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HYPERTENSION ASSOCIATED WITH EXPERIMENTAL SERUM NEPHRITIS.

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RECENTLY much interest has been shown in the nature of the arteriolar hypertonicity which produces sustained vascular hypertension. Such an increase of arteriolar tonus may be due to (1) an increased nervous vasoconstrictor activity, or (2) an increase of the intrinsic tonus that the arteriolar wall shows in common with other forms of plain muscle.

Very thorough clinical research carried out by Pickering (1936), and Prinzmetal and Wilson (1936), has failed to demonstrate any increase of sympathetic nervous tonus in the chronic hypertensive states that occur in advanced chronic nephritis and in essential hypertension. The nature of this increase in the intrinsic arteriolar tonus is unexplained as, so far, there is no reliable evidence of the presence of any circulating chemical pressor body in either renal or non-renal hypertensive states.

On the other hand, the possibility of a nervous origin for the vasoconstriction of renal hypertension was suggested by Loeb (1905-06) who thought that this might be produced

by means of a nervous reflex originating in the damaged kidney. Menendez (1933) produced hypertension in dogs by constricting the lumen of the renal veins to a degree sufficient to cause very pronounced pathological changes in the kidney. He found that this hypertension did not occur if the kidneys had previously been denervated. Page (1935) and Collins (1936) produced a severe and sustained hypertension in dogs by compression of the renal arteries. They found that this hypertension was not prevented by previous denervation of the kidneys.

We have already shown (Arnott and Kellar, 1935) that hypertension occurs in rabbits with kidneys damaged by intravenous injection of sodium oxalate. We found (Arnott and Kellar, 1936) that this hypertension did not develop in animals whose right kidney had been removed and whose left kidney had been denervated. We were dissatisfied with sodium oxalate as a nephrotoxic agent in that the lesion was mainly tubular and bore no resemblance to human glomerulonephritis. We found that the method of producing renal damage described by Masugi (1933-34) was practicable and resulted in a type of lesion very similar to human glomerulonephritis. We have already described the method and its histological results in detail (Arnott, Kellar, and Matthew, 1936), but a brief summary is indicated.

Using rigid aseptic technique, rabbits' kidneys are rendered blood-free by perfusion with saline and are then ground and suspended in saline. This suspension is injected intraperitoneally into ducks in 15-20 c.c. doses. The procedure is repeated at four-day intervals on 25-30 occasions. The ducks are then killed by withdrawing as much heart blood as possible. The serum is obtained and is heated to 56° C. for thirty minutes in order to destroy the primary toxicity. Approximately 50 c.c. of serum are obtained from each animal, and in order to obtain a reasonable quantity of serum of constant potency it is our practice to pool the blood from a batch of six ducks. The serum is injected intravenously into rabbits, usually in three successive daily doses of 3-5 c.c. The histological changes consist of swelling and proliferation of the endothelial cells of the capillaries of the glomeruli proceeding in the more advanced stages to the formation of epithelial crescents and the complete hyalinisation of the glomeruli with degeneration and fibrosis of the attendant tubules.

Hypertension Associated with Serum Nephritis

Blood pressure is estimated by the carotid loop method of Van Leersum, which consists of the operative exteriorisation of the common carotid artery and its inclusion in a tube of skin. Estimations are made with the aid of the apparatus we have already described (1936*a*). Using the above method of producing renal damage we have conducted the following investigations into the resulting blood pressure changes :—

(1) A study of the hypertension that accompanies serum nephritis.
(2) The effect of previous renal denervation on the intensity of the renal lesion.
(3) The effect of previous renal denervation on the hypertension.
(4) The effect of renal denervation on an established hypertension.

1. Hypertension in Serum Nephritis.

It was soon discovered that each batch of serum showed a different nephrotoxic activity, therefore the results of each serum used will be illustrated by a typical example. The hypertensive response has been observed in thirty animals.

