STUDIES IN EDEMA.

VI. THE INFLUENCE OF ADRENALIN ON ABSORPTION FROM THE PERITONEAL CAVITY, WITH SOME REMARKS ON THE INFLUENCE OF CALCIUM CHLORIDE ON ABSORPTION.¹

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In some earlier papers (1, 2, 3) on the production of peritoneal transudates in rabbits by the intravenous infusion of large quantities of sodium chloride solution or of mixtures of a sodium chloride and calcium chloride solution, or of these solutions with the addition of adrenalin, we found that both calcium chloride and adrenalin increased the amount of peritoneal transudate. We pointed out that the increased amount of peritoneal transudate could be due to two conditions, namely, either an actual increase in the transudation under the influence of these substances, or a decrease in the rapidity of absorption of fluid from the peritoneal cavity, or to a combination of these factors. It was, therefore, necessary for us to determine the influence of adrenalin and calcium chloride on absorption.

We used the following method of experimentation: we injected definite quantities of 0.85 per cent. sodium chloride solution, warmed to body temperature, into the peritoneal cavity of rabbits, by means of a syringe and needle, especial care being taken not to injure the intestines. In the individual experiments concerning the influence of calcium chloride, the amounts of fluid injected into the peritoneal cavity varied between 110 and 150 cubic centimeters. However, in all experiments relating to the influence of adrenalin on absorption, 120 cubic centimeters of 0.85 per cent. sodium chloride solution were injected. After the injection of the fluid, and during the period of the experiment, the rabbit was in no way restrained, being

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allowed to move about freely in its cage. After a period of time, which in the experiments with calcium chloride varied between two and three hours, but which in the other experiments was always two hours and a half, the animal was killed, and the fluid was recovered from the peritoneal cavity by widely opening the abdomen and draining the fluid contents into a dish or beaker.

**THE ABSORPTION OF SODIUM CHLORIDE AND SODIUM CHLORIDE-CALCIUM CHLORIDE SOLUTIONS FROM THE PERITONEAL CAVITY.**

In these experiments with sodium chloride and sodium chloride-calcium chloride solutions, our aim was merely to determine the comparative absorption of fluid as influenced by these solutions. Thus, we carried out experiments in which two animals of equal weight were injected with equal quantities of either sodium chloride or sodium chloride-calcium chloride solutions; in every pair of animals of equal weight injected with equal quantities of fluid, the duration of the experiment was the same.

In sixteen experiments in which one animal was injected with 0.85 per cent. sodium chloride solution and another animal with a mixture of four parts of 0.85 per cent. sodium chloride and one part of 1.22 per cent. calcium chloride solution, we found the average amount of fluid recovered from the peritoneal cavity in the first series to be 59 cubic centimeters; in the second, 64 cubic centimeters. We can, therefore, conclude that the addition of calcium chloride, in such an amount as we have used in our experiments, to sodium chloride solution has an insignificant action on absorption. It possibly delays absorption to a very slight degree. The difference here is within the limits of experimental error. It is, therefore, not possible to account for the considerable differences in the quantities of peritoneal transudate noted after the intravenous infusion of sodium chloride solution and sodium chloride-calcium chloride solution through the influence of calcium chloride upon absorption from the peritoneal cavity; but we must consider this increase of peritoneal transudate under the influence of calcium chloride as due to a direct influence on the transudation into the peritoneal cavity.

We found many individual variations in the amounts of fluid
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absorbed; it was therefore necessary to make a large series of experiments and to take the mean. However, notwithstanding individual variations, if, in considering a large series of experiments, one compares the mean of the whole series with the mean of six or seven successive experiments of the series, it will be found that the two are very similar.

For this reason we feel quite confident that notwithstanding the individual variations, our experiments permit us to draw definite conclusions and this applies also to the following series of experiments.

THE INFLUENCE OF ADRENALIN UPON ABSORPTION FROM THE PERITONEAL CAVITY.

In order to determine the influence of adrenalin upon absorption from the peritoneal cavity, we carried out two series of experiments, which differed in the manner in which adrenalin was administered. In one series, we injected 0.25 cubic centimeter of adrenalin (Parke, Davis and Co., 1:1000 solution) into the peritoneal cavity, every thirty minutes after the sodium chloride solution had been injected. Thus, a total of 1.25 cubic centimeters of adrenalin was administered. In another series, the adrenalin was injected intravenously. Usually, 0.2 cubic centimeter was given at each injection. In the majority of cases, four injections were given, at intervals of thirty minutes; when the rabbits appeared to be very much affected by the injection, a longer interval was allowed between the injections. In the majority of cases, a total of 0.8 cubic centimeter of adrenalin was injected in these animals. In all these experiments, a constant amount of fluid (120 cubic centimeters) was injected into the peritoneal cavity; and the experiment extended over a period of two hours and a half. The animals used in these experiments had not received any food for twenty-four hours previous to the experiment.

In a third series of experiments, instead of 120 cubic centimeters of 0.85 per cent. sodium chloride solution, 120 cubic centimeters of distilled water were injected into the peritoneal cavity of rabbits. Half of these were used as controls, while the other half received intraperitoneal injections of adrenalin, in the same quantity as in
In a fourth series of experiments, 120 cubic centimeters of a 1.5 per cent. sodium chloride solution were injected intraperitoneally; in this series also control and adrenalin experiments were made.

