# REDUCTION OF ARTERIAL BLOOD PRESSURE OF HYPERTENSIVE PATIENTS AND ANIMALS WITH EXTRACTS OF KIDNEYS

By IRVINE H. PAGE, M.D., O. M. HELMER, Ph.D., K. G. KOHLSTAEDT, M.D., P. J. FOUTS, M.D., and G. F. KEMPF, M.D.

*(From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital, Indianapolis)*

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An increasing body of evidence suggests that not only can the kidneys initiate arterial hypertension but also counteract it. The evidence for the latter may be briefly summarized as follows:—

Many investigators following Goldblatt (1937) found that when the renal artery of one kidney is constricted by a clamp or the renal parenchyma compressed by the scar of cellophane perinephritis (Page, 1939*a*), removal of the other kidney hastens and intensifies the rise in arterial pressure. This suggests that normal renal tissue is concerned in preventing the rise of blood pressure to abnormal levels. Indeed Katz, Friedman, Rodbard, and Weinstein (1939) believe that the severity of the hypertension depends on the ratio of ischemic to normal renal tissue.

A second fact of great importance, originally demonstrated by Tigerstedt and Bergmann (1898), is that bilateral nephrectomy greatly increases the sensitivity of test animals to extracts of kidney containing renin. They interpreted this as indicating that renin was excreted by the kidneys. Subsequent work by Merrill, Williams, and Harrison (1938) confirmed this observation, but, since the hypersensitivity appeared only after several hours, they suggested that it was due not to excretion of renin but to the loss of an anti-pressor substance.

Evidence of a different nature has come from studies on renin and the pressor substance, angiotonin, derived from interaction of renin and renin-activator (Page and Helmer, 1939). If sufficient renin is injected into an animal so that it no longer responds by a rise of arterial pressure (tachyphylaxis), plasma from it with added renin no longer causes vasoconstriction when perfused through an isolated rabbit's ear (Page, 1939*b*). More important, even the addition of renin-activator does not impart vasoconstriction properties. In contrast, normal blood with added renin causes vasoconstriction. Administration of renin thus appears to call forth a substance which counteracts its action.

A fourth observation of importance is that removal of the kidneys of the donor animal greatly enhances the vasopressor response to both renin and angiotonin when they are mixed with blood and perfused through an isolated rabbit's ear. The observation that blood from a nephrectomized dog when perfused through a rabbit's ear greatly enhances the vasoconstrictor action of angiotonin as compared with blood from a normal dog, demonstrates that the influence exerted by the operation of nephrectomy is of humoral nature. These facts clearly suggest that the removal of the kidneys abolishes a

source of a substance which inhibits the vasopressor action of angiotonin and renin (Page, 1939*b*).

Further evidence in support of the view that an inhibitor occurs in the body is furnished by the observation that the hypersensitivity of the bilaterally nephrectomized dog to renin and angiotonin may be reduced or abolished by transfusion of large amounts of blood from normal animals or animals made tachyphylactic to renin (Page and Helmer, 1940). This appears to constitute a transfer of inhibitor from one animal to another. Further, according to Rodbard, Katz, and Sokolow (1940), the arterial pressure of hypertensive dogs is reduced by transplanting renal tissue into the dog and allowing degeneration to occur. This requires confirmation.

Attempts to extract such an inhibitor or anti-pressor substance from the kidneys have been successful both in the hands of Grollman, Harrison, and Williams (1940) and in ours (1940). The evidence at present available indicates that we are dealing with the same active principle as that reported shortly before by Harrison, Grollman, and Williams. Our work was based on different reasoning and was done independently. The two groups are now collaborating toward a further solution of the problem.

The object of this paper is to present the evidence gathered from a study of dogs, rats, and patients with hypertension which leads us to believe that a substance is present in normal kidneys which is extractable, having the property of reducing arterial blood pressure over prolonged periods of time. Experience to date suggests that it may have therapeutic properties.