Serum " *A*."—Rabbit " 68 " received two successive daily doses of 3 c.c. of serum. Blood pressure rose after 24 hours,

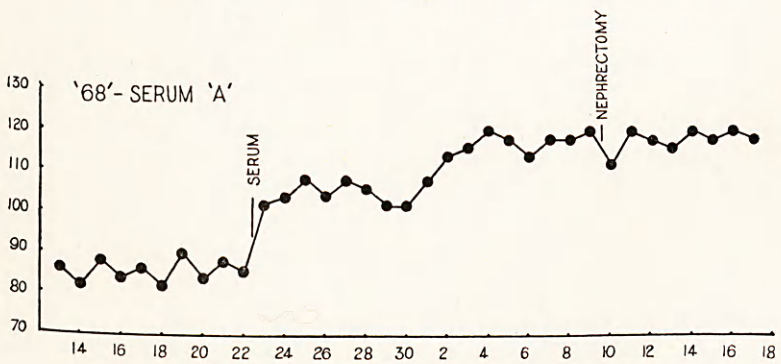

CHART 1.
Simple Hypertension.

and the average pressure for the following 25 days was 139 per cent. The hypertension lasted 36 days. Albuminuria was present at the end of 24 hours and rapidly became heavy.

Unilateral nephrectomy 18 days after the giving of serum showed very extensive glomerular changes of the type already described. This operation did not influence the blood pressure. At 80 days the animal was killed, and the remaining kidney showed many renal units to be completely destroyed and fibrosed. The whole histological picture, however, gave the impression that the pathological process had produced a certain degree of damage and had then ceased to advance (Chart 1).

Serum "*B.*"—Rabbit "75" received three successive daily doses of 3, 3, and 5 c.c. of serum. Blood pressure rose after 9 days. The average pressure for the following 22 days was 130 per cent. Albuminuria appeared 12 days after the first injection, and soon became heavy. The hypertension lasted 87 days, at which time the animal was given a further course of serum which, unfortunately, produced that type of protracted anaphylactic shock which has been described by Coca (1927). There was a progressive fall in blood pressure, and death occurred 10 days later. This later course of injections somewhat marred the original histological picture, but there was definite scarring, indicative of the original lesion (Chart 2).

Serum "*C.*"—Rabbit "80" received three successive daily injections of 2, 4, and 4 c.c. of serum. The blood pressure rose after 10 days, and the average pressure for the following 20 days was 119 per cent. The hypertension lasted 70 days. Albuminuria appeared 4 days after the first injection and became moderate in intensity. This animal is still alive (Chart 3).

Serum "*D.*"—Rabbit "128" received three successive daily doses of 4 c.c. serum. Hypertension appeared in 5 days, and the average pressure for the following 19 days was 120 per cent. The duration of hypertension was 27 days. Albuminuria appeared on the 8th day and became heavy. This animal is still alive (Chart 4).

To illustrate the occurrence of definite renal damage with a relatively slight hypertension the case of rabbit "126" is described. This animal received three successive daily injections of 5 c.c. of serum "D." The blood pressure rose in 2 days, and the average pressure for the following 14 days was only 111 per cent. The animal died from a hæmorrhage from the carotid loop. Histologically the glomerular tufts

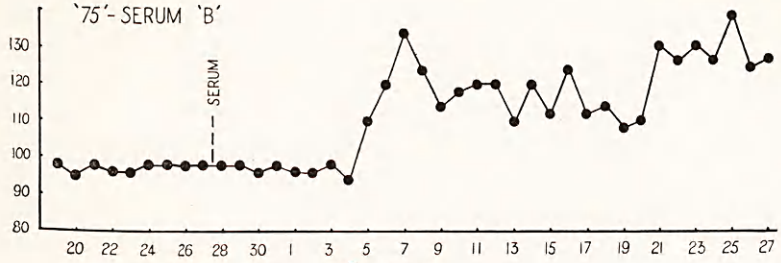

CHART 2.
Simple Hypertension.

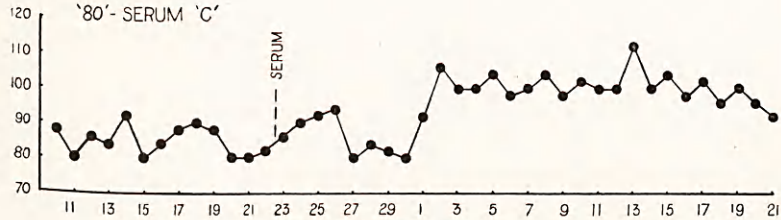

CHART 3.
Simple Hypertension.