In a series of thirty-one control experiments, in which 0.85 per cent. sodium chloride solution was injected into the peritoneal cavity, we recovered, after a period of two hours and a half, an average of 77 cubic centimeters of fluid, and collected an average of 11 cubic centimeters of urine. In twenty-nine experiments in which adrenalin was injected intraperitoneally in addition to the 0.85 per cent. sodium chloride solution, an average of only 41 cubic centimeters of fluid was recovered; and an average of 41 cubic centimeters of urine was excreted by the animals during the period of the experiment.

In a series of 20 experiments, adrenalin was injected intravenously and in these experiments, we recovered an average of 62 cubic centimeters of fluid, and collected an average of 11 cubic centimeters of urine. In almost every experiment of this last series, the animal was very markedly affected by the adrenalin, showing weakness and dyspnea. It may be noted that adrenalin caused no increased diuresis in this series, while, when injected intraperitoneally, its diuretic action is marked. In experiments in which, instead of 0.85 per cent. sodium chloride solution, we injected the same amount of distilled water (120 cubic centimeters) into the peritoneal cavity, we recovered in a series of thirteen control animals, an average of 44 cubic centimeters of fluid while in the same number of animals in which, in addition to the distilled water, adrenalin was injected intraperitoneally, only 21 cubic-centimeters of fluid were recovered. In the latter cases, an average of 49 cubic centimeters of urine was excreted; in the former an average of fourteen cubic centimeters of urine was collected.

When 120 cubic centimeters of a 1.5 per cent. sodium chloride solution were used, in a fourth series of experiments, 120 cubic centimeters of a 1.5 per cent. sodium chloride solution were injected intraperitoneally; in this series also control and adrenalin experiments were made.

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solution were injected intraperitoneally, we recovered, in a series of six experiments, an average of 116 cubic centimeters of fluid. Thus, almost no fluid had been absorbed. These animals secreted, during the period of the experiment, an average of 8 cubic centimeters of urine. When adrenalin was injected intraperitoneally, in addition to the hypertonic chloride solution, we recovered an average of 81 cubic centimeters of fluid and found an average of 30 cubic centimeters of urine secreted. Thus, in every case the injection of adrenalin has increased to a very marked extent the absorption of fluid from the peritoneal cavity.

Exner (4) and Meltzer and Auer (5) have held that adrenalin delays the absorption from the peritoneal cavity. Exner found that the intraperitoneal injection of adrenalin delayed the absorption from the peritoneal cavity of strychnine, potassium cyanide, physostigmin, and various emulsions, such as liquid paraffin or proteus vulgaris cultures. He believed that adrenalin delayed the absorption through the lymphatics, but did not affect the absorption through the capillaries. Meltzer and Auer have shown that strychnine and fluorescine are more slowly absorbed from the peritoneal cavity when adrenalin is injected subcutaneously or intravenously and they believe that adrenalin increases the tonicity of the endothelial cells of the peritoneum and of the bloodvessels, thus causing a narrowing the "stomata" between the cells.

Achard and Caillard (6) found that when, in addition to a solution of glucose, adrenalin was injected into the peritoneal cavity of a guinea-pig, very slightly less fluid was found here at the conclusion of the experiment than in control experiments. They also found that less sodium chloride had passed into the peritoneal fluid when adrenalin was injected intraperitoneally, and that less glucose was absorbed. When adrenalin was injected subcutaneously the processes of absorption were left unchanged. These observers, however, performed only one experiment of each kind.

The experiments both of Exner and of Meltzer and Auer3 dealt

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3 Since the appearance of our preliminary report (Proc. of the Soc. for Exper. Biol. and Med., 1909, vi, 115), Falta and Jvovic (Berliner klin. Woch., 1909, xlvii, 1929), have stated that the influence of adrenalin in preventing the appearance of the symptoms of strychnine poisoning is not due to a delayed absorption of this substance but to a "biological antagonism" between adrenalin and strychnine.
mainly with the absorption of dissolved substances, and not with the absorption of the solvent (water); and since we had obtained results contrary to those obtained by these observers when we studied the influence of adrenalin on the absorption of fluid, we determined in a number of experiments the amounts of sodium chloride in the fluid recovered from the peritoneal cavity. We were thus able to determine the amount of sodium chloride absorbed from the peritoneal cavity. In addition, we determined the sodium-chloride content of the blood serum and also of the urine. For the determination of the chlorides, Volhard's method was used.

In some of these experiments, the osmotic pressure of the blood-serum and of the recovered peritoneal fluid was also determined with Beckmann's freezing point apparatus.

According to most observers, the freezing point of the blood serum of normal rabbits varies between $-0.56^\circ$ and $-0.60^\circ$. In three normal animals, we found it to be $-0.60^\circ$. Two hours and a half after the injection into the peritoneal cavity of 0.85 per cent. sodium chloride solution, part of which had been absorbed, we found the average lowering of the freezing point in the serum of both control animals and of animals intraperitoneally injected with adrenalin to be $-0.583^\circ$. In animals which received adrenalin intravenously, the average freezing point was $-0.593^\circ$. The freezing point of the recovered peritoneal fluid averaged the same in all three series of experiments, being $-0.593^\circ$. Thus, in experiments in which adrenalin was injected intravenously, the osmotic pressure of the serum after absorption of sodium chloride solution was slightly greater than in control animals or in animals in which adrenalin was injected intraperitoneally. The osmotic pressure of the peritoneal fluid is usually higher than that of the blood; this applies to both the individual cases and to the averages. After the intravenous injection of adrenalin, it is identical in both fluids.

