STUDIES IN EDEMA.

VII. The Influence of Nephrectomy and other Surgical Operations and of the Lesions produced by Uranium Nitrate upon Absorption from the Peritoneal Cavity.¹

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In order to determine further the factors which influence absorption from the peritoneal cavity, we studied the absorption in nephrectomized animals and in animals injected with uranium nitrate, twenty and seventy-two hours after the injection.

All details regarding experimentation will be found in a previous communication (1).

The following table shows the principal figures to which we shall refer in this communication.

Absorption from the Peritoneal Cavity in Nephrectomized Animals.—In these experiments the kidneys were removed or the vessels were ligated through lumbar incisions. In the majority of the animals the peritoneum was not injured during the operation, but in a few cases it was slightly torn. We find by comparing the results in experiments in which the peritoneum was injured with the results in those in which we found the peritoneum intact, that such injury does not influence the absorption to any great extent. In some of our experiments the absorption was tested immediately after the operation; in the majority of our experiments we waited for eighteen to twenty hours after the operation before the absorption was tested. The results, however, were the same under both conditions. It also appeared that the results were the same in experiments in which we tied off the whole kidney stump, including vessels and ureter, and in experiments in which we tied off the

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### Absorption from the Peritoneal Cavity.

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<th>Condition</th>
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<td>Sodium chloride per cent.</td>
<td>Amount in c.c.</td>
<td>Sodium chloride per cent.</td>
<td>Amount in c.c.</td>
<td>Sodium chloride per cent.</td>
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<tr>
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<td>-0.60</td>
<td>77</td>
<td>53</td>
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<tr>
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<td>-</td>
<td>62</td>
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<td>Normal; distilled water</td>
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<td>-</td>
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<td>Normal; distilled water; adrenalin intraperitoneally</td>
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<td>-</td>
<td>21</td>
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<td>3 day uranium nitrate</td>
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<td>Peritonitis</td>
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ureter close to the pelvis of the kidney and left the renal circulation intact. In four instances in which the ureter was ligated we found that the results did not differ from those obtained when both the vessels and ureter were ligated.

In twenty-two experiments in which sodium chloride solution was injected into the peritoneal cavity of nephrectomized animals, an average of 47 cubic centimeters of fluid was recovered, while in nineteen experiments in which adrenalin was injected intraperitoneally in addition to the sodium chloride solution, an average of 43 cubic centimeters of fluid was recovered from the peritoneal cavity. We have found that in normal animals 77 cubic centimeters of fluid was recovered from the peritoneal cavity when 120 cubic centimeters of sodium chloride solution had been injected two and a half hours previously. We can, therefore, confirm the statements of Meltzer and Salant (2), and Achard and Caillard (3), that nephrectomy increases the absorption from the peritoneal cavity. In nephrectomized animals the influence of adrenalin in increasing the absorption from the peritoneal cavity has been markedly lessened.

von Koranyi (4) found the osmotic pressure of the blood in nephrectomized animals to be increased even after a period of four hours. In four nephrectomized animals we found the freezing point of the serum twenty-four hours after operation to be on the average — 0.64⁰, a distinct increase over the normal osmotic pressure of the serum. In animals in which 0.85 per cent. sodium chloride solution had been injected into the peritoneal cavity, the mean of the lowering of the freezing point of the blood serum at the end of the experiment is — 0.62⁰, and the mean of the lowering of the freezing point of the recovered peritoneal fluid is — 0.59⁰.

Concerning the absorption of sodium chloride from the peritoneal cavity, we find that in the nephrectomized animals an average of 0.796 gram of sodium chloride was absorbed when 1.02 grams were injected, or .010 gram with every cubic centimeter of fluid. At the end of the experiment the sodium chloride percentage of the peritoneal fluid is 0.505 per cent.; in the blood serum the sodium chloride percentage is 0.487 per cent. In the nephrectomized animals which received injections of adrenalin, an average of
0.861 gram of sodium chloride was absorbed; thus 0.010 gram was
absorbed with every cubic centimeter of fluid. The sodium chloride
percentages in these latter experiments are practically the same as
in the control experiments, namely, 0.49 per cent. in the peritoneal
fluid and 0.49 per cent. in the blood serum.

It has been shown by Bence and Sarvonat (5) that in nephre-
rectomized animals the blood becomes diluted a short time after
the operation. We have found in four cases similar results and
in four other cases the opposite results; in the latter, the blood
became more concentrated. In the experiments of Bence and
Sarvonat the increased amount of water in the blood was in many
cases only relative, for they compared the loss of body weight and
the change of the refractive index of the serum. In our experi-
ments we made no comparison between body weight and refractive
index of the serum, so that our results are expressed by the absolute
figures.

After the injection of sodium chloride into the peritoneal cavity
of nephrectomized rabbits, the blood became more dilute; the re-
fractive index of the serum fell 0.0015. In nephrectomized ani-
imals into whose peritoneal cavities adrenalin was injected, the dilu-
tion of the blood was somewhat less, namely, 0.00105. The average
refractive index of the recovered peritoneal fluid was 1.3361 in
the control experiments and 1.3364 in the experiments in which
adrenalin was injected.