## *Methods*

Renal extracts were assayed for their ability to reduce arterial blood pressure by subcutaneous injection into dogs or rats made hypertensive by the silk or cellophane perinephritis method of Page (1939*a*). 51 per cent of the dogs at some time during the course of the hypertension exhibited signs and symptoms of the malignant phase of the disease. Blood pressure was measured daily in the dogs by direct intra-arterial puncture of the femoral artery and in the rats by the method of Williams, Harrison, and Grollman (1939). The animals were not employed unless the pressure on 4 or more days was reasonably stable above the level of 170 to 190 mm. Hg mean pressure. In the rats each pressure was an average of not less than five readings. Unless a consistent fall of 40 mm. or more was observed, the extract was not considered active. The diet of the animals was constant and they were handled by the same men each day. The dogs weighed from 10 to 14 kilos and the rats, 200 to 300 gm.

The patients were for the most part cases with known histories who had been studied for long periods of time in the Lilly Clinic. Some were ambulant while receiving daily treatment and others were confined to bed. All except two of the patients with malignant hypertension had been studied for a month or more in bed in the hospital. The methods of study were similar to those which we have employed for the past 9 years (Page and Heuer, 1937). Patients exhibiting marked lability of the blood pressure, except in one case, were not used for treatment because of the obvious difficulty of interpreting the results. All of them except the five patients with malignant hypertension exhibited so called "fixed hypertension," though arteriosclerosis, as ascertained by examination of the eyegrounds, was not unusually severe. Urea clearance, maximal

ability to concentrate urine, and the Addis sediment count indicated no severe renal damage excepting in the cases of malignant hypertension. Electrocardiographic and roentgenographic changes in the heart varied markedly.

Three of the patients with malignant hypertension were in desperate condition before treatment was started. They had severe reduction of vision and urea clearance below 10 per cent of normal. The disease in two of the patients was less severe and the renal function was not gravely reduced.

### *Preparation of Renal Extracts*

A number of different kinds of extracts have been found active. Some of these have been studied since the publication of our first paper (1940). Grollman, Harrison, and Williams (1940) have also published methods for the preparation of renal extracts.

Probably the simplest method for the preparation of the kidney extracts is as follows:—

10 kilos of finely ground fresh kidneys are extracted with 15 liters of 2 per cent sodium chloride with rapid stirring for 15 to 30 minutes. The extract is freed from the bulk of the insoluble residue by squeezing it through cheese-cloth. Glacial acetic acid is added until a pH of 4.7 is obtained (brom-cresol green). The precipitate which is formed is removed by centrifuging and the clear, supernatant fluid concentrated *in vacuo* at a low temperature and dialyzed against running tap water. The dialyzed extract is again concentrated to the desired volume.

This extract can be further purified by means of fractionation with ammonium sulfate.

The above method yields extracts of fair potency but difficulties with filtration make it unsatisfactory for preparation on a large scale. The application of heat during the extraction, as described in the following method, overcomes this difficulty.

*Preparation of Extracts with the Aid of Heat.*—

10 kilos of fresh pork kidneys are ground through a fine meat chopper into 15 liters of distilled water to which 300 gm. of sodium chloride and 300 cc. of glacial acetic acid have been added. The vessel containing the mixture is immersed in a water bath which is maintained at 70–76°C. The mixture is stirred rapidly with a mechanical stirrer while the temperature is raised to 56°C. This temperature is reached in about 10 to 15 minutes and held there for 15 minutes. The extract is then filtered by gravity through Eaton-Dikeman paper No. 617.