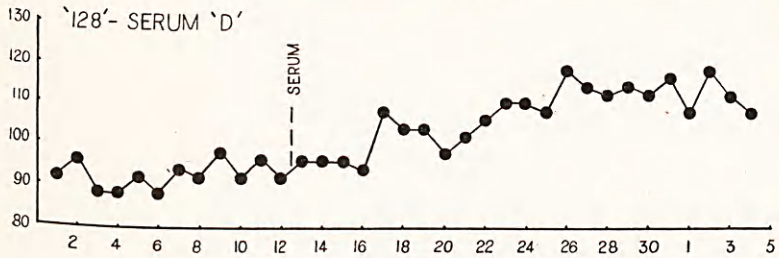

CHART 4.
Simple Hypertension.

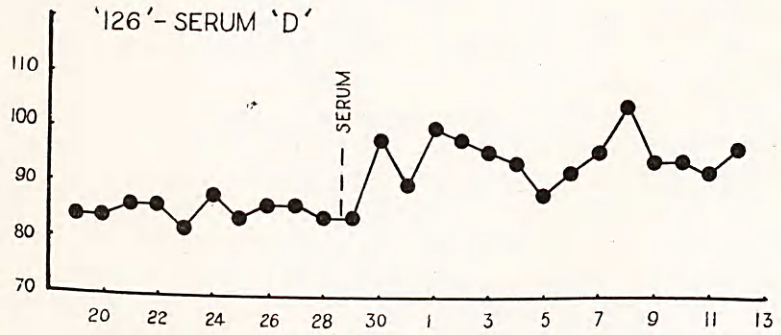

CHART 5.
Simple Hypertension.

showed very definite swelling and nuclear increase with several "epithelial crescents," a degree of renal damage found to be associated with a more pronounced hypertension in other animals (Chart 5).

Serum "*L.*"—Rabbit "5" received two successive daily doses of 5 c.c. serum. Hypertension appeared in 4 days, and the average pressure during the ensuing 19 days was 129 per cent. Albuminuria appeared on the third day, and became heavy. The animal is still alive and no histology available, but other observations show that this serum has never failed to produce a severe lesion when used in the above doses (Chart 6).

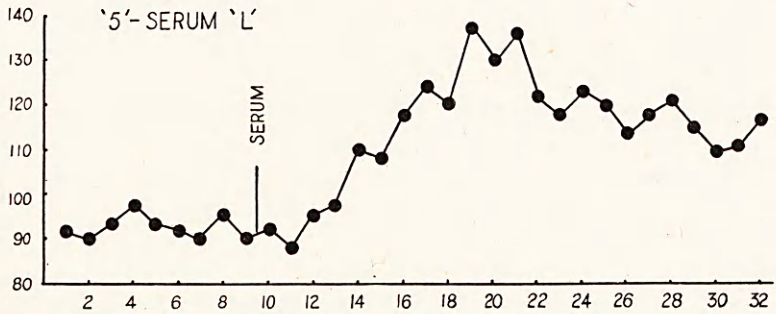

CHART 6.

Simple Hypertension.

Summary.

Our results indicate that serum nephritis is associated with a definite hypertension, the characteristics of which vary considerably when different batches of serum are used. The interval between the first injection and the onset of hypertension may be as short as 24 hours or as long as 10 days, and the duration of the hypertension ranges from a fortnight to a permanent elevation of pressure, although the usual period lies between 30 and 40 days. It has also been found that the intensity of the histological changes does not appear to parallel the degree of hypertension; for instance, serum "B" produced a very pronounced hypertension with a degree of histological change not nearly so severe as in some examples of serum "D" in which hypertension was relatively slight. Albuminuria may precede or follow the onset of hypertension.

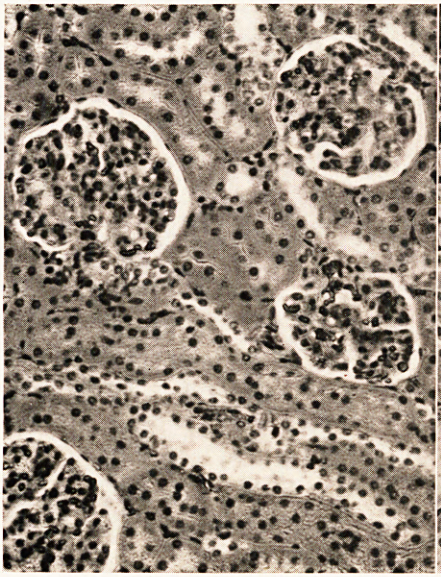

FIG. 1.—Left.

