six milligrams of salvarsan per kilo. in 0.2 per cent. alkaline solution had been infused in six minutes. The blood pressure and heart rate were practically unaltered after the infusion; the heart, however, showed a moderate dilatation which persisted for about twenty minutes after the infusion (text-figure 1, a, b, and c.). Thirty-five minutes after the infusion, the heart was apparently normal (text-
Effect of Salvarsan upon the Heart in Dogs.

figure 1, c). But on removing the heart from the oncometer, and handling it very gently, it passed at once into fibrillation, from which it did not recover. Similar effects were observed in other experiments where the alkaline solution was infused. On the other

TEXT-Figure I. April 5, 1911. Dog 4,400 grams; 36 mgm. per kilo., 0.2 per cent. alkaline solution into jugular vein. a = curve obtained 1 minute before infusion. b = curve obtained 6 minutes after infusion. c = curve obtained 24 minutes after infusion.

In all the tracings the upper curve represents ventricular volume; downstroke, systole. The horizontal line transecting this curve is the atmospheric pressure line.

The second curve is the blood pressure obtained by a Hürltche manometer connected with the carotid artery; its value in mm. of mercury may be obtained from the calibration in 20 mm. intervals (shown by dots in figures 1 and 2). The straight line below the blood pressure curve is the zero pressure.

Time is marked in all tracings in four second intervals.

hand some hearts of the same series of experiments stood manipulation very well, and only a very transitory change in the heart's action was observed.
Acid Solution.—This solution was employed in 0.5 per cent. solution only because with this strength toxic symptoms could be easily obtained. With a weaker solution, slight or no toxic effects were noticed, which is in accord with observations made in rabbits, where it was found that the toxicity of acid solutions of salvarsan varied directly with the concentration.⁴

With an animal prepared for the registration of blood pressure and heart volume, as described above, the infusion of 0.5 per cent.

Acid salvarsan produces swiftly a moderate dilatation of the heart; then the blood pressure begins to fall and reaches a low level rather promptly. During this fall, the pulse pressure diminishes rapidly, and at the lowest level of blood pressure the heart rate is very slow. After a low blood pressure has been reached, the heart

Effect of Salvarsan upon the Heart in Dogs.

dilates still more and may even stop in diastole for a period of seconds (plate 28, figure 1). Then the heart begins to beat again, but the beats are weak and hardly affect the lever of the membrane manometer which is connected with the carotid artery. From this state the animal does not recover, though the heart, as a rule, keeps on beating feebly for a number of minutes.

Results similar to those described above were obtained in practically all of the ten experiments which were made with the 0.5 per cent. acid solution. Some apparent exceptions will be discussed later.

DISCUSSION.

In the preceding pages, experimental evidence has been given which shows that both alkaline and acid solutions in 0.5 per cent. strength may affect the heart. With the alkaline solution, this action is not so obvious as with the acid solution, nor is it as constant. Neither the blood pressure nor the volume changes of the heart form a safe guide with the alkaline solution, for it was shown above (text-figure 1) that both these indicators may be but moderately affected by as much as thirty-six milligrams of salvarsan per kilo., and yet a comparatively slight extra strain put upon the heart was sufficient to throw it into a fatal fibrillation. It must also be especially noted that this occurred with a weak solution,—only 0.2 per cent. Fortunately, however, this does not occur regularly, even when 0.5 per cent. is used, and, as stated before, the heart may then withstand severe treatment. This failure is probably due to an inherent weakness of the cardiac muscle which is brought out by the injection of salvarsan, and the contention of Ehrlich and many clinicians that myocarditis be regarded as a contra-indication for the intravenous injection of salvarsan has thus experimental support. This danger of sudden cardiac failure will always be present as long as the functional capacity, the factors of safety, of the heart tested is not known, for it is well known that a heart may be perfectly able to meet all ordinary requirements, and thus seem normal, and yet these ordinary requirements may demand all that the heart is able to give; when an extraordinary occasion arises this heart is

unable to respond, and is forced into fibrillation and diastolic stoppage.

When salvarsan is employed in 0.5 per cent. acid solution, the effect on the heart is obvious; the tracing in plate 28, figure 1, shows it better than a mere description could. This tracing shows that the profound weakening of the heart contractions is preceded by a marked drop in blood pressure. But this drop in pressure cannot be attributed entirely to a vasomotor disturbance, as is done by Hoke and Rihl, for the volume record (upper curve in plate 28, figure 1) demonstrates that the ventricles are full of blood but are practically unable to expel their contents, at least as far as the left ventricle is concerned, and the carotid blood pressure manometer shows only slight or no pressure waves. Moreover, the dilatation cannot be attributed to a too rapid infusion, as only twenty-two cubic centimeters were injected and the incorporation of this small quantity consumed four minutes. These facts clearly indicate that an effect upon the heart itself is produced by acid salvarsan.