It appears that nephrectomy has increased the relative absorption
of sodium chloride from the peritoneal cavity. The remaining
peritoneal fluid in normal animals, into whose peritoneal cavities
we had injected 0.85 per cent. sodium chloride solution, contained
0.53 per cent., while the blood serum in such animals contained
0.49 per cent. of this salt; thus the sodium chloride percentage of
the recovered peritoneal fluid is slightly lower in nephrectomized
animals than in normal animals, while the sodium chloride per-
centage of the blood serum is approximately the same in both
cases. In nephrectomized animals which were injected with
adrenalin, the relative absorption of sodium chloride is also in-
creased.

The absolute amount of sodium chloride absorbed in nephrec-
tomized animals is increased, inasmuch as only 0.588 gram was absorbed in the experiments with normal animals, as compared to 0.796 gram absorbed in nephrectomized animals. The absolute amount of sodium chloride absorbed in nephrectomized animals which were injected with adrenalin was 0.861 gram as compared to 0.811 gram absorbed in normal animals injected with adrenalin. Thus in nephrectomized animals injected with adrenalin, a greater quantity of sodium chloride has been absorbed.

The dilution of the blood is slightly greater in the nephrectomized than in the normal animals. In nephrectomized animals we find slightly less fluid retained in the blood when adrenalin is injected than in control experiments, although the difference is not quite as marked as in the normal series. Here again adrenalin causes an additional elimination of fluid from the blood vessels.

Achard and Caillard (3) in studying the absorption in nephrectomized guinea pigs also found that the absorption of sodium sulphate or of sodium chloride of fluid was increased; and the movement of sodium chloride or urea into the peritoneal cavity appeared to be increased.

This increased absorption of fluid noted in nephrectomized animals is supposed by Meltzer and Salant (2) to be due to the increase in the osmotic pressure of the blood. They believe this increase in the osmotic pressure to be due to substances retained in the body as a result of the removal of the kidneys, and they assumed, therefore, that the increased absorption is a specific effect of the elimination of the kidney. The possibility existed that irritation of the peritoneum or some influence of the operative procedure, and not only the nephrectomy, might be a factor in increasing the absorption. We, therefore, determined the influence of irritation of the peritoneum and various other operative procedures on absorption.

As a mild irritant of the endothelial cells of the peritoneal cavity, we first used Lugol's solution. Two cubic centimeters of Lugol's solution were added to 120 cubic centimeters of sodium chloride solution, which were injected into the peritoneal cavity. We find in these experiments that the rate of absorption is not altered, inasmuch as we recovered from the peritoneal cavity an average of 71 cubic centimeters of fluid two and one-half hours after the injection.
It was necessary to determine the influence of etherization on absorption. We anesthetized six rabbits for fifteen minutes and on the following day tested the absorption in the usual manner. We recovered an average of 70 cubic centimeters of fluid and found the lowering of the freezing point of the blood serum to be $-0.59^\circ$. We also determined the freezing point of the blood of animals which had been anesthetized twenty-four hours previously, but which had not been injected with sodium chloride solution, and found the average freezing point of the blood to be $-0.60^\circ$, the same as we had found in normal animals. In one case we found the freezing point to be $-0.64^\circ$, but since in the other four cases the freezing point was normal we must consider this as an exception. It appears that, when a rabbit has been deeply anesthetized twenty-four hours previously, the osmotic pressure of the blood is normal and the rate of absorption of fluid from the peritoneal cavity is not increased. It is true that Carlson, Greer and Becht (6) have shown that in dogs the osmotic pressure of the blood is increased during and for a short time after ether narcosis, but it appears from the experiments of Carlson and Luckhardt (7) that this increase in the osmotic pressure, which they suppose to be due to the ether dissolved in the blood, soon disappears and the osmotic pressure falls to an approximately normal level in a few hours.

In a third series of animals we operated in exactly the same manner as we would have done if we had intended to remove both kidneys. We made two lumbar incisions, separated the muscles until we brought into view the retroperitoneal tissues, then inserted a finger into the wound and irritated the peritoneum by friction on the external surface. We avoided as much as possible an injury or disturbance of the kidney. In these animals twenty-four hours after operation, we find the lowering of the freezing point of the blood increased, the average being $-0.625^\circ$. When 120 cubic centimeters of 0.85 per cent. sodium chloride solution were injected into such animals, an average of 57 cubic centimeters of fluid was recovered from the peritoneal cavity. During this time 18 cubic centimeters of urine were secreted and the refractive index of the blood was diminished by 0.0015. Since in animals in which we
made a lumbar incision, the field of operation was in close proximity to the kidney and we might have slightly injured these organs, we carried out another series of experiments in which we made an abdominal incision in the linea alba, opened the peritoneal cavity and irritated the peritoneal surface. In such animals, on the day following the operation, the osmotic pressure of the blood is markedly increased; the lowering of the freezing point here shows an average of $-0.663^\circ$. In two experiments we find an average of 54 cubic centimeters of fluid recovered from the peritoneal cavity after the injection of 120 cubic centimeters of sodium chloride solution and we find the freezing point of the blood to be $-0.64^\circ$.

