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THE
INFLUENCE OF INTRAVENOUS INJECTIONS
OF NEO-SALVARSAN ON THE ARTERIAL
BLOOD PRESSURE.*

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THE blood pressure was investigated in a hundred consecutive cases in which neo-salvarsan was given intravenously for syphilis, in almost all in the secondary stage. The patients were in the Royal Naval Hospital, Haslar, under the care of Staff Surgeon J. S. Dudding, R.N., who kindly gave me every facility for examining them. Their average age was 24 years, and except for twelve who were 30 years of age and over, and for six under 20, were all between 20 and 30 years of age. The amount of neo-salvarsan varied between 0.9 and 0.6 gram. The blood pressure (systolic and diastolic) was taken (i) on one or more days before the injection was given, (ii) about seven hours after the injection, and (iii) on three or sometimes four subsequent mornings. In 19 of these cases the blood pressure was also taken during the intravenous injection of neo-salvarsan. Included in the 100 cases were 12 cases in which the blood pressure was investigated in connexion with both first and second injections of neo-salvarsan—usually at a month's interval. Mercer's sphygmomanometer, with an arm-cuff of 14 cm., was used. The auscultatory method was employed, the maximum systolic pressure being estimated as the mean between the points where the auscultatory sound disappeared and reappeared, and the diastolic pressure at the time of the so-called fourth phase, where the intensity of the auscultatory sound suddenly diminishes. I took all the blood pressure estimations myself, so that errors from more than one personal equation were avoided.

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*Comparison of the Blood Pressure before and after the
Intravenous Injection of Neo-salvarsan.*

In every case the average of the blood pressure estimations taken before injection was compared with the average of the blood pressure estimations taken on the days subsequent to the injection. The blood pressure estimations taken seven hours after the injection were not included here, and are dealt with below. In 77 out of the 100 cases the intravenous injection was followed by a fall in both the systolic and diastolic pressures. The average fall of the systolic pressure was 16 mm. Hg, and of the diastolic pressure 13 mm. Hg. Out of the 23 remaining cases there were 8 in which both the systolic and diastolic pressures were higher after than they were before the injection, the average increase in both the pressures being 11 mm. Hg; 8 cases in which the systolic pressure was higher after than before injection (average increase 5.2 mm. Hg), while the diastolic pressure was lower after than before injection (average fall 6.5 mm. Hg); 6 cases in which the diastolic pressure after was higher than before injection (average increase 4.5 mm. Hg), while the systolic pressure after was lower than before injection (average fall 8 mm. Hg); and one case in which both the systolic and diastolic pressures were the same before and after injection. By arranging these figures rather differently it is seen that after injection there is

A fall in both the systolic and diastolic pressures in	77
A fall in the systolic alone in	6
Making a fall in the systolic pressure in 83	
A fall in the diastolic alone in	8
Making a fall in the diastolic pressure in 85	
A rise in both the systolic and diastolic pressures in	8
A rise in the systolic pressure alone in	8
Making a rise in the systolic pressure in 16	
A rise in the diastolic pressure alone in	6
Making a rise in the diastolic pressure in 14	
No change in either the systolic or diastolic pressure in	1

It is therefore clear that the average of the blood pressure estimations taken after injection is usually lower than that before injection. In the systolic blood pressure there was a fall in 83 cases, as compared with a rise in 16, or in the proportion of 5 to 1. The average fall in the systolic pressure was 15.4 mm. Hg. In the diastolic blood pressure there was a fall in 85 cases, as compared with a rise in 14, or in the proportion of 6 to 1. The average fall in the diastolic pressure was 12.4 mm. Hg. The fall was therefore slightly less in the diastolic than in the systolic blood pressure. But before assuming that the fall in blood pressure is the direct result of the injection of neo-salvarsan, two factors must be taken into account:

1. That the patients were kept in bed from the day before the injection until some days after, and that the blood pressure estimations were nearly always taken early in the mornings of the days subsequent to the injection

when the patients were in bed, even though they sometimes got up later in the day. In some cases the last blood pressure was taken when the patient was up, and in these cases the pressure was usually higher than those taken in bed. The fall of blood pressure may, therefore, have been partly due to rest in bed.

2. Mental excitement, although guarded against as far as possible, may have raised the blood pressures before injection; and hence the fall in the average of the blood pressure estimations taken after injection may have been more apparent than real.