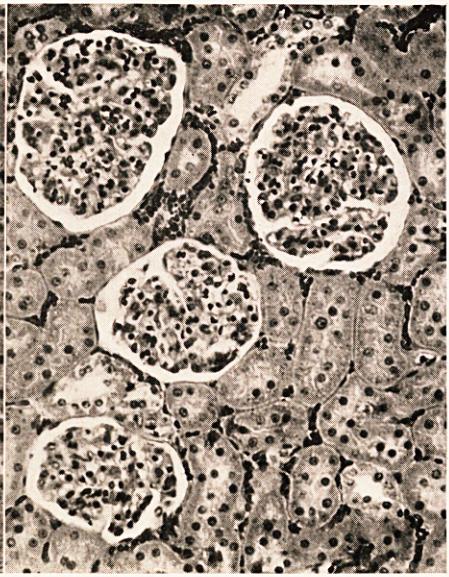

FIG. 2.—Right.

Early Nephritis. Left Kidney Denervated

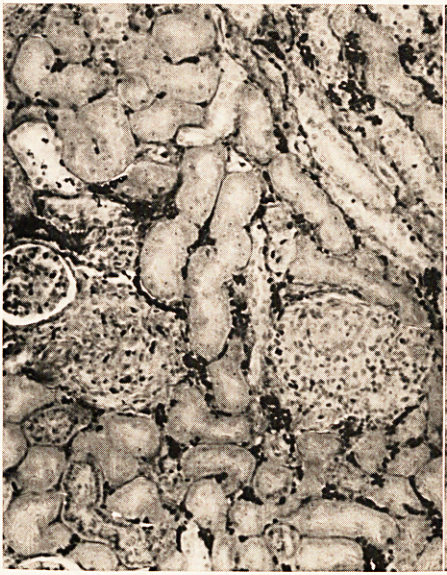

FIG. 3.—Left.

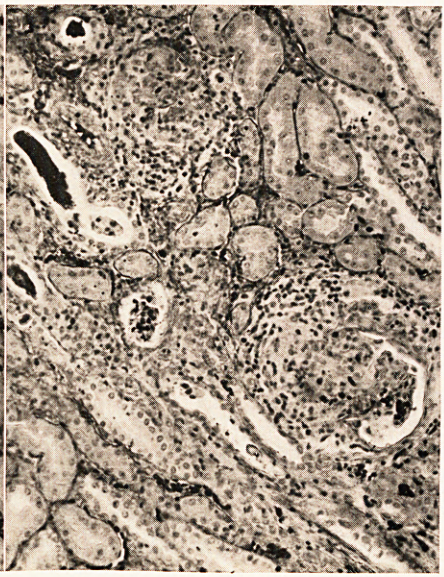

FIG. 4.—Right.

Late Nephritis. Left Kidney Denervated.

2. The Effect of Previous Renal Denervation on the Intensity of the Renal Lesion.

Before proceeding to study the effect of renal denervation on the hypertension of serum nephritis it was obviously desirable to ascertain whether the denervation altered the intensity of the renal lesion. Müller, Petersen, and Rieder (1930) reported some experiments in which they subjected dogs, with one kidney denervated, to heavy intravenous injections of *B. coli* followed in 30 minutes by chilling. Albumin, erythrocytes, and bacteria appeared promptly in the urine from the normally innervated kidney; whereas the urine from the denervated side continued to be normal. Milles, Müller, and Petersen (1931) considered that renal denervation in the dog is followed by degenerative changes in the intima of the blood vessels.

In five rabbits denervation of the left kidney was performed and they were then given three successive daily injections of 5 c.c. of serum. The animals were killed at intervals varying from 10 to 56 days. The histological changes in the two kidneys were compared, the intact organ serving as a control for the denervated kidney. In no case was there found to be any detectable variation in the intensity of the changes on the two sides. Illustrations of the normal and denervated kidneys—one early and the other late—of two of these animals are shown.