*We obtained the serum by bleeding the rabbit. The blood was whipped, in order to defibrinate it; and the serum was separated from the corpuscles by centrifugalizing. It appears that the serum obtained from blood that is exposed to the air during defibrination has a slightly different sodium chloride content from that of the serum obtained from clotted blood or blood that is not exposed to the air during defibrination.
### Absorption from the Peritoneal Cavity

<table>
<thead>
<tr>
<th></th>
<th>Blood before experiment</th>
<th>Recovered peritoneal fluid</th>
<th>Blood</th>
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<tr>
<td></td>
<td>Sodium chloride, per cent.</td>
<td>Δ</td>
<td>Cubic centimeters</td>
<td>Sodium chloride, per cent.</td>
</tr>
<tr>
<td>Normal 0.85 per cent. sodium chloride, control.</td>
<td>.455</td>
<td>-0.60°</td>
<td>77</td>
<td>.53</td>
</tr>
<tr>
<td>Normal 0.85 per cent. sodium chloride — adrenalin, intraperitoneal.</td>
<td>-0.62</td>
<td>41</td>
<td>.52</td>
<td>.811</td>
</tr>
<tr>
<td>Normal 0.85 per cent. sodium chloride — adrenalin, intravenous.</td>
<td>62.5</td>
<td>.58</td>
<td>.72</td>
<td>-0.593</td>
</tr>
<tr>
<td>Normal distilled water, control.</td>
<td>44</td>
<td>.40</td>
<td>—</td>
<td>-0.57</td>
</tr>
<tr>
<td>Normal distilled water — adrenalin, intraperitoneal.</td>
<td>21</td>
<td>.36</td>
<td>—</td>
<td>-0.553</td>
</tr>
<tr>
<td>Normal 1.5 per cent. sodium chloride, control.</td>
<td>116</td>
<td>.59</td>
<td>1.1565</td>
<td>-0.634</td>
</tr>
<tr>
<td>Normal 1.5 per cent. sodium chloride — adrenalin, intraperitoneal.</td>
<td>81</td>
<td>.62</td>
<td>1.2852</td>
<td>-0.654</td>
</tr>
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1 The averages of the individual determinations are grouped together on the table which is added to this communication. Our experiments were made on 161 rabbits.
In animals that were injected with distilled water, instead of the 0.85 per cent. sodium chloride solution, we found in control animals that the freezing point of the blood serum at the end of the experiment was within the normal limits, averaging $-0.583^\circ$, and that the freezing point of the fluid recovered from the peritoneal cavity averaged slightly less, namely, $-0.57^\circ$. In animals into whose peritoneal cavity adrenalin was injected, in addition to the distilled water, the freezing point of the serum averaged $-0.58^\circ$; that of the peritoneal fluid, $-0.553^\circ$. Here the normal osmotic pressure of the blood was retained, in spite of the large amount of distilled water absorbed from the peritoneal cavity; and the osmotic pressure of the fluid in the peritoneal cavity was raised to almost that of the serum.

In control experiments, in which we injected 1.5 per cent. sodium chloride solution, we found the lowering of the freezing point of the serum to be increased to $-0.648^\circ$. When, in addition, adrenalin was injected, the freezing point was slightly lower, namely, $-0.656^\circ$. In the latter case the freezing point of the peritoneal fluid was also lower than in the experiments with 0.85 per cent. sodium chloride solution, averaging $-0.634^\circ$ in the control experiments, and $-0.654^\circ$ in the adrenalin experiments. Here the osmotic pressure of the serum appears to be slightly greater in the adrenalin experiments. The osmotic pressure of the peritoneal fluid was certainly greater in the adrenalin experiments. The molecular concentration of the blood serum was greater than that of the peritoneal fluids in both control and adrenalin experiments.

**SODIUM CHLORIDE PERCENTAGES IN CONTROL ANIMALS.**

In animals into whose peritoneal cavity 120 cubic centimeters of an 0.85 per cent. sodium chloride solution had been injected, we found an average of .588 gram of sodium chloride absorbed of a total of 1.02 grams injected. In these cases, the fluid recovered from the peritoneal cavity at the end of the experiment showed an average of .53 per cent. sodium chloride, while the blood serum showed an average of .49 per cent., and the urine, which in individual cases varied quite widely, showed .46 per cent. For every cubic centimeter of fluid absorbed, .014 gram of sodium chloride was absorbed.
SODIUM CHLORIDE PERCENTAGES IN ANIMALS INJECTED WITH ADRENALIN.

When, in addition to the 120 cubic centimeters of sodium chloride solution, adrenalin was injected intraperitoneally, we found that an average of .811 gram of sodium chloride was absorbed. The fluid recovered from the peritoneal cavity in such cases contained an average of .52 per cent. of sodium chloride; the blood serum, .47 per cent.; and the urine, .53 per cent. For every cubic centimeter of fluid absorbed, .010 gram of sodium chloride was removed from the peritoneal cavity.