To the clear filtrate 632 gm. of ammonium sulfate per liter are added with stirring. The mixture is allowed to stand overnight at room temperature. The precipitate is then collected on Büchner funnels, No. 54 Whatman paper being used. This precipitate is dissolved in 2 liters of distilled water, the ammonium sulfate content is determined and then solid ammonium sulfate added until the solution is 0.25 saturated. The precipitate which is formed is removed by gravity filtration in the cold through No. 5 Whatman paper and discarded. To the filtrate solid ammonium sulfate is added until a concentration of 0.6 saturation is obtained. The precipitate formed is allowed to stand overnight at room temperature and collected on Büchner funnels, using No. 50 Whatman

paper. It is then dissolved in 1 liter of distilled water, the ammonium sulfate content of the solution determined, and solid ammonium sulfate added to produce 0.6 saturated solution. The precipitate which is formed is collected on Büchner funnels, using No. 50 Whatman paper, a small amount of diatomaceous earth (hyflo-super-cel) being added to insure a clear filtrate. It is dissolved in the minimum amount of water and dialyzed in cellophane sacs to remove the excess ammonium sulfate. Any precipitate that forms during dialysis is removed and the extract concentrated *in vacuo* such that 1 cc. is equivalent to 100 to 200 gm. of original kidney.

The concentrated extract is centrifuged at a high speed to remove any sediment which forms during concentration. Sodium chloride is added to a concentration of 0.8 per cent and the extract filtered through a Seitz filter. Merthiolate[1] may be added in a concentration of 1 : 20,000 before the extract is put through the Seitz filter.

This type of extract has generally been active. Various modifications of this method have been used. The temperature of the original extraction has been varied from 38°C. to 58°C. With the higher temperatures a shorter extraction period is required than with the lower temperatures. The concentration of ammonium sulfate has also been varied from one-half to full concentration. Most of the activity is present in the fractions precipitated between 0.3 to 0.6 saturation with ammonium sulfate.

Instead of dialyzing the final precipitate obtained in the above method, the excess of ammonium sulfate can be removed by means of barium hydroxide or calcium hydroxide.

We have also used saturated sodium chloride as a precipitating agent but the activity of this preparation is not as high as that when ammonium sulfate is used.

In some instances the bulk of the proteins was removed by means of a 2.5 to 5.0 per cent concentration of trichloracetic acid, the activity in the filtrate being precipitated by saturation with ammonium sulfate. More work will be required to prove whether consistently satisfactory results can be obtained by this procedure.

### *Preparation of Alcohol and Acetone Extracts*

10 kilos of finely ground kidneys are stirred with 10 liters of water; then alcohol or acetone is added with stirring to the desired concentration, that is, from 50 to 70 per cent. The insoluble residue is removed by filtration and the filtrate is freed of alcohol or acetone by distillation *in vacuo*. The aqueous residue is extracted with ether, the ether discarded, and the aqueous phase dialyzed after removal of the ether *in vacuo*. The dialyzed extract is concentrated *in vacuo* to the desired volume.

The alcohol and acetone extracts have not been as uniformly active as those prepared by aqueous extraction; consequently, most of the extracts have been prepared by the latter method.

[1] Merthiolate (sodium ethyl mercuri thiosalicylate, Lilly).

All of the following methods have yielded active extracts but whether they are as efficient as the methods described seems doubtful.

*Acetic Acid.*—Kidneys extracted with 2 per cent acetic acid in 2 per cent sodium chloride at 56°C. Filtrate concentrated and dialyzed.

*Acetic-Ammonium Sulfate.*—Kidneys extracted with 2 per cent acetic acid in 2 per cent sodium chloride at 56°C. Ammonium sulfate added to filtrate. Precipitate dissolved in water, dialyzed, and concentrated to desired volume.

*Isoelectric Precipitation.*—Kidneys extracted with 2 per cent sodium chloride. Residue removed by centrifuging. Supernatant fluid adjusted to pH 4.0. Filtrate concentrated and dialyzed.

*Alcohol.*—Kidneys extracted with alcohol in concentrations varying from 50 to 70 per cent. Alcohol removed from filtrate by distillation at low temperature. Aqueous residue washed with ether and ether removed by distillation. Aqueous residue dialyzed and concentrated to desired volume.