In the light of these considerations, it does not appear that the fall in blood pressure was necessarily due to the intravenous injection of neo-salvarsan. At any rate intravenous injection of neo-salvarsan does not tend to raise the blood pressure on the following days.

Comparison between the Blood Pressure taken before and that taken Seven Hours after the Intravenous Injection of Neo-salvarsan.

In 55 out of 99 cases both the systolic and the diastolic pressures were lower seven hours after the intravenous injection of neo-salvarsan than they were before; the average fall of the systolic pressure was 16 and of the diastolic pressure 10 mm. Hg. In 16 of these 55 cases the temperature rose to 100° F. or higher, and in these the average fall in the systolic pressure was 19 and in the diastolic pressure 11 mm. Hg. Among these 16 febrile cases, 7 showed Herxheimer's reaction, and presented an average fall in the systolic pressure of 19 and in the diastolic of 13 mm. Hg. In the other 39 cases the averages of the falls in the systolic and diastolic blood pressures were 15 and 9 mm. Hg. The influence of fever caused by excessive liberation of spirochaetal toxins was not marked, as the average fall of the systolic and diastolic blood pressures was 4 mm. Hg only. In the remaining 44 cases the following results were obtained: In 19 cases both the systolic and diastolic pressures were higher after than before injection. The average rise in the systolic pressure was 8.4 and in the diastolic pressure 9 mm. Hg. In 4 of these 19 cases the temperature rose to 100° F. or above, and the average rise in the systolic pressure was 6 and in the diastolic pressure 9 mm. Hg. In the other 15 cases the average rise in the systolic pressure was 9 and in the diastolic pressure 10.6 mm. Hg. In 7 cases the systolic pressure was higher (the diastolic being on an average 7 mm. Hg lower) after than before injection. The average rise in the systolic pressure was 5 mm. Hg. In 1 of these 7 cases the temperature rose to 100° F., with a rise of 2 mm. Hg in the systolic pressure and a fall of 14 mm. Hg in the diastolic pressure. In 18 cases the diastolic pressure was higher (the systolic pressure being on an average 8 mm. Hg lower) after than before injection; the average rise in the diastolic pressure was 7 mm. Hg. In 9 of these 18 cases the temperature rose to 100° F. or above, and the average rise in the diastolic

pressure was 8 mm. Hg and the average fall in the systolic pressure 11 mm. Hg. In the other 9 cases the average rise in the diastolic pressure was 6 mm. and the average fall in the systolic pressure was 5.5 mm. Hg. By arranging these figures rather differently it is seen that seven hours after injection there is

A fall in both the systolic and diastolic pressures in	55
A fall in the systolic pressure alone in... ..	18
Making a fall in the systolic pressure in 73	
A fall in the diastolic alone in	7
Making a fall in the diastolic pressure in 62	
A rise in both the systolic and diastolic pressures in	19
A rise in the systolic pressure alone in... ..	7
Making a rise in the systolic pressure in 26	
A rise in the diastolic pressure alone in	18
Making a rise in the diastolic pressure in 37	

The blood pressure seven hours after the intravenous injection of neo-salvarsan is therefore usually lower than the blood pressure before injection. In the systolic blood pressure there was a fall in 73 cases, as compared with a rise in 26, or, approximately, in the proportion of 3 to 1. The average fall in the systolic blood pressure was 14 mm. Hg. In the diastolic blood pressure there was a fall in 62 cases, as compared with a rise in 37, or in the proportion of 5 to 3. The average fall in the diastolic pressure was 9.6 mm. Hg. The fall in the diastolic pressure is therefore slightly less than in the systolic pressure. The fall of blood pressure seven hours after injection cannot be explained as due to fever, for a rise to 100° F. or more occurred in 30 cases only. Out of these 30 febrile cases the systolic pressure was lower in 25 and higher in 5 cases seven hours after injection than it was before injection. The average additional fall of the systolic blood pressure in the 25 cases was 4.5 mm. Hg, while the diastolic was lower in 17 and higher in 13 of the 30 febrile cases; and the average additional fall in the 17 cases was 2.6 mm. Hg. The influence of fever so far as it goes in depressing the blood pressure is even less marked on the diastolic than on the systolic blood pressure.

Comparison of the Blood Pressure taken Seven Hours after Intravenous Injection of Neo-salvarsan with the Average of the Blood Pressure Estimations on Subsequent Days.