In cases in which the adrenalin was injected intravenously, the absolute amount of sodium chloride absorbed from the peritoneal cavity was .72 gram. The sodium chloride content of the recovered fluid averaged .58 per cent.; of the blood serum, .52 per cent.; and of the urine, .51 per cent. Here .011 gram of sodium chloride was absorbed with every cubic centimeter of fluid.

Comparing these results with the results in control animals, we note that the adrenalin, whether injected intraperitoneally or intravenously, increases the absolute amount of sodium chloride absorbed from the peritoneal cavity. The sodium chloride percentage of the recovered fluid in control animals is slightly greater than in animals injected with adrenalin intraperitoneally. The percentage of the latter fluid is higher in the animals injected intravenously than in the controls, even though the actual amount of sodium chloride absorbed in such animals is greater than in the controls.

The sodium chloride content of the blood is slightly greater in control animals than in animals that received adrenalin intraperitoneally. In animals injected with adrenalin intravenously, the percentage of sodium chloride in the serum is higher than in the serum of the controls.

The sodium chloride percentage of the urine varied markedly in individual experiments. We find, however, the average in both the adrenalin series slightly higher than in the control series; so that in the course of the experiments in which adrenalin was administered, more sodium chloride must have been eliminated from the body than in the control experiments. The difference between the absolute quantities excreted by the control animals and those ex-
creted by the animals that had received adrenalin intravenously is slight; but between the control animals and the animals that had received the adrenalin intraperitoneally, the difference is very considerable.

**SODIUM CHLORIDE PERCENTAGES IN ANIMALS INJECTED WITH DISTILLED WATER.**

When, instead of the sodium chloride solution, distilled water was injected into the peritoneal cavity, we were able to determine the influence of adrenalin on the movement of salt into the peritoneal cavity. Thus in control animals into whose peritoneal cavity distilled water was injected, the average sodium chloride percentage of the recovered fluid was .40 per cent.; while the average sodium chloride percentage of the blood serum was .41 per cent.

In animals into which adrenalin was injected intraperitoneally, the sodium chloride percentage of the blood serum was the same as in the control series (.41 per cent.); but the average sodium chloride percentage of the recovered fluid was lower than that of the controls, being .36 per cent. It appears that sodium chloride passes more slowly from the blood into the peritoneal cavity when adrenalin is injected intraperitoneally. This finding corresponds with the results that Achard and Caillard obtained in guinea-pigs.

**SODIUM CHLORIDE PERCENTAGES IN ANIMALS INJECTED WITH 1.5 PER CENT. SODIUM CHLORIDE SOLUTION.**

In control experiments in animals into whose peritoneal cavity 1.5 per cent. sodium chloride solution was injected, we found the recovered fluid to contain an average of .59 per cent. sodium chloride. Thus, of 1.8 grams of sodium chloride injected, 1.1565 grams were absorbed, on the average. We found .55 per cent. of sodium chloride in the blood serum, and about .92 per cent. of sodium chloride in the urine.

In adrenalin experiments, the recovered fluid contained an average of .62 per cent. sodium chloride. Here 1.2852 grams of sodium chloride were absorbed. The blood serum contained .51 per cent. of sodium chloride; and the urine, .92 per cent. of the salt.
Thus, the injection of adrenalin has interfered with the relative absorption of sodium chloride, but increased the absolute absorption. There was less sodium chloride in the blood serum in the experiments with adrenalin. This may have been due to the increased amount of urine secreted in these experiments, thus freeing the body of the sodium chloride. In both series, the sodium chloride percentage in the blood was considerably higher than in experiments in which instead of the hypertonic solution 0.85 per cent. sodium chloride solution was injected intraperitoneally. The increase in sodium chloride excretion through the urine caused by the hypertonic solution did not seem to be influenced by the adrenalin. There was a slight difference between the average lowering of the freezing point of the recovered peritoneal fluid in the adrenalin and in the control series, this difference corresponding very closely to the difference in average sodium chloride percentages noted in these fluids.

**DILUTION OF THE BLOOD IN ANIMALS INJECTED WITH 0.85 PER CENT. SODIUM CHLORIDE SOLUTION.**

We also determined the degree of dilution of the blood as the result of the absorption of fluid from the peritoneal cavity. For this purpose, we determined the refractive index of the blood. The blood for the readings was taken at the beginning of the experiment—that is, before the injection of the fluid—and again, at the time the animal was killed. The readings were made with the Abbe Refractometer. The refractive index of the peritoneal fluid was also determined in a number of cases.

In the control animals into whose peritoneal cavity 0.85 per cent. of sodium chloride solution had been injected, the refractive index of the serum was reduced by 0.00133, on the average; while in animals in which adrenalin was injected intraperitoneally, the index was reduced by only 0.00065, the decrease in the refraction being about half as much as in the controls. This indicates that, under the influence of adrenalin, fluid leaves the blood vessels—an observation that is in agreement with the results obtained by Hess (7), Erb (8), and Böhm (9). They all agree in the fact that the blood is more concentrated after the injection of adrenalin.
The refractive index of the recovered peritoneal fluid averaged about the same in both cases (1.3354).

Thus, it appears that, in spite of a much increased absorption from the peritoneal cavity under the influence of adrenalin, less fluid is retained in the vascular system.