Might the increased absorption noted in these last two series be due to the irritation of the peritoneal endothelia or would a simple operation with a small degree of injury to the muscle and connective tissue, in which, however, the peritoneum was not injured, also cause increased absorption of fluid? An incision was made on both sides of the spinal column, well above the lower margin of the ribs; the aponeurosis and muscles were divided until the ribs and intercostal muscles were exposed. The muscles and skin were then sutured separately. About twenty-four hours after this operation the blood of such animals showed a lowering of the freezing point of $-0.665^\circ$; thus the osmotic pressure of the blood was increased. When 120 cubic centimeters of an 0.85 per cent. sodium chloride solution were injected into the peritoneal cavity of rabbits which had been so operated on, we recovered at the end of two and one-half hours an average of 53 cubic centimeters of fluid and found an average of 18 cubic centimeters of urine excreted. The recovered fluid showed an average freezing point of $-0.609^\circ$, and the blood serum, $-0.635^\circ$.

Reviewing these last few series of experiments, we find that neither etherization nor mild peritoneal irritation with Lugol’s solution increases the osmotic pressure of the blood or the absorption of fluid from the peritoneal cavity. On the other hand, any operative procedure which involves more or less injury of the tissues increases the osmotic pressure of the blood and also the absorption of fluid from the peritoneal cavity.

From the results of the experiments in which a thoracic incision
was made, it is apparent that peritoneal irritation is not a necessary condition for increased absorption. Indeed, in three animals in which peritonitis developed following the abdominal incision, we recovered an average of 133 cubic centimeters of fluid two and one-half hours after the injection of 120 cubic centimeters of sodium chloride solution. In such animals we find the average of the freezing point of the blood serum to be \(-0.71^\circ\) at the termination of the experiments, showing thus a markedly increased osmotic pressure of the blood.

In these latter experiments we have recovered from the peritoneal cavity more fluid than had been injected. We have to deal here not only with absorption from but also with transudation into the peritoneal cavity. The fluid recovered in these experiments was turbid and contained shreds of fibrin. In one case in which we determined the freezing point of the recovered fluid, it was \(-0.66^\circ\), showing a considerably higher osmotic pressure of the peritoneal fluid than we had noted in any other experiment.

The amounts of fluid absorbed in nephrectomized animals and in animals with operations not directly affecting the kidneys differed but slightly, so that the increased absorption noted in nephrectomized animals was, in the main, not a result of the removal of the kidneys but was due to an operation as such. In view of the fact that the rapidity of absorption in all operated animals was slightly less than in nephrectomized animals we cannot exclude the possibility that the removal of the kidneys has had some slight additional effect in increasing the absorption.

We find in all these experiments, in which animals were operated upon, that with increased osmotic pressure of the blood there is associated increased absorption of fluid and that in every case the osmotic pressure of the blood appears to be somewhat lowered by the absorption of fluid. In those cases in which the osmotic pressure of the blood is not increased—etherization and injection of Lugol's solution—we find no increased absorption of fluid. It thus appears that the absorption of fluid from the peritoneal cavity is mainly influenced by the osmotic pressure of the blood, a fact which agrees well with the results obtained in the experiments in which we tested the influence of adrenalin upon absorption.
We have found that the injection of adrenalin increases the absorption and that nephrectomy has the same action. Inasmuch as it is held by some authors that there exists an antagonism between the action of the adrenals and the kidneys, there is a possibility that removal of the adrenals may have an effect opposite to that of the injection of adrenalin and removal of the kidneys, in other words, that it may decrease the absorption from the peritoneal cavity.

In a series of five experiments we removed both adrenals. The animals so operated upon lived, as a rule, less than twenty-four hours. In only two animals did we determine the absorption of fluid twenty-four hours after operation; in the three others the absorption was determined about six hours after the operation, at which time the animals appeared to have completely recovered from the direct effect of the operation. The average amount of fluid recovered from the peritoneal cavity in such rabbits was 61 cubic centimeters. We find, therefore, that the rate of absorption is increased in rabbits from which the adrenals have been removed.

It is thus apparent that in such animals no specific influence of the loss of the adrenal glands is noted. The effect has been practically the same as that noted after any operation which does not affect the kidney, and it is probable that the increased absorption of fluid in animals in which the adrenals have been extirpated, is due to an increase of the osmotic pressure of the blood, such as has been noted after operations in which the kidneys and adrenals are not injured. This agrees well with our conception of the factors determining the absorption from the peritoneal cavity, inasmuch as adrenalin, extirpation of the kidneys and other operations, in the main, increase the absorption from the peritoneal cavity in direct proportion to the influence they exert on the osmotic pressure of the blood.

ABSORPTION IN ANIMALS INJECTED WITH URANIUM NITRATE ONE DAY PREVIOUSLY.

The rabbits used in this series of experiments had received a subcutaneous injection of five milligrams of uranium nitrate about twenty-four hours previous to the time at which the absorption was
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studied. At this stage of the uranium nitrate poisoning the animal appears perfectly well and the only symptom manifest is an increased secretion of urine.