*70 Per Cent Acetone.*—Kidneys extracted with 70 per cent acetone. Acetone removed by distillation at low temperature. Aqueous concentrate shaken with ether. Aqueous phase dialyzed and concentrated to desired volume.

*Sodium Chloride.*—Kidneys extracted with 2 per cent acetic acid in 2 per cent saline at 56°C. Filtrate saturated with sodium chloride at pH 3.4. Precipitate dissolved in water and dialyzed.

*Barium.*—Ammonium sulfate precipitate obtained in acetic-ammonium sulfate method dissolved in water and the ammonium sulfate removed by precipitation as barium sulfate and distillation to remove ammonia.

*Ammonium Sulfate-Sodium Chloride.*—Ammonium sulfate precipitate obtained in acetic-ammonium sulfate method dissolved in water, sodium chloride added to a concentration of 10 per cent and the pH adjusted to 3.0 with hydrochloric acid. The precipitate is discarded. Filtrate saturated with ammonium sulfate. Precipitates dissolved in water and dialyzed.

*Trichloracetic Acid.*—Ammonium sulfate precipitate obtained in acetic-ammonium sulfate method dissolved in water, trichloracetic acid added to 2.5 to 5.0 per cent, and resulting filtrate saturated with ammonium sulfate. Precipitate which formed was dissolved in water and dialyzed.

All extracts that were given to the animals were treated by the addition of 1 part of merthiolate to 20,000 of extract. Sterility was insured in the extracts for human use by filtration through a Seitz filter.

We have not decided as yet which of the several methods is best. For the sake of brevity the methods have been labelled with the name of the key substance involved (Tables I to V).

### *The Action of Renal Extracts in Dogs*

Subcutaneous or intramuscular injection of renal extracts causes no immediate change in blood pressure. Intravenous injection, however, results in a sharp, prolonged rise, probably the result of contained renin.

The fall in blood pressure usually begins after 2 to 4 days. In some it is more rapid and in others may be prolonged for 6 to 8 days. Its effect appears to be cumulative, for if an excess is given the pressure continues to fall progressively until death occurs.

A fatal dose of extract causes a shock-like syndrome to appear. Among the first signs are tachycardia, weakness, and loss of appetite. This is followed by oliguria, cold, bloodless extremities, and elevated blood urea

TABLE I

*Reduction of Arterial Pressure of Dogs for Short Periods by Renal Extracts*

(Decrease to 152 mm. Hg or less, lasting 4 days, followed by rise to 160 mm. Hg or more)

| Dog No. | Nature of extract | Equivalent of fresh kidney administered per kilo | Period of injection | Average initial blood pressure | Blood pressure after discontinuing extract | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | 24 hrs. | 48 hrs. | 72 hrs. | 96 hrs. |
| | | *gm.* | *days* | *mm. Hg* | *mm. Hg* | *mm. Hg* | *mm. Hg* | *mm. Hg* |
| 3-86 | Acetic acid | 54 | 6 | 190 | 120 | 150 | 160 | 180 |
| 4-79 | Isoelectric precipitation | 257 | 6 | 176 | 150 | 130 | 140 | 170 |
| 5-49 | Acetic-ammonium sulfate | 317 | 8 | 200 | 138 | 168 | 146 | 190 |
| 5-87 | " " " | 300 | 6 | 182 | 148 | 166 | 146 | 172 |
| | Isoelectric precipitation | 240 | 8 | 175 | 148 | 152 | 154 | 180 |
| 6-00 | " " | 65 | 3 | 173 | 148 | 144 | 156 | 180 |
| 5-97 | " " | 260 | 8 | 186 | 162 | 152 | 156 | 184 |
| 6-17 | Acetic-ammonium sulfate | 216 | 2 | 200 | 152 | 148 | 134 | 178 |
| | " " " | 273 | 5 | 193 | 144 | 164 | 198 | 210 |
| 6-70 | " " " | 161 | 3 | 188 | 160 | 158 | 172 | 180 |
| 7-83 | " " " | 293 | 6 | 193 | 152 | 158 | 174 | 180 |

nitrogen. A similar syndrome has been observed by Harrison, Grollman, and Williams (1940).