**Dilution of the Blood in Animals Injected with Distilled Water.**

In control animals into whose peritoneal cavity 120 cubic centimeters of distilled water were injected, we found the refractive index of the blood reduced, on an average by .00136; while in animals that were injected with adrenalin in addition to the distilled water, we found the average reduction of the refractive index to be .0012. Here the average reduction in the adrenalin animals was about as great as in the controls. In spite of the increased amount of fluid absorbed from the peritoneal cavity of rabbits injected with distilled water, the dilution of the blood was not increased in the latter animals, the dilution being practically the same in the sodium chloride solution and distilled water series.

In this series the refractive index of the peritoneal fluid averaged 1.3361 in the control animals, and 1.3359 in the adrenalin animals; thus, slightly more than in the animals that were injected with sodium chloride solutions. A relatively greater amount of proteid material remained in the peritoneal cavity in the experiments with distilled water.

**Dilution of the Blood in Animals Injected with 1.5 Per Cent. Sodium Chloride Solution.**

In these experiments the averages showed the refractive index of the blood serum to be lowered by 0.00026 in the control experiments, and by 0.00035 in the adrenalin experiments. From the results, it appears that the dilution of the blood was slight in both series; and possibly that there was a greater amount of water retained in the blood in the adrenalin experiments.

In the recovered peritoneal fluid, the refractive index averaged 1.3352 in the control experiments, and 1.3353 in the adrenalin experiments. These figures are slightly lower than in the experiments in which 0.85 per cent. sodium chloride solution was injected.
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Discussion of Results.—Our experiments show conclusively that adrenalin increases the absorption of fluid from the peritoneal cavity and, at the same time, increases the amount of urine excreted. Is the absorption of fluid secondary to the diuresis? We believe that our experiments tend to prove that such a relation between absorption and diuresis does not exist. In the first place, after the intravenous injection of adrenalin, the amount of urine secreted was identical with the amount secreted in the control experiments; notwithstanding this fact, the absorption of fluid from the peritoneal cavity was increased in animals injected intravenously with adrenalin. Secondly, in individual experiments we did not find the relation between the amounts of fluid absorbed and the amounts of urine excreted to be very distinct. Thirdly, in experiments that we shall report more fully at some later date, we found that a substance that has a much more marked diuretic action than has adrenalin did not increase the absorption of fluid from the peritoneal cavity.

There does, however, appear to be a certain relation between the increased diuresis and increased absorption of fluid. In many of the individual experiments, we found that where more fluid was absorbed, more urine was excreted; although there cannot be said to be any direct relation between these two. Whether there exists an indirect relation between the absorption of fluid from the peritoneal cavity and the secretion of urine remains to be determined by further experiments.

Our experiments show that distilled water is more rapidly absorbed from the peritoneal cavity than an 0.85 per cent. sodium chloride solution, and that 0.85 per cent. sodium chloride solution is more rapidly absorbed than a 1.5 per cent. sodium chloride solution. These results are in conformity with previous experiments of Hamburger, Roth, Starling, O. Cohnheim and others. These facts suggested to us that adrenalin also may increase the absorption by increasing the molecular concentration of the blood.

In order to determine whether adrenalin, when injected intraperitoneally, changes the osmotic pressure of the blood, we injected normal rabbits with this substance every half-hour. These experiments, therefore, were carried out in exactly the same way as were
the absorption experiments, with the exception that no sodium chloride solution was injected into the rabbit. The animals were killed at various times after the third or fourth injection of adrenalin, and the blood was collected. One rabbit, killed very soon after the third injection, showed a lowering of the freezing point of $-0.67^\circ$. Another animal was killed fifteen minutes after the last injection; and in this animal, the lowering of the freezing point of the blood serum was $-0.62^\circ$. A rabbit killed twenty minutes after the last injection showed a lowering of the freezing point of $-0.625^\circ$. Half an hour after the last injection, the freezing point was $-0.605^\circ$. In two rabbits killed three quarters of an hour after the last injection, the freezing point was $-0.605^\circ$ and $-0.57^\circ$.

Thus, it appears that adrenalin increases the osmotic pressure of the blood serum, when injected intraperitoneally. This increase is quite evident fifteen to twenty minutes after the injection of adrenalin, but gradually disappears; so that three quarters of an hour after the injection, the freezing point of the serum has almost returned to normal.

Thus the probability is strong that the repeated increases in the osmotic pressure of the serum caused by the repeated injections of adrenalin explains the increase in absorption of fluid.

It may be due to two causes that we did not note this greater lowering of the freezing point of the blood serum in the experiments in which we injected adrenalin intraperitoneally together with 0.85 per cent. sodium chloride solution: namely, the blood was usually not taken until half to three quarters of an hour after the last injection, when the effect had already largely disappeared; and, furthermore, it appears that the absorption of an 0.85 per cent. sodium chloride solution (which is slightly hypotonic as compared with the blood) will itself slightly lower the freezing point of the serum. Thus, while we found $-0.60^\circ$ to be the lowering of the freezing point in normal rabbits, we found an average of $-0.586^\circ$ in animals that had been injected with the sodium chloride solution.

A definite statement that the increased osmotic pressure of the blood is the sole factor that increases the absorption of fluid from the peritoneal cavity, when adrenalin is injected intraperitoneally
would not yet be warranted; but certainly this is the most important factor.