When 120 cubic centimeters of 0.85 per cent. sodium chloride solution were injected into the peritoneal cavity of such rabbits, we recovered, at the end of two and one-half hours, an average of 74 cubic centimeters of fluid. When in addition to the sodium chloride solution adrenalin was injected intraperitoneally, an average of 46 cubic centimeters of fluid was recovered. Here the adrenalin increased the absorption as markedly as it did in the normal animals. The conditions present in the rabbit one day after the injection of uranium nitrate do not seem to have influenced the absorption of fluid.

The sodium chloride percentage of the recovered peritoneal fluid in the control2 animals in this series was .58 per cent, and, therefore, considerably higher than in normal animals, whereas the total amount of sodium chloride absorbed was 0.606 gram. In the adrenalin experiments the sodium chloride percentage of the recovered fluid was .60 per cent., rather higher than in the controls; the total amount of sodium chloride absorbed was 0.794 gram. With every cubic centimeter of fluid leaving the peritoneal cavity, .012 gram of sodium chloride was absorbed in the control experiments and .0095 gram in the adrenalin experiments.

It appears from the figures of the amounts of sodium chloride absorbed from the peritoneal cavity that more sodium chloride was absorbed in animals one day after the injection of uranium nitrate than in normal animals, in spite of the fact that the amount of fluid absorbed in these latter animals was only a few cubic centimeters more than in the normal animals, while the sodium chloride percentage in the remaining peritoneal fluid was considerably greater in the former. This discrepancy is due to the fact that the sodium chloride percentages in each series were estimated in only five or six individual experiments. In this latter small series the average amount of fluid recovered in normal animals was 80 cubic centimeters.

2 By "control-animals" we mean animals injected with uranium nitrate, but not with adrenalin or another additional substance. In control as well as in the other animals the absorption of solutions from the peritoneal cavity was determined.
therefore slightly above the average attained in the larger series in which all experiments were included. For the uranium nitrate series the average amount of fluid recovered in the experiments in which simultaneously sodium chloride determinations were made, was 71 cubic centimeters, therefore slightly less than the average obtained in the whole series of experiments. Thus in these smaller series of experiments, in which sodium chloride determinations had been made, the variations, although slight, followed opposite directions, so that the difference between the amounts of fluid absorbed is larger than in the more complete series of experiments. If we readjust the figures of the amounts of sodium chloride absorbed in accordance with the figures of the absolute amounts of fluid absorbed in the larger series of experiments, we will find that actually a little less sodium chloride is absorbed in the one day uranium nitrate animals than in normal animals. With this correction we find that about .612 gram of sodium chloride is absorbed in normal animals and .587 gram in animals which had received an injection of uranium nitrate. In the animals in which adrenalin was injected, we find less sodium chloride absorbed in experiments carried out with uranium nitrate animals than in the case of normal animals.

The lowering of the freezing point of the blood serum in rabbits one day after the injection of uranium nitrate is slightly increased; we have found this lowering to be approximately —0.615°. After absorption of sodium chloride solution, the freezing point of the blood rose to the level noted in the serum of normal animals, namely, —0.60°, but it did not rise to the level of the freezing point in normal animals in which absorption of a sodium chloride solution had taken place. The lowering of the freezing point of the recovered peritoneal fluid in control uranium nitrate animals is —0.59°, slightly less than in the serum.

One day after the injection of uranium nitrate, but before the intraperitoneal injection of sodium chloride solution, the sodium chloride content of the serum in rabbits was 0.495 per cent.; it was, therefore, increased over the normal sodium chloride content, which we found to be 0.455 per cent. on the average. This increase may perhaps be due to the increased diuresis, which, in the case of uranium nitrate animals, is accompanied by a decreased sodium chlo-
ride elimination, and we may thus have a relative retention of sodium chloride in the blood. It appears, however, more probable that the increased sodium chloride content of the blood is the primary condition and that the diminished sodium chloride elimination is due to this retention. After the absorption of a sodium chloride solution the sodium chloride content of the blood serum was 0.54 per cent. in animals which had been injected with uranium nitrate. The same percentage was found in animals which received additional injections of adrenalin. We find an increased sodium chloride percentage in the blood in spite of the increased diuresis and in spite of the fact that absolutely more sodium chloride is excreted in both these cases. This increased percentage of sodium chloride in the blood after absorption of a sodium chloride solution corresponds to the increased amount of sodium chloride noted in the blood before the injection of fluid into the peritoneal cavity.

In all the animals injected with uranium nitrate one day previously, the refractive index of the blood shows a reduction after the absorption of fluid. In control animals treated with uranium nitrate it is reduced by .0015 and in those which in addition received injections of adrenalin, by .0005. In the control uranium nitrate animals the dilution of the blood is slightly greater than in normal animals and we find that adrenalin diminished markedly the dilution of the blood here, as well as in normal animals.

As stated above, the animals injected with uranium nitrate one day previously secreted large quantities of urine, an average of 34 cubic centimeters of urine being secreted which contained .41 per cent. of sodium chloride, while in the animals which, in addition to the uranium nitrate received injections of adrenalin, an average of 64 cubic centimeters of urine was secreted, containing .55 per cent. of sodium chloride.