Out of 98 cases there were 58 in which the averages of both the systolic and diastolic pressures on the days subsequent to injection were lower than those seven hours after the injection. The average fall in the systolic pressure was 7.3 mm. Hg and in the diastolic pressure 10.4 mm. Hg. Among these 58 cases there were 17 with a temperature of 100° F. or more seven hours after injection, showing an average fall of 10 mm. Hg in the

systolic and 11 mm. Hg in the diastolic pressure; whereas in the other 41 cases the corresponding average falls in blood pressure were 8.7 and 10 mm. Hg. Out of the remaining 40 cases there were 13 in which the averages of both the systolic and diastolic estimations on the subsequent days were higher than the blood pressure seven hours after injection. The average difference in the systolic pressure was 9.5 mm. Hg and in the diastolic 8 mm. Hg. In 4 of these cases there was, seven hours after injection, a rise of temperature to 100° F. or more with corresponding differences of 13 mm. Hg and 16 mm. Hg, contrasting with differences of 8 mm. Hg (systolic) and 5 mm. Hg (diastolic) in the remaining 9 cases. In 21 cases the average of the systolic blood pressure estimations on the subsequent days was higher and the average of the diastolic blood pressure estimations on the subsequent days lower than seven hours after injection. The average difference in the systolic pressure was 5 mm. Hg, and in the diastolic 6 mm. Hg. In 8 of these 21 cases there was a temperature of 100° F. or more seven hours after the injection, and the corresponding differences were on an average 3.5 mm. Hg (systolic rise) and 6.5 mm. Hg (diastolic fall); whereas in the remaining 13 cases the difference was 6 mm. Hg in both cases. In 6 cases the systolic pressure was higher and the diastolic pressure lower seven hours after injection than the average of the blood pressure estimations on subsequent days, the average differences being 4.3 mm. Hg and 3 mm. Hg respectively.

By arranging these figures rather differently it is seen that, as compared with the blood pressure seven hours after intravenous injection, there is on the subsequent days:

A fall in both the systolic and diastolic pressures in	58
A fall in the systolic pressure alone in	6
Making a fall in the systolic pressure in	64				
A fall in the diastolic pressure alone in	21
Making a fall in the diastolic pressure in	79				
A rise in both the systolic and diastolic pressures in	13
A rise in the systolic pressure alone in	21
Making a rise in the systolic pressure in	34				
A rise in the diastolic pressure alone in	6
Making a rise in the diastolic pressure in	19				

This shows that the average of the blood pressure estimations taken on the subsequent days is usually lower than the blood pressure taken seven hours after the intravenous injection. The systolic blood pressure was lower in 64 cases and higher in 34, or roughly in the proportion of 2 to 1; while the diastolic pressure was lower in 79 and raised in 19 cases, or in the proportion of 4 to 1. The fall, therefore, is more marked in the diastolic than in the systolic pressure. The modifications in the blood pressure in the cases with fever seven hours after injection are not sufficiently constant or definite to justify any conclusions as to the influence of fever.

Blood Pressures taken during the Intravenous Injection of Neo-salvarsan.

As already mentioned, this was done in 19 cases. In 15 cases both the systolic and diastolic pressures were higher during the injection than they were on the previous days or day. The average rise in the systolic pressure was 22 mm. Hg, and the greatest 46 mm. Hg. The average rise in the diastolic pressure was 14 mm. Hg. In 2 cases the systolic pressure was higher, but the diastolic pressure lower, than on the days or day before the intravenous injection. In 1 case the systolic pressure was lower, while the diastolic pressure was higher than before injection. In 1 case both the systolic and diastolic pressures during injection were slightly lower (systolic by 1 mm. Hg, diastolic by 3 mm. Hg) than before injection. By taking the blood pressure throughout the process of injection it was shown that the systolic pressure may fluctuate considerably; the maximum variation was 28 mm. Hg, and the average 15 mm. Hg. It may be highest before the skin is punctured; thus, in 1 case the systolic blood pressure was 160 mm. Hg just before the injection was actually given and fell while it was going on to 140 mm. Hg. In most instances it was lower at the end than at the beginning of the *séance*. The diastolic pressure fluctuated less than the systolic pressure during the performance of intravenous injection; the maximum variation was 14 and the average 6.5 mm. Hg. In 18 out of the 19 cases both the systolic and diastolic pressures were higher during the injection than they were seven hours later, the average systolic difference being 23 mm. Hg, and the average diastolic difference 12.8 mm. Hg. In the remaining case the systolic pressure was higher, but the diastolic pressure was lower during injection than seven hours later. In 18 out of the 19 cases both the systolic and diastolic pressures during the injection were higher than the average of these blood pressure estimations taken on the subsequent days. In the remaining case the systolic pressure during injection was 22 mm. Hg higher than the average of the systolic estimations on subsequent days, but the diastolic was 3 mm. lower than the average of the diastolic pressures on subsequent days. It appears that the rise of blood pressure during the intravenous injection of neo-salvarsan is due to mental excitement.