Of interest is the fact that the increased absorption of fluid from the peritoneal cavity takes place notwithstanding the contracted condition of the blood vessels prevailing under the influence of adrenalin, and that, in spite of the increased absorption of fluid, the dilution of the blood in animals injected with adrenalin is considerably less marked than in the control animals. That fluid passes from the peritoneal cavity into the blood vessels is apparent from the fact that in spite of the marked diuresis occurring in the adrenalin animals, we still found a small degree of dilution of the blood.

This lessened dilution of the blood cannot be due to the marked diuresis, since we found that the larger amount of fluid eliminated by the kidneys in the adrenalin experiments was compensated for by the increased amount of fluid absorbed from the peritoneal cavity. This effect of adrenalin is due to a specific action, causing more fluid to pass out of the vessels into the tissues of the body.

Does a relation exist between the rapidity of absorption and the size of the animal? Hamburger (10) has shown that when the intra-abdominal pressure is increased, the rate of absorption of fluid from the peritoneal cavity increases. If, however, the intra-abdominal pressure is increased above a certain limit, the rate is slowed. The differences between the periods of time required for a fixed amount of fluid to be absorbed at the varying degrees of pressure are quite marked.

In our experiments, we injected relatively large quantities of fluid into the peritoneal cavity of rabbits of various sizes. Could the size of the rabbit have influenced the intra-abdominal pressure in our experiments, and thus have influenced the absorption? If such were the case, we should find the average amount of fluid absorbed in small animals to differ from the average amount absorbed in large animals. In order to determine the influence of the size of the animals upon absorption, we have arranged our experiments in two groups: large animals, weighing 1600 grams or more; and small animals, weighing under 1600 grams. The average weight of the group that includes the heavier animals is 1770 grams; and of the group that includes the smaller animals, it is 1220 grams.
In the control series into which 0.85 per cent. sodium chloride solution was injected, the average amount of fluid absorbed was exactly the same in both groups; and in the other series of experiments, the differences between the averages in the two groups were very slight. If, in our experiments, the size of the animal influenced the intra-peritoneal pressure, this influence was so slight as to be entirely negligible. The absorption, therefore, was not influenced by the variations in size of the animals used in our experiments.

It would, therefore, be incorrect to reduce the amount of fluid injected or absorbed to a certain unit of weight of the animal. We see from our results that it is not to be expected that a rabbit of twice the weight of another should absorb double the amount of fluid in a given time.

Concerning the influence of adrenalin on the absorption of sodium chloride, we found that in every case the absolute quantity of this salt absorbed from the peritoneal cavity was increased under the influence of adrenalin. There existed, however, certain differences in the relative absorption of sodium chloride in the different series. When adrenalin was injected intraperitoneally, in combination with 0.85 per cent. sodium chloride solution, the relative sodium chloride absorption was slightly increased; when adrenalin was injected intravenously, the relative sodium chloride absorption was diminished. The slight increase in the relative absorption of sodium chloride after the intraperitoneal injection of adrenalin may have been due to the increased amount of sodium chloride excreted through the kidneys, causing a decrease in the amount of sodium chloride in the blood, which, in turn, would cause more sodium chloride to be taken up from the injected fluid. In experiments with the intravenous injection of adrenalin the apparent decrease in absorption was probably due to the increase in the amount of sodium chloride in the blood.

When 1.5 per cent. sodium chloride solution is injected, adrenalin seems to delay slightly the relative absorption of sodium chloride, which procedure was used, for instance, in the experiments of Melzer and Salant (Jour. of Med. Research, 1903, ix, 33), in their study of the absorption in nephrectomized animals. By relative absorption of sodium chloride, we understand the absorption of sodium chloride as compared with that of the solution.
in spite of the fact that the sodium chloride percentage in the blood of such animals in our experiments was slightly less than in controls. This lower sodium chloride content of the blood was probably due to the increased elimination of sodium chloride through the kidneys.

When distilled water was injected intraperitoneally, the movement of sodium chloride into the peritoneal fluid was diminished more in the adrenalin experiments than in the controls. This may have been due to the increased excretion of sodium chloride in the urine, which would decrease the amount of sodium chloride in the blood; and thus, there would be less of this salt free to pass into the peritoneal fluid.

It seems, therefore, that although in experiments in which adrenalin was injected intravenously, and also in experiments in which, in addition to the 1.5 per cent. sodium chloride solution, adrenalin was injected intraperitoneally, the absolute amount of sodium chloride absorbed was increased, the relative amount of sodium chloride in the fluid remaining in the peritoneal cavity was somewhat greater than in controls. To what this effect of adrenalin is due, we cannot state; but it appears not to be of very great importance, since in experiments in which, in addition to 0.85 per cent. sodium chloride solution, adrenalin was injected intraperitoneally, we found the relative absorption of sodium chloride to be increased. It may be noted that we found the sodium chloride percentage of the blood slightly higher after the absorption of 0.85 per cent. sodium chloride solution than it was in normal animals. The average sodium chloride content of the blood serum of six normal rabbits was .45 to .46 per cent.; while in control experiments we found .49 per cent., and in adrenalin experiments, .47 per cent. As was to be expected, after an injection of 1.5 per cent. sodium chloride solution, we found the sodium chloride content of the blood even more increased in both control and adrenalin experiments. The absorption of distilled water, on the other hand, decreased the sodium content of the blood serum in both control and adrenalin experiments.