Some dogs with severe experimental hypertension have nitrogen retention. Administration of renal extract to such animals often reduces not only the blood pressure but also the blood urea nitrogen. Such a result is illustrated in Fig. 1. Noteworthy is the close parallelism of arterial blood pressure and blood urea nitrogen.

Reduction of arterial pressure to relatively low levels is tolerated differently in various animals. For instance in one dog (No. 7-83) the blood

TABLE II

*Reduction of Arterial Pressure for Longer Periods by Renal Extracts*

(Decrease to 150 mm. Hg or less lasting from 4 to 41 days followed by rise to 160 mm. Hg or more)

| Dog No. | Nature of extract | Equivalent of fresh kidney administered per kilo | Period of injection | Average initial blood pressure | Lowest blood pressure after extract | Blood pressure decreased | Duration of period of reduced blood pressure |
|---|---|---|---|---|---|---|---|
| | | *gm.* | *days* | *mm. Hg* | *mm. Hg* | *mm. Hg* | *days* |
| 1-88 | Acetic-ammonium sulfate | 480 | 3 | 180 | 134 | 46 | 7 |
| 1-96 | " " " | 940 | 7 | 190 | 126 | 64 | 6 |
| | " " " | 500 | 5 | 187 | 138 | 49 | 25 |
| 5-47 | Ammonium sulfate | 500 | 5 | 207 | 130 | 77 | 10 |
| 5-87 | Acetic-ammonium sulfate | 784 | 8 | 184 | 128 | 56 | 13 |
| | " " " | 756 | 7 | 180 | 124 | 56 | 21 |
| 5-97 | Isoelectric precipitation | 438 | 3 | 206 | 100 | 106 | 6 |
| 6-13 | 70% acetone | 330 | 5 | 180 | 140 | 40 | 15 |
| 6-17 | Zinc sulfate acetic-ammonium sulfate | 964 | 7 | 224 | 140 | 84 | 13 |
| | Sodium chloride | 1094 | 7 | 210 | 142 | 68 | 10 |
| | Acetic-ammonium sulfate | 945 | 7 | 170 | 124 | 46 | 27 |
| 7-52 | " " " | 884 | 7 | 185 | 146 | 39 | 8 |
| 7-90 | Trichloracetic | 508 | 4 | 187 | 136 | 51 | 14 |
| | Acetic-ammonium sulfate | 658 | 7 | 188 | 114 | 74 | 30 |
| 8-51 | Acetic-ammonium sulfate 5% kaolin | 900 | 6 | 220 | 126 | 94 | 4 |
| 8-76 | Acetic-ammonium sulfate | 196 | 2 | 192 | 96 | 96 | 10 |
| 9-21 | " " " | 320 | 4 | 202 | 146 | 56 | 5 |
| 8-77 | " " " | 945 | 5 | 185 | 118 | 67 | 41 |
| 8-99 | " " " | 480 | 4 | 191 | 140 | 51 | 15 |
| 9-03 | " " " | 260 | 4 | 192 | 132 | 60 | 12 |
| 9-10 | Sodium chloride | 237 | 3 | 174 | 132 | 42 | 4 |
| 9-14 | Acetic-ammonium sulfate | 644 | 7 | 200 | 154 | 46 | 8 |
| 9-39 | " " " | 580 | 7 | 209 | 162 | 47 | 7 |

pressure decreased from 200 mm. Hg to 118 mm. Hg within 48 hours after five injections of extract (Fig. 2). When the lower blood pressure was observed, the pulse rate was 88 beats per minute, but the urea nitrogen had increased from 56 mg. per 100 cc. of blood to 115 mg. Contrasting with this is dog 8-76 in which the blood pressure was reduced to 96 mm. Hg within the same period, yet the blood urea nitrogen was 26 mg.