Comparison between the Blood Pressure Estimations taken in Connexion with (1) First and (2) Second Injections of Neo-salvarsan.

In 12 cases the blood pressure estimations were carried out in connexion with two intravenous injections of neo-salvarsan given at an interval of about one month. In 10 of these cases both the systolic and diastolic blood pressures taken before the second injections were lower than they had been before the first injection; in one case the systolic before the second injection was higher

than it had been before the first injection, and in one case the diastolic pressure before the second injection was higher than it was before the first injection. The fall in 10 out of the 12 cases might be interpreted to mean that the remote effect of treatment was to lower the arterial blood pressure. But this must not be insisted upon, as the pressor effect of excitement would be much more powerful when the estimation was first done than on the occasion before the second injection. In addition 12 cases is too few to justify any far-reaching conclusion.

A comparison between (*a*) the average of the blood pressure estimations made on the days subsequent to the first injection, and (*b*) the blood pressure taken before the second injection, shows that in two-thirds of the 12 cases the blood pressure was higher in (*b*). But it must be remembered that in (*a*) the patients had been in bed for some five days, which would tend to lower the blood pressure, whereas in (*b*) they had been up.

CONCLUSIONS.

1. The average of both the systolic and diastolic blood pressures on the days after injection is generally lower than before injection, the fall in the systolic being slightly more marked than in the diastolic pressure. This fall, however, is very probably not a direct result of the action of neo-salvarsan, and, in part at least, may be due to rest in bed.

2. The blood pressure seven hours after the intravenous injection of neo-salvarsan is usually lower than it was before. The fall in the diastolic pressure is slightly less than that of the systolic pressure. The fall cannot be explained as due to fever.

3. As compared with the blood pressure taken seven hours after the intravenous injection of neo-salvarsan, the average of the blood pressure estimations on subsequent days is usually lower. This is more marked in the diastolic than in the systolic blood pressure.

4. During the actual intravenous injection of neo-salvarsan both the systolic and diastolic pressures are nearly always higher than on other occasions. This appears to be due to excitement. During the operation the pressures may vary considerably, the systolic blood pressure being more affected than the diastolic.

5. The blood pressure before the first injection of neo-salvarsan is nearly always higher than the blood pressure before the second injection of neo-salvarsan, but here again mental excitement may be responsible.

6. Finally, the general effect of intravenous injections of neo-salvarsan is rather to lower, certainly not to increase, the arterial blood pressure.

The first part of the paper is devoted to a general discussion of the problem. It is shown that the problem is well-posed in the sense of Hadamard. The second part is devoted to the construction of the solution. The third part is devoted to the study of the properties of the solution. The fourth part is devoted to the study of the stability of the solution. The fifth part is devoted to the study of the convergence of the solution. The sixth part is devoted to the study of the error of the solution. The seventh part is devoted to the study of the numerical solution. The eighth part is devoted to the study of the application of the solution. The ninth part is devoted to the study of the conclusion. The tenth part is devoted to the study of the references.

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2. The second part of the paper is devoted to the construction of the solution. It is shown that the solution can be constructed in the form of a series. The third part is devoted to the study of the properties of the solution. It is shown that the solution is unique and stable. The fourth part is devoted to the study of the stability of the solution. It is shown that the solution is stable in the sense of Hadamard. The fifth part is devoted to the study of the convergence of the solution. It is shown that the solution converges in the sense of Hadamard. The sixth part is devoted to the study of the error of the solution. It is shown that the error is of order $O(\epsilon)$. The seventh part is devoted to the study of the numerical solution. It is shown that the numerical solution is stable and convergent. The eighth part is devoted to the study of the application of the solution. It is shown that the solution can be applied to a wide range of problems. The ninth part is devoted to the study of the conclusion. It is shown that the problem is well-posed and the solution is unique and stable. The tenth part is devoted to the study of the references.

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