The results, therefore, indicate that denervation does not alter the intensity of the nephritic process.

3. The Effect of Previous Renal Denervation on the Hypertension.

Denervation of the kidney in the rabbit is not a difficult operation, although it is very easy to damage the renal vein, especially on the right side where the renal pedicle is short. In order to minimise this risk the right kidney is excised and the left kidney denervated. The details of the operation of denervation are as follows: After the blood pressure has been controlled for a suitable period, the operation is performed under nembutal and ether anæsthesia. The left kidney is entirely separated from its fascial attachments and the fat around the renal pelvis and ureter carefully removed. The

artery, after being gently separated from the vein for a distance of 1 cm. or so, is held on the blade of a blunt dissector and gently scraped with the edge of a sharp knife. With experience it is possible to remove all the nerve fibres and areolar tissue that surrounds the vessel. The ureter is then gently scraped. The kidney is then secured in position by suturing the peritoneum of the posterior abdominal wall across the kidney; failure to do this has led to a torsion of the renal pedicle with subsequent atrophy of the organ. It is found that approximately 75 per cent. of the animals survive this operation. It does not produce any change in the blood pressure.

Seven animals which had made a satisfactory recovery from the operation of left denervation and right nephrectomy were subjected, after a suitable interval, to a series of injections of serum of known hypertensive power. It has already been shown that the hypertensive characteristics of each serum vary. Therefore, in illustrating the results, those obtained from each of the three sera are grouped separately. For comparison, the pressures of the control group of normally innervated animals are illustrated on the same chart. The pressures are calculated as percentages of the average normal pressure during the control period.

Group 1, *Serum* "*B*."—The average pressure of the three denervated animals, after the injection of serum, was 98 per cent., whereas that of the control group was 130 per cent. (Chart 7).

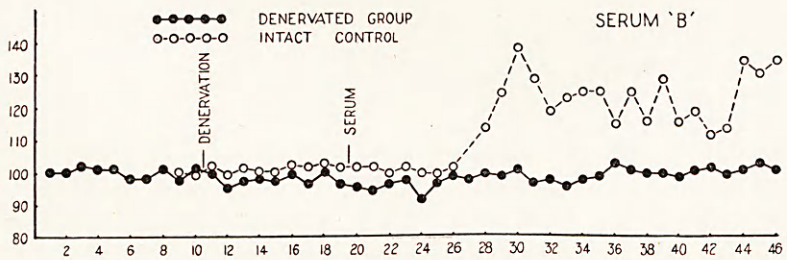

CHART 7.

Prevention of Hypertension.

Group 2, *Serum* "*C*."—The average pressure of the denervated animal, after the injection of serum, was 101 per

cent., whereas that of the control group was 119 per cent. (Chart 8).

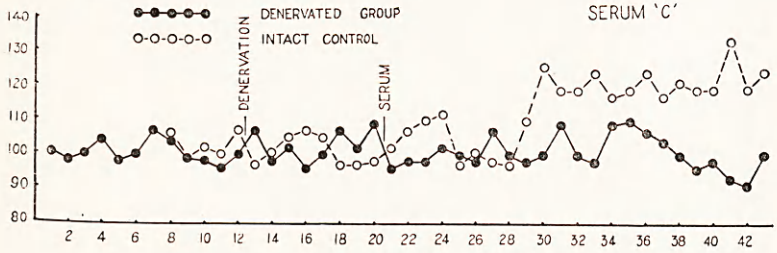

CHART 8.

Prevention of Hypertension.

Group 3, *Serum* " *L.*"—The average pressure of the three denervated animals, after the injection of serum, was 100 per cent., whereas that of the control group was 129 per cent. (Chart 9).