Therefore, we find that in animals which have been injected with uranium nitrate one day previously the rate of absorption of fluid from the peritoneal cavity is the same as in normal animals, and that adrenalin increases the absorption in such animals in a similar measure, as it does in normal animals. The relative absorption of sodium chloride from the peritoneal cavity is diminished in experiments with animals one day after the injection of uranium nitrate,
both with and without the injection of adrenalin, as shown by the high sodium chloride percentage of the remaining fluid. The diminished relative absorption of sodium chloride stands in relation to the high sodium chloride percentage in the blood serum. In this case the movement of sodium chloride appears, therefore, to have been regulated in conformity with the laws of diffusion. The absolute amount of sodium chloride absorbed is also diminished in animals injected with uranium nitrate one day previously. The fluid content of the blood is somewhat greater in these experiments than in experiments with normal animals, in spite of the markedly increased diuresis. This increased retention of fluid in the blood vessels may be due to the increased osmotic pressure of the blood. The influence of adrenalin causing fluid to pass out of the vessels is quite evident in this case, and the dilution of the blood following the injection of adrenalin is even slightly less in experiments with one day uranium nitrate animals than in experiments with normal animals.

As we saw in animals which were injected with uranium nitrate one day previously, adrenalin caused simultaneously increased absorption of fluid, increased diuresis with increased elimination of sodium chloride and lessened retention of fluid in the blood vessels in a similar manner as in normal animals. It appears that a correlation exists between these various phenomena caused by the injection of adrenalin.

ABSORPTION IN ANIMALS INJECTED WITH URANIUM NITRATE THREE DAYS PREVIOUSLY.

The rabbits used in these experiments were given an injection of five milligrams of uranium nitrate three days previous to the absorption experiments. The injection of this quantity of uranium nitrate is sufficient in most cases to produce renal insufficiency at the end of three days, so that little or no urine is secreted. The rabbits are not in a moribund condition and it is rare that edema is present at this stage.

In such uranium nitrate animals, after an intraperitoneal injection of 120 cubic centimeters of 0.85 per cent. sodium chloride solution, we recovered 77 cubic centimeters of peritoneal fluid at
the end of two and one-half hours. When, in addition to the sodium chloride solution, adrenalin was injected intraperitoneally, we recovered on the average 64 cubic centimeters of fluid. The rate of absorption of fluid from the peritoneal cavity was not changed by the anuria or the associated conditions produced by the injection of uranium nitrate. Under these conditions adrenalin, however, seems to have lost to a considerable extent its power to increase the absorption of fluid.

Richter (8) has shown that the lowering of the freezing point of the blood serum is increased in animals in which a nephritis has developed as a result of the injection of uranium nitrate. In four experiments we have found the average freezing point of the blood to be about \(-0.675^\circ\) under such conditions. In the three day uranium nitrate animals which had received an injection of 120 cubic centimeters of 0.85 per cent. sodium chloride solution intraperitoneally, the average freezing point of the blood serum was \(-0.63^\circ\), while that of the peritoneal fluid was \(-0.60^\circ\) at the end of the experiment. We found, therefore, the osmotic pressure of the blood serum increased in rabbits three days after the injection of uranium nitrate, and we also found that absorption of the injected sodium chloride solution caused a lowering of the osmotic pressure of the blood in a similar manner as in normal animals; however, the osmotic pressure did not fall to normal but remained still slightly higher at the end of the experiment.

The sodium chloride percentage of the blood serum has been found by some observers to be decreased, by others to be increased, in uranium nitrate nephritis. We have found the sodium chloride percentage in the blood serum in rabbits three days after the injection of uranium nitrate to be 0.466 per cent., which represents a very slight increase over the normal percentage.

In uranium nitrate animals into whose peritoneal cavities 120 cubic centimeters of 0.85 per cent. sodium chloride solution were injected, the sodium chloride content in the blood serum was 0.50 per cent., and in the peritoneal fluid, 0.0595 per cent. at the conclusion of the absorption experiments. When, in addition, adrenalin was injected intraperitoneally, the sodium chloride percentage in the blood serum was the same as in the uranium nitrate control
experiments, namely, 0.50 per cent.; the percentage in the peritoneal fluid was 0.57 per cent.

In the uranium nitrate control experiments, an average of 0.587 gram of sodium chloride was absorbed from the peritoneal cavity of each rabbit. Here, as in some previous experiments, the sodium chloride determinations had been made in a limited number of experiments and the estimate of the absolute amount of sodium chloride absorbed from the peritoneal cavity was based on the figures of the fluid recovered from the peritoneal cavity in those particular cases. If, however, these estimations had been calculated on the basis of the average of fluid absorbed in all experiments, the figure of the amount of sodium chloride absorbed from the peritoneal cavity would have been 0.574 gram, as compared with 0.612 gram in normal animals. In the adrenalin experiments an average of 0.624 gram of sodium chloride was absorbed from the peritoneal cavity. Adrenalin increases, therefore, the absorption of sodium chloride from the peritoneal cavity even in animals injected with uranium nitrate three days previously. If we compare, however, the absorption in normal animals and in these uranium nitrate animals, we find that both with and without the injection of adrenalin the relative absorption of sodium chloride and the absolute amounts of sodium chloride absorbed are reduced under the influence of uranium nitrate. It is not possible to explain the decreased sodium chloride absorption in animals three days after the injection of uranium nitrate on the basis of an increased sodium chloride percentage of the blood serum, as we did in the experiments with rabbits one day after the injection of uranium nitrate, inasmuch as three days after the injection of uranium nitrate the sodium chloride content of the blood was not found to be increased.