The movement of osmotically active substances other than sodium chloride into or from the peritoneal cavity does not appear to have been much influenced by the intraperitoneal injection of adrenalin.

After the intraperitoneal injection of 0.85 per cent. sodium
chloride solution and adrenalin, the sodium chloride percentages and freezing points of the recovered peritoneal fluids were approximately the same as in the controls in which no adrenalin had been administered. In such cases, the osmotic pressure of the blood serum was also the same as in the blood serum of control experiments, in spite of the fact that its sodium chloride content was less in the adrenalin experiments.

In the experiments in which 1.5 per cent. sodium chloride solution was injected intraperitoneally, the greater sodium chloride percentage in the peritoneal fluid noted in the adrenalin experiments was associated with the higher osmotic pressure. In the blood serum, the osmotic pressure was likewise greater in the adrenalin experiments than in the controls; but the sodium chloride content of the blood serum was less in the adrenalin experiments.

When distilled water was injected intraperitoneally, we found in the adrenalin experiments a lower osmotic pressure of the peritoneal fluid, associated with a lower sodium chloride content. In the blood serum, the sodium chloride percentages were approximately the same in control and in adrenalin experiments, but the osmotic pressure of the blood serum in adrenalin experiments was slightly lower than in control experiments.

It appears, therefore, that in these experiments there exists a certain parallelism between the osmotic pressure of the recovered peritoneal fluid and the sodium chloride content in each series. The amounts of osmotically active substances other than sodium chloride present in the peritoneal fluid must therefore have been approximately the same in the adrenalin and in the control experiments.

When, however, adrenalin was injected intravenously we found that, while the osmotic pressure of the recovered peritoneal fluid was the same as in the control experiments, the sodium chloride content of the recovered fluid was relatively greater. In the blood serum of such animals, we found both the osmotic pressure and the sodium chloride percentages higher than in the control experiments. In these experiments there was therefore a relatively smaller quantity of osmotically active substances other than sodium chloride present in the peritoneal fluid than in control experiments.
We found, both in experiments with the intravenous injection of adrenalin and in those with the injection of 1.5 per cent. of sodium chloride solution and adrenalin, that under the influence of adrenalin the osmotic pressure of the blood serum was higher than in the corresponding control experiments. In the former, this was accompanied by an increased sodium chloride percentage in the blood; in the latter, by a lower sodium chloride percentage. The sodium chloride percentage of the peritoneal fluid was higher than in controls in both of these sets of experiments; the osmotic pressure of the peritoneal fluid was higher than that of the blood serum in experiments with 1.5 per cent. sodium chloride solution and adrenalin, and the same as that of the serum in experiments in which adrenalin was injected intravenously.

It thus appears that, under certain conditions, adrenalin inhibits the normal movements of sodium chloride and other osmotically active substances to or from the blood or the peritoneal cavity. Thus, although in both these cases (mentioned above) we found relatively less absorption of sodium chloride from the peritoneal cavity, we found an increased osmotic pressure of the blood, which in one case was entirely or partly due to the increase in chlorides, but which in the other case was not due to an increase in chlorides; so that in the latter case, other osmotically active substances must have been drawn from the tissues into the blood, in order to maintain this higher osmotic pressure. Under these conditions, adrenalin maintained an increase in the osmotic pressure of the blood, just as it did in control experiments in which adrenalin was injected without an additional intraperitoneal injection of some fluid.

In experiments in which 0.85 per cent. sodium chloride solution was injected intraperitoneally, we found, both in controls and in those in which adrenalin was injected intraperitoneally, that the osmotic pressure of the peritoneal fluid was slightly higher than that of the blood serum, in spite of the fact that the injected salt solution was somewhat hypotonic as compared with the blood serum.

When adrenalin was injected intravenously, the osmotic pressure of the recovered peritoneal fluid was the same as that of the blood serum.

There existed, therefore, after the intraperitoneal injection of
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0.85 per cent. sodium chloride solution, and also when adrenalin was added intraperitoneally, a tendency of the intraperitoneal fluid to attain a greater osmotic pressure than that of the blood serum. This is of especial interest, because we note a similar condition in cases of general edema in man, in which the osmotic pressure of the ascitic fluid surpasses that of the other edematous fluids and also that of the blood serum. Thus there exists, normally, a mechanism that causes the passage of osmotically active substances from the blood or the tissues into the peritoneal cavity to such an extent that the osmotic pressure of the peritoneal fluid surpasses that of the blood; and it follows from our experiment that such a mechanism is not dependent upon pathological changes, inasmuch as we found it apparent even in normal animals that had received an intraperitoneal injection of a slightly hypotonic salt solution.

When distilled water was injected into the peritoneal cavity, we found, as might have been expected, that the osmotic pressure of the recovered peritoneal fluid in both control and adrenalin experiments was lower than that of the blood serum. On the other hand, when hypertonic sodium chloride solutions were injected, the osmotic pressure of the blood serum had risen and was greater in both adrenalin and control animals at the end of the experiments than was the osmotic pressure of the peritoneal fluid.