Many extracts were inactive or an insufficient amount was given. The blood pressure often rose while these animals were receiving extract, only to fall when an active extract was given. The length of time before the arterial pressure rises after a course of treatment is discontinued varies

TABLE III

*Prolonged Reduction of Arterial Pressure by Renal Extracts*

(Decrease to 150 mm. Hg or less lasting 44 days or more)

| Dog No. | Nature of extract | Equivalent of fresh kidney administered per kilo | Period of injection | Average initial blood pressure | Lowest blood pressure after extract | Blood pressure decreased | Duration of period of reduced blood pressure |
|---|---|---|---|---|---|---|---|
| | | *gm.* | *days* | *mm. Hg* | *mm. Hg* | *mm. Hg* | *days* |
| 5-49 | Acetic-ammonium sulfate | 295 | 3 | 185 | 126 | 59 | 97 |
| 8-02 | " " " | 660 | 7 | 190 | 140 | 54 | 44* |
| 7-54 | " " " | 719 | 8 | 170 | 130 | 40 | 60† |
| 8-60 | " " " | 4072 | 8 | 192 | 118 | 74 | 75 |

* Clamp applied to renal artery during period of reduced pressure. Arterial pressure increased sharply and dog died with malignant hypertension.

† Dog died suddenly during period of reduced arterial pressure. Autopsy, pulmonary edema found.

greatly (Figs. 3 and 4). In general the larger the dose of extract the more prolonged the effect. In the minority it rises above the hypertensive level (150 mm. Hg mean pressure) within 4 days after stopping treatment (Table I). In the majority from 4 to 41 days are required (Table II) and in a few it has not risen even after 97 days (Table III).

The amount of extract given has been measured in terms of original whole kidney substance employed in the preparation of the extract. Roughly from 400 to 900 gm. of kidney are required for the preparation of sufficient extract to reduce the mean arterial pressure of a 12 kilo dog from 200 to 130 mm. Hg (Table II).

The clinical condition of the animals remains excellent even when the pressure has fallen 100 mm. Hg or more, provided the drop does not occur

TABLE IV

*Reduction of Arterial Pressure by Renal Extracts in Dogs with Malignant Hypertension*