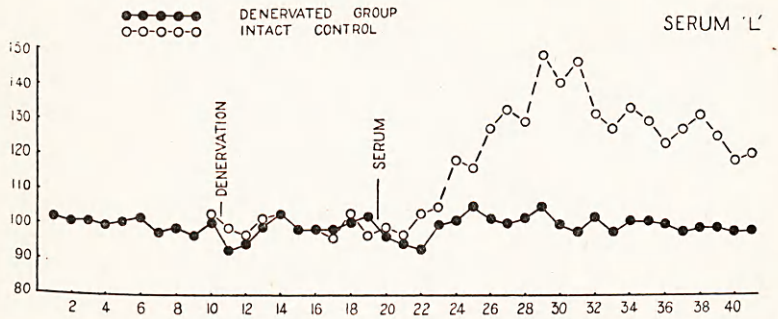

CHART 9.

Prevention of Hypertension.

Summary.

Previous renal denervation prevents the occurrence of the hypertension of serum nephritis.

4. Renal Denervation in Established Hypertension.

Having found that renal denervation prevented the occurrence of the hypertension of serum nephritis it was obviously desirable to study the effect of renal denervation on an established hypertension. It seemed likely that there would be considerable risk in carrying out the operation of

right nephrectomy and left renal denervation in an animal suffering from acute serum nephritis. In order to minimise this risk the operation was performed in two stages. In four animals left renal denervation was done prior to giving serum

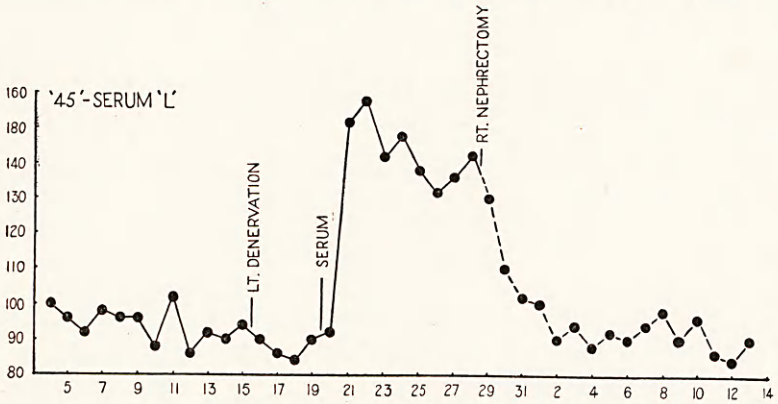

CHART 10.
Termination of Hypertension.

and the right kidney removed when hypertension was well-established. In one animal the reverse procedure was adopted, *i.e.* right nephrectomy was performed first and the left kidney denervated during the hypertensive phase. Several animals

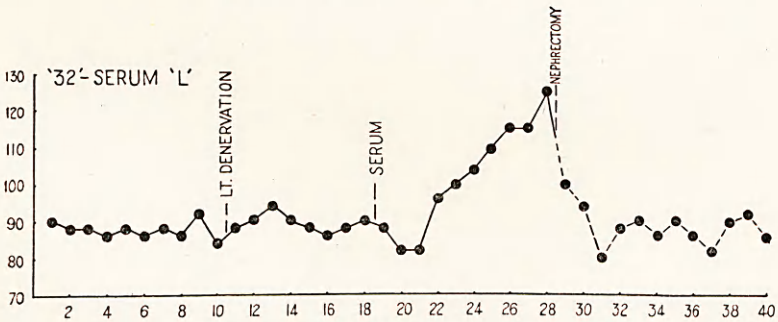

CHART 11.
Termination of Hypertension.

were rejected for the purpose of this experiment because the hypertension that followed the serum injections was not considered sufficiently adequate to demonstrate an unquestionable termination.

It will be seen from the five charts illustrated that the final severance of the renal nerves was followed by a dramatic

fall in blood pressure (Charts 10-14). Reference to the charts illustrating the first section of this paper will show the type of hypertension which sera " D " and " L" produce in the

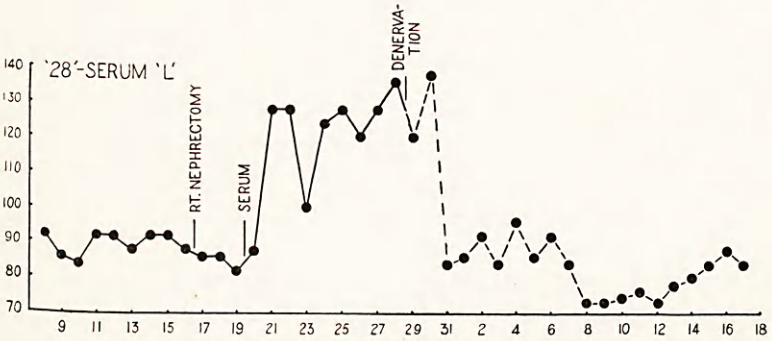

CHART 12.
Termination of Hypertension.