Bence (9) has shown that in the early stages of the uranium nitrate nephritis in rabbits the blood becomes more diluted, its refractive index being lowered; but later on, according to this author, the dilution of the blood gradually disappears and at one time, namely, towards the end of the period of increased diuresis, the blood even becomes slightly more concentrated. Afterwards the blood again becomes more diluted simultaneously with the appearance of edema. In four rabbits we determined the refractive index of the
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blood before the injection of uranium nitrate and also three days after the injection; in one the refractive index was unchanged, in the other three there was considerable dilution of the blood. It appears, therefore, that the period at which we made our absorption experiments was near the beginning of the period of anuria when edema had not as yet developed.

The blood in animals three days after the injection of uranium nitrate, into whose peritoneal cavity sodium chloride solution was injected, showed an average decrease of the refractive index of .0022. The same average decrease of the refractive index was noted in the rabbits poisoned with uranium nitrate three days previously which received injections of adrenalin during the time of absorption of the sodium chloride solution. The average refractive index of the recovered peritoneal fluid was 1.3364 in experiments in which adrenalin was not injected, and 1.3358 in experiments in which it was injected.

In these experiments the blood has, therefore, the tendency to retain fluid even when no solution has been injected into the peritoneal cavity. When, however, such an injection has been made, this tendency toward retention of fluid in the blood becomes still more marked, inasmuch as the fluid content of the blood has appeared to be greater in experiments with animals three days after the injection of uranium nitrate than in any other series of experiments. This occurred in spite of the fact that the amount of fluid absorbed from the peritoneal cavity was not increased, so that the increased amount of water in the blood must in part have been drawn from the tissues.

The anuria and any other conditions which may be present in rabbits three days after the injection of uranium nitrate do not change the rate of absorption of fluid from the peritoneal cavity. It is very probable that the effect of the increase in the osmotic pressure of the blood is neutralized by some other condition. The influence of adrenalin in increasing the rate of absorption is, however, distinctly less marked and has almost disappeared in these animals. The relative absorption of sodium chloride from the peritoneal cavity is delayed in these experiments and the percentage of the sodium chloride in the recovered peritoneal fluid is, there-
fore, slightly higher in animals three days after the injection of uranium nitrate than in normal animals. The absolute amount of sodium chloride absorbed is also less. The injection of adrenalin increases slightly the relative as well as the absolute absorption of sodium chloride. As we stated above, the dilution of the blood after the injection of sodium chloride solution is greater in animals which were injected with uranium nitrate than in normal animals and adrenalin is no longer able to diminish the amount of fluid retained in the blood after administration of uranium nitrate.

We notice, therefore, that three days after an injection of uranium nitrate adrenalin is able to increase only slightly the absorption of fluid from the peritoneal cavity, that it does not exert any influence on the secretion of urine and that it does not cause more fluid to pass out of the blood vessels. It thus appears that there is a distinct relation between these three phenomena.

Achard and Caillard (3) found in guinea pigs which had been injected with uranium nitrate some days previously that less sodium sulphate was absorbed from the peritoneal cavity; when, however, the uranium nitrate was injected intraperitoneally simultaneously with the sodium sulphate solution, the sodium sulphate was absorbed more rapidly.

**DISCUSSION.**

We find in rabbits both one and three days after the injection of uranium nitrate that the osmotic pressure of the blood is increased, slightly in the former case and quite markedly in the latter, and yet the absorption from the peritoneal cavity is not increased in either of these series of experiments. We also note in experiments with animals in which peritonitis had developed increased osmotic pressure of the blood and yet decreased absorption. In these experiments some new and complicating factor comes into play, the character of which we cannot determine at the present time. It has been held by Richter (8) and Heinecke and Meyerstein (10) that uranium nitrate affects the endothelial cells of the blood vessels. If we accept provisionally this explanation of the action of uranium nitrate, we may assume that under its influence alterations in the blood vessels and perhaps also in the endothelial lining of the peritoneal cavity occur which produce changes in the
permeability of the membranes separating the peritoneal cavity from the blood. In a similar manner peritonitis may influence the endothelium of the peritoneum.

That there exists no direct relation between diuresis and absorption becomes quite evident in the nephrectomized animals in which the absorption is quite markedly increased, while in animals which were injected with uranium nitrate one day previously and which show a marked increase in diuresis, the absorption is in no way increased over that noted in normal animals. While no direct relation can be said to exist between increased diuresis and increased absorption yet in certain cases we find these two conditions associated. Thus in all the animals in which an operation, which did not directly affect the kidney was performed, as well as in normal animals injected with adrenalin intraperitoneally, we find the rate of absorption increased and also a slight increase in diuresis. After an operation the increased absorption of fluid from the peritoneal cavity is in all probability the primary condition and the increased diuresis is secondary.