The movement of albuminous material does not seem to have been much influenced by adrenalin. However, the various solutions injected changed somewhat the amounts of albuminous material found in the peritoneal fluid. In those experiments in which the smallest amount of fluid was recovered (namely, the experiments in which distilled water was injected), we found relatively the greatest amount of albuminous matter. In experiments in which the largest amounts of fluid were recovered (namely, when 1.5 per cent. sodium chloride solution was injected), we found relatively the smallest amount of proteid matter in the peritoneal fluid. In the experiments in which 0.85 per cent. sodium chloride solution was injected intraperitoneally, and in which the amounts of fluid recovered stood midway between the amount recovered in the experiments in which distilled water and those in which 1.5 per cent. sodium chloride solution were used, we found in the recovered peri-
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toneal fluid a relative amount of albuminous matter that stood midway between the amounts found in these two former series.

We have found that adrenalin distinctly increases the absorption of fluid from the peritoneal cavity. Therefore, the influence of adrenalin in increasing the amount of peritoneal transudate, when large amounts of 0.85 per cent. sodium chloride solution, to which adrenalin had been added, were infused into rabbits, must have been due to an increase in the transudation into the peritoneal cavity. Indeed, this increase in transudation must have been far greater than is shown by comparisons of the amounts of peritoneal transudate found in the sodium chloride and the adrenalin-sodium chloride experiments; for in the latter, as the result of the increased absorption, a greater amount of fluid is constantly being withdrawn from the peritoneal cavity.

CONCLUSIONS.

1. Adrenalin injected intraperitoneally increases the rapidity of absorption of fluid from the peritoneal cavity, independently of whether the solution to be absorbed is hypotonic or hypertonic or is approximately isotonic with the blood serum. The intravenous injection of adrenalin also increases the absorption of fluid, but not so markedly as does the intraperitoneal injection.

2. Adrenalin injected either intraperitoneally or intravenously increases the quantity of sodium chloride absorbed. The relative absorption of sodium chloride—the movement from the peritoneal cavity of sodium chloride, as compared with the movement of water—is slightly increased when 0.85 per cent. of sodium chloride solution and adrenalin are injected intraperitoneally; but it is diminished when adrenalin is injected intravenously, or when 1.5 per cent. sodium chloride solution and adrenalin are injected. When distilled water has been injected intraperitoneally, adrenalin decreases the relative amount of sodium chloride in the peritoneal fluid—a fact that is evidently related to the increased elimination of sodium chloride through the kidneys under the influence of adrenalin.

3. When 0.85 per cent. sodium chloride solution is injected into the peritoneal cavity, the blood becomes diluted after two hours
and a half. When adrenalin is also injected, the dilution of the blood is less marked, in spite of the increased absorption under the influence of adrenalin. When distilled water is injected into the peritoneal cavity, the blood is diluted equally in control and adrenalin experiments. When 1.5 per cent. sodium chloride solution is injected, the dilution of the blood is very slight, and in adrenalin experiments it is the same as in control experiments or very slightly greater than in control experiments.

4. The increase of absorption from the peritoneal cavity caused by the injection of adrenalin is not due to the increased diuresis caused by the injection of this substance.

5. The injection of adrenalin causes a temporary increase in the osmotic pressure of the blood, which gradually returns to normal. Under certain conditions, after the injection of adrenalin, there is a tendency toward maintaining the higher osmotic pressure of the blood serum, even up to the end of the experiment. We have reason to believe that this increase in the osmotic pressure of the blood is the main factor in increasing the absorption of fluid from the peritoneal cavity.

6. In experiments in which 0.85 per cent. sodium chloride solution has been injected intraperitoneally, either with or without adrenalin, there exists a tendency of the peritoneal fluid to attain a greater osmotic pressure than the blood serum, in spite of the fact that the injected fluid is slightly hypotonic as compared with the blood serum. We note a similar condition in cases of general edema in man, in which the osmotic pressure of the ascitic fluid is greater than that of the other edematous fluids, or even that of the blood serum. There exists, therefore, a mechanism that causes the passage of osmotically active substances from the blood or from the tissues into the peritoneal cavity, and that causes the osmotic pressure of the peritoneal fluid to become higher than that of the blood. It follows from our experiments that this mechanism, which causes the ascites in edematous persons to have such a high osmotic pressure, is not dependent upon certain pathological changes in the lining membranes or upon other pathological conditions, but exists already in normal animals.

7. The addition of 1.22 per cent. calcium chloride solution to
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0.85 per cent. sodium chloride solution, in such proportions as we used in our infusion experiments, in which we determined the transudation into the peritoneal cavity, delays the absorption of fluid from the peritoneal cavity but very slightly. Therefore, calcium chloride increases directly the transudation into the peritoneal cavity and does not cause an increase in the amount of fluid in the peritoneal cavity merely by inhibiting the absorption.

8. It follows that adrenalin does not increase the amount of peritoneal transudate found after the intravenous infusion of large quantities of sodium chloride solution, to which adrenalin has been added, by delaying the absorption from the peritoneal cavity. The increased amounts of peritoneal fluid must be due to increased transudation into the peritoneal cavity; and the adrenalin, in view of its marked effect on absorption from the peritoneal cavity, must increase the movement of fluid into the peritoneal cavity much more strongly than could be assumed from the figures obtained in the infusion experiments.

BIBLIOGRAPHY.