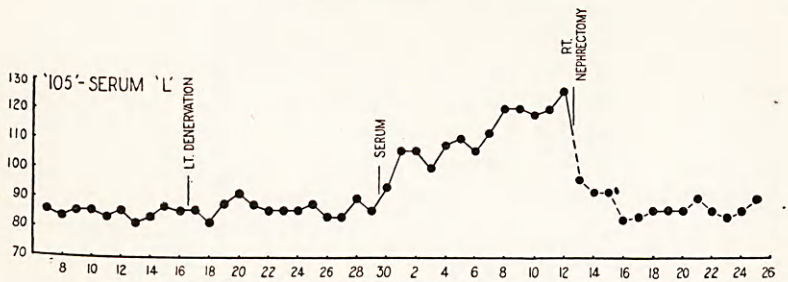

CHART 13.
Termination of Hypertension.

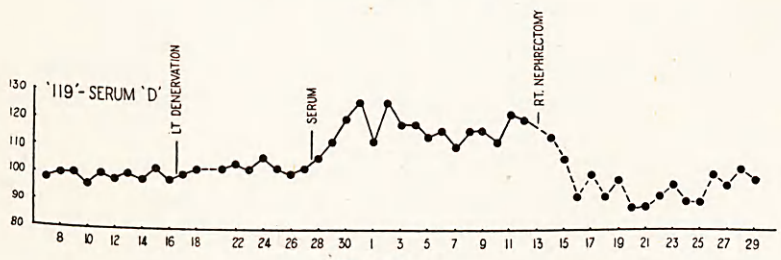

CHART 14.
Termination of Hypertension.

normally innervated animal. It was noted that the termination of the hypertension did not lessen albuminuria, and that there was no obvious change in the animals' general condition. That laparotomy *per se* does not lower the blood pressure is

made abundantly clear by the fact that none of the operations carried out prior to giving serum altered the blood pressure, and reference to the chart of rabbit "68" will show that nephrectomy was carried out without effect upon blood pressure.

Summary.

Bilateral section of the renal nerve supply terminates the hypertension of serum nephritis.

Discussion.

The results described confirm those obtained with oxalate nephritis (Arnott and Kellar, 1936) and they strengthen the contention that the hypertension of acute diffuse renal disease depends for its occurrence upon the integrity of the renal nerve supply. This points to two possibilities—(1) that the hypertension is produced by an autonomic vasoconstrictor reflex originating in the damaged kidneys, or (2) that the hypertension is produced by some chemical mechanism which depends for its operation on the integrity of the renal nerve supply. There is at present no collateral evidence in support of the second hypothesis, whereas the first hypothesis receives striking confirmation from recent work by Pickering (1936*b*) on the nature of the arteriolar hypertonicity in human cases of acute glomerulo-nephritis. He used the same methods which had already led him to the conclusion (Pickering, 1936*a*) that the *chronic* hypertension of advanced nephritis and essential hypertension was not due to excessive nervous vasoconstrictor tonus. These methods applied to a series of cases of acute glomerulo-nephritis led to the opposite conclusion—that the hypertension was due to an abnormal degree of such tonus.

These results of Pickering may also throw light on the discrepancy between our results and those of Page (1935) and Collins (1936), who found that the hypertension produced by constriction of the renal artery could not be prevented by previous renal denervation. This hypertension was probably of the chronic type and is more comparable with the chronic hypertensive states of advanced renal damage than with the hypertension of acute renal disease. It may well be that integrity of the renal nerves is necessary for the production of acute renal hypertension only.

Conclusions.

1. Hypertension is associated with experimental serum nephritis.

2. Previous renal denervation does not alter the intensity of the lesion of serum nephritis.

3. Previous renal denervation prevents the occurrence of hypertension in serum nephritis.

4. Renal denervation terminates the hypertension of serum nephritis.

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