If we summarize the influence of adrenalin on absorption from the peritoneal cavity under the conditions which we have considered in this paper, we find in all the series that the absolute amount of sodium chloride absorbed is increased. The relative amount of sodium chloride absorbed in experiments in which adrenalin was injected is slightly increased in nephrectomized animals and in animals injected with uranium nitrate three days previously. In animals, however, which have received an injection of uranium nitrate one day previously the relative amount of sodium chloride absorbed is diminished. Thus although adrenalin uniformly increases the absolute amount of sodium chloride absorbed, its influence on the relative absorption of sodium chloride varies.

In all the series of experiments reported in this paper we find the sodium chloride content of the blood to be greater at the end than at the beginning of the absorption. In the nephrectomized animals the sodium chloride percentage in the blood before the intraperitoneal injection of fluid is the same as in animals injected with uranium nitrate three days previously; but after the absorption of the sodium chloride solution the percentage is greater in the latter
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(uranium nitrate) animals. After the absorption of fluid from the peritoneal cavity the dilution of the blood is also greater in animals three days after the injection of uranium nitrate than in the nephrectomized animals, so that the amount of sodium chloride retained in the blood in the former animals is even greater than appears from the percentage. From these considerations it follows that since in nephrectomized animals none of the sodium chloride can leave the body through the kidneys—as it does in small amounts in the three-day uranium nitrate animals or in quite large quantities in the one day uranium nitrate animals—a very large quantity of sodium chloride must be retained in the tissues of nephrectomized animals.

It may be that the decreased sodium chloride percentage in both the blood and the recovered peritoneal fluid of the nephrectomized animals is due to a change in the tissues of the body, as a result of which the absorptive power of the tissues for sodium chloride is increased.

The main difference between nephrectomized and normal animals, on the one hand, and animals injected with uranium nitrate, on the other, is that in the former the sodium chloride is to a great extent removed from the blood or peritoneal fluid either by elimination through the kidneys or by passing into the tissues, while in the latter condition a much smaller quantity of sodium chloride accumulates in the tissues. This lessening of the accumulation of sodium chloride in the tissues under the influence of uranium nitrate may be due either to decreased permeability of the vessels and peritoneal endothelium for sodium chloride or to a diminished capability of the tissues to bind the sodium chloride.

The amount of fluid retained in the blood after the intraperitoneal injection of fluid is the same in nephrectomized animals, and in animals injected with uranium nitrate one day previously. In animals, however, injected with uranium nitrate three days previously, the amount of fluid retained in the blood is considerably greater. The higher osmotic pressure of the blood in these latter animals may be a contributing factor in causing the greater dilution of the blood. That this is, however, not the only cause becomes evident when we consider the influence of the injection of adrenalin
in this condition; we note that here adrenalin does not diminish the dilution of the blood. It is possible that in agreement with the views of Richter (8), Heinecke and Meyerstein (10) and Schlayer, Hedinger and Takayasu (11), the reactions of the blood vessels are changed under the influence of uranium nitrate and that, therefore, after the administration of uranium nitrate, adrenalin is no longer able to cause more fluid to pass out of the blood vessels.

In nephrectomized animals larger amounts of osmotically active substances other than sodium chloride must pass into the peritoneal cavity than in normal animals; this follows from the fact that the freezing point of the recovered peritoneal fluid is approximately the same in both series of experiments notwithstanding the diminution in the sodium chloride percentage of the recovered peritoneal fluid in nephrectomized animals.

One day after the injection of uranium nitrate the freezing point of the peritoneal fluid differs very little from that noted in normal animals, but its sodium chloride content is considerably greater; the quantity of substances other than sodium chloride which might increase the osmotic pressure, and which have passed into the peritoneal cavity from the surrounding tissues and fluids, must, therefore, be smaller. Likewise three days after the injection of uranium nitrate the freezing point of the peritoneal fluid is very nearly the same as in normal animals, but the sodium chloride percentage is higher; consequently in these experiments again a smaller quantity of osmotically active substances other than sodium chloride must have passed into the peritoneal cavity.

In all the experiments reported in this paper we note that the osmotic pressure of the blood is slightly lower at the end than at the beginning of the experiments, a condition which we also noted in our previous paper, and, in view of the fact that the solution injected into the peritoneal cavity had a slightly lower osmotic pressure than the normal serum, this lowering of the osmotic pressure of the blood may easily be understood.