These two series of experiments, therefore, show quite well that salvarsan, either in alkaline or acid solution, may exert a harmful effect upon the heart. Whether this action is exerted upon the cardiac muscle, or upon the vagus endings, or upon both structures, cannot be definitely stated. The action seemed to be chiefly muscular, although in a few experiments, where the vagi were cut, it seemed as if the cardiac vagus endings became more irritable to faradic stimulation for a short period of time after the infusion of salvarsan.

Relative Toxicity of Acid and Alkaline Solutions.—The experiments which have been briefly described in the preceding pages showed strikingly that the 0.5 per cent. acid solution is much more toxic than the 0.5 per cent. alkaline solution. With the acid solution, ten experiments were carried out, and eight of the dogs died during or shortly after the infusion. With the alkaline solution in 0.2 per cent. or 0.5 per cent., eight experiments were made. The dosage per kilo. was about the same in both series, ranging between 20 and 40 milligrams. All of these animals stood the alkaline solution well as far as blood pressure and ventricular volume were concerned, and no fatalities occurred within an hour.

1 Hoke and Rihl, Kongress für innere Medizin, Wiesbaden, 1911, Deutsch. med. Wehnschr., 1911, xxxvii, 839.
Effect of Salvarsan upon the Heart in Dogs.

after which the animals were usually killed. It has already been stated that manipulation of the heart of some of these animals caused marked changes and even stoppage, while the others recovered very promptly.

Relative Toxicity of Some Preparations of Salvarsan.—While experimenting with the acid solution of the drug, some evidence was encountered which seemed to show that different preparations of salvarsan do not possess the same toxicity. The earlier experiments with the acid 0.5 per cent. solution were chiefly made with preparation marked "606, 1/250," while in the later experiments, a preparation marked "Salvarsan Op. 130" was employed. With the acid 0.5 per cent. solution of "606" eight out of ten dogs died in a short time after a dose varying from 14 to 33 mgm. per kilo. "Salvarsan Op. 130" was used in the same concentration in four additional dogs. These received from 30 to 40 mgm. per kilo and none of them died; the blood pressure of all of these animals, three to four hours after the infusion, varied from 140 to 190 mm. of mercury, and they seemed to be in excellent condition. In three of these animals the vagi had been severed in order to study the cardiac vagus during the action of salvarsan; in the fourth animal these nerves were intact.

This difference in toxicity of the two preparations may, however, be due to the fact that the four dogs of the last series, where "Salvarsan Op. 130" was injected, were not subjected to the same severe operation as the dogs of the earlier series: merely the blood pressure was recorded, and no tracing of the heart volume was taken. It may be, therefore, that the animals were in better physical shape and could withstand the action of the drug better, and that there is no real difference in the toxicity of the two preparations. This explanation, however, is not adequate, for two experiments with "606" were carried out with dogs where no operation was performed beyond the introduction of a cannula into the external jugular vein. These animals received 20 mgm. of acid "606" in 0.5 per cent. solution. One died during the infusion and the other died twenty-five minutes after it. In both, the heart was no longer beating on immediate autopsy, and this organ was so dilated that it snugly filled the entire pericardial sac. These data show that "606" was surely more toxic than "Salvarsan Op. 130."

This varying toxicity must, therefore, be taken into consideration, especially as other observers have also described differences in the various preparations of the drug. Thus J. and L. Camus* report some apparent variations, and recently Hoke and Rihl" state that "hyperideal" is twenty times more toxic than salvarsan, and that these differences in toxicity are especially pronounced in the acid solutions.

SUMMARY.

The intravenous infusion of 0.5 per cent. acid "606" causes a weakening of the heart which is usually fatal.

The intravenous infusion of 0.5 per cent. alkaline "606" causes no marked apparent effect upon the heart, but its factors of safety

"Hoke and Rihl, Deutsch. med. Wchnschr., loc. cit.
may be so reduced in some instances that a slight extra strain produces fibrillation and death.

EXPLANATION OF PLATE 28.

Fig. 1. April 12, 1911. Dog ♂ 5,100 grams; 21 mgm. per kilo., 0.5 per cent. acid solution into jugular vein.

The waves shown during the stoppage of the heart are caused by the remissions of pressure in the lung produced by the method of insufflation.