| Dog No. | Nature of extract | Equivalent of fresh kidney administered per kilo | Period of injection | Average initial blood pressure | Lowest blood pressure | Blood pressure decreased | Duration of period of reduced blood pressure | Duration of malignant phase | Comment |
|---|---|---|---|---|---|---|---|---|---|
| | | *gm.* | *days* | *mm. Hg* | *mm. Hg* | *mm. Hg* | *days* | *days* | |
| 3-86 | Acetic-ammonium sulfate | 826 | 7 | 182 | 126 | 56 | 17 | 15 | Detached retina. Papilledema. Fresh hemorrhage 4 wks. after extract stopped |
| | " " " | 148 | 1 | 224 | 102 | 122 | 2 | 30 | No change |
| | " " " | 79 | 1 | 182 | 138 | 44 | 1 | 36 | Some regression of hemorrhages when extract given. Rapid recurrence after extract was stopped |
| 5-93 | Acetone | 200 | 6 | 179 | 120 | 59 | 5 | 4 | Convulsion, detached retina. No new hemorrhages for next 4 mos. |
| | Trichloracetic | 700 | 6 | 180 | 126 | 54 | 21 | 184 | No change, either before or after extract. Hemorrhagic phase stationary |
| | Barium | 221 | 3 | 208 | 118 | 90 | 25 | 240 | Intestinal hemorrhages. Eyes, no more hemorrhages |
| | Acetic-ammonium sulfate | 700 | 7 | 207 | 128 | 79 | 26 | 270 | Recurrence of hemorrhages from bowel and in eyes, before extract. Stopped after extract |
| | " " " | 696 | 6 | 220 | 146 | 74 | 4 | 280 | Recurrence of tarry stools |
| 4-18 | Acetic acid | 480 | 8 | 220 | 140 | 80 | 5 | 1 | Detached retina both eyes, before extract. Soon after extract stopped, fresh hemorrhage |
| 6-70 | Acetic-ammonium sulfate | 210 | 3 | 170 | 134 | 36 | 24 | 10 | Convulsions, retina detached, pupils dilated (B.U.N. = 11.3 mg. per 100 cc.). Dog survived 6 mos. after extract |
| 7-33 | Acetic acid | 254 | 6 | 195 | 148 | 47 | 3 | 12 | Slight detachment retina. Bloody diarrhea |
| 7-66 | Acetic-ammonium sulfate | 945 | 5 | 185 | 118 | 67 | 30 | 8 | Pupils did not react to light, eyes protrude. Retina widely detached, both eyes |
| | " " " | 578 | 7 | 184 | 134 | 50 | 12 | 38 | Extract given as soon as hypertension reappeared. No change in eye findings |
| 6-16 | " " " | 880 | 5 | 197 | 138 | 59 | 5 | 0 | Onset sudden, 2 days after treatment begun. Detached retina. Convulsion |
| 8-76 | " " " | 600 | 4 | 217 | 156 | 61 | 10 | 25 | Definite hemorrhages in retina. Papilledema. No detachment observed |
| 7-83 | " " " | 982 | 6 | 202 | 122 | 80 | 25 | 5 | Detached retina. Cardiac arrhythmia |
| 7-62 | " " " | 1008 | 6 | 212 | 144 | 68 | 79* | 40 | Detached retina, convulsions, bloody diarrhea. Weak, unable to stand |
| 7-77 | Calcium hydroxide ammonium sulfate | 240 | 2 | 193 | 146 | 47 | 3 | 50 | Detached retina. Had had bloody diarrhea |
| | Ammonium sulfate | 364 | 4 | 197 | 130 | 67 | 7 | 60 | Recurrence of bloody diarrhea. Increase in blood urea nitrogen from 32 mg. to 55.6 mg. per 100 cc. |
| 8-97 | Acetic-ammonium sulfate | 573 | 6 | 202 | 146 | 56 | 5 | 0 | Hematuria, bloody diarrhea. Detached retina appeared after 3rd injection |
| 9-84 | " " " | 106 | 1 | 198 | 128 | 70 | 2 | 1 | Detachment of retina one day before extract started. No recurrence of hemorrhages after extract stopped |
| 8-96 | " " " | 711 | 6 | 192 | 91 | 101 | 13 | 0 | Bloody diarrhea appeared on last day extract was given. Detached retina next day |

*Dog used for another experiment before arterial pressure had returned to hypertensive level.

within too short a space of time. The appetite is good and the animals run and play normally.

TABLE V

*The Effect on Arterial Blood Pressure of Administration of Renal Extracts* to Normal Dogs*

| Dog No. | Nature of extract | Equivalent of fresh kidney administered per kilo | Period of injection | Average initial blood pressure | Blood pressure 24 hrs. after last dose of extract |
|---|---|---|---|---|---|
| | | *gm.* | *days* | *mm. Hg* | *mm. Hg* |
| 9-08 | Acetic ammonium sulfate | 490 | 7 | 146 | 142 |
| | Barium | 552 | 6 | 122 | 144 |
| 8-24 | Acetic ammonium sulfate | 420 | 6 | 107 | 114 |
| | " " " | 720 | 6 | 96 | 112 |
| | " " " | 700 | 7 | 126 | 130 |

* These extracts reduced arterial pressure when administered in similar quantities to dogs with experimental hypertension.