Throughout these experiments we find the osmotic pressure of the recovered peritoneal fluid to be less than that of the blood serum, while in experiments with normal animals into whose peritoneal cavity we had injected 0.85 per cent. sodium chloride
solution the reverse condition was found. Georgopulos (12) who studied the relative osmotic pressure of the edematous fluid and of the blood in animals at various stages of uranium nitrate nephritis found the osmotic pressure of the ascitic fluid to be the same as or less than that of the blood serum. On the other hand, Richter (8), who also studied the osmotic pressure of the ascitic fluid and the blood in animals injected with uranium nitrate, found the osmotic pressure of the ascitic fluid greater than that of the blood. Richter's determinations were made at a later stage of the intoxication than were ours and since we examined our rabbits at one period only—a period when edema had not yet appeared—our conclusions do not contradict those of Richter.

The absence of renal secretion may be a factor in causing this difference in the distribution of the osmotically active substances in the blood and peritoneal fluid. That there are, however, other factors present which influence this condition becomes apparent if we take into consideration the fact that, notwithstanding the increase in diuresis one day after the injection of uranium nitrate, the osmotic pressure of the blood in such animals is greater than that of the peritoneal fluid.

In both nephrectomized animals as well as in animals injected with uranium nitrate three days previously, the albumin content of the recovered peritoneal fluid is slightly higher than in normal animals.

Observations on the dilution of the blood and the occurrence of edema in nephrectomized and in uranium nitrate rabbits led Bence (9) to the conclusion that the conditions leading to the production of edema in both these animals were essentially the same; from our experiments it appears, however, that there exist marked differences between nephrectomized rabbits and rabbits with uranium nitrate poisoning. Such differences concern the absorption of fluid from the peritoneal cavity, the distribution of sodium chloride and other osmotically active substances in the blood and in the peritoneal cavity, and also the retention of fluid in the blood. These are factors of fundamental importance in the production of edema and the differences between nephrectomized animals and animals treated with uranium nitrate, which we have established; let us
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expect that corresponding differences exist in regard to the readiness with which edema appears in these two classes of animals.

CONCLUSIONS.

1. In the experiments recorded in this paper the influence of the osmotic pressure of the blood upon absorption of fluid from the peritoneal cavity becomes apparent. Nephrectomy, removal of the adrenals, and other operations increase the osmotic pressure of the blood and increase the absorption of fluid from the peritoneal cavity. On the other hand, ether narcosis, at the period at which we tested its influence, causes neither an increase of osmotic pressure of the blood nor an increase in the absorption of fluid from the peritoneal cavity.

2. The increased osmotic pressure and increased absorption of fluid in nephrectomized animals is to a great extent not a specific effect of the removal of the kidneys, but approximately the same conditions can be observed after incisions of the skin and muscles.

3. After poisoning with uranium nitrate and in cases of peritonitis, complicating factors come into play, and under such conditions the absorption from the peritoneal cavity is not increased, notwithstanding the higher osmotic pressure of the blood.

4. In conditions in which the osmotic pressure of the blood is very high before the injection of sodium chloride solution into the peritoneal cavity (nephrectomized rabbits or rabbits injected with uranium nitrate three days previously), adrenalin causes no increase, or only a very slight one, in the absorption of peritoneal fluid. On the other hand, one day after the injection of uranium nitrate the osmotic pressure of the blood is only slightly increased before the injection of the sodium chloride solution into the peritoneal cavity, and here adrenalin causes a marked increase in absorption of fluid from the peritoneal cavity.

5. In animals injected with uranium nitrate the retention of sodium chloride and other osmotically active substances in the blood is not entirely due to interference with the functions of the kidney.

We did not include in this paper the records of the individual experiments in order to limit the size of this communication. It may, however, be stated that the results communicated in this paper are based on 199 experiments carried out in an identical number of rabbits.
This retention may be explained either by an inability of the tissues to bind the sodium chloride and other osmotically active substances or to a diminished permeability of the blood vessels for such substances.

6. While in nephrectomized animals the elimination of sodium chloride from the peritoneal cavity and also from the blood is increased, in animals injected with uranium nitrate such an elimination is diminished. This increase in the sodium chloride content of the peritoneal fluid in animals treated with uranium nitrate is accompanied by a decrease in the diffusion of other osmotically active substances into the peritoneal cavity.

7. While in nephrectomized animals and in animals injected with uranium nitrate one day previously, adrenalin causes a diminution of the fluid retained in the blood-vessels similar to the diminution noted in normal animals, adrenalin no longer exerts such an effect at a later stage of the uranium nitrate poisoning. At this period after the administration of uranium nitrate, the retention of fluid in the blood vessels is apparently equal in experiments with and without the injection of adrenalin, and following the absorption of fluid from the peritoneal cavity, the retention of fluid in the blood vessels in the uranium nitrate animals is increased comparatively to a greater extent than in normal animals.

8. Our experiments show a marked difference in the distribution of fluid and of osmotically active substances in nephrectomized animals and in animals injected with uranium nitrate. This difference may explain the much greater liability to the development of edema in animals injected with uranium nitrate.

BIBLIOGRAPHY.
3. Achar and Caillard, Arch. de méd. expér., 1905, xvii, 669.
5. Bence and Sarvonat, Rev. de méd., 1907, xvi, 620.
6. Carlson, Greer and Becht, American Jour. of Physiol., 1907, xix, 377.
7. Carlson and Luckhardt, American Jour. of Physiol., 1908, xx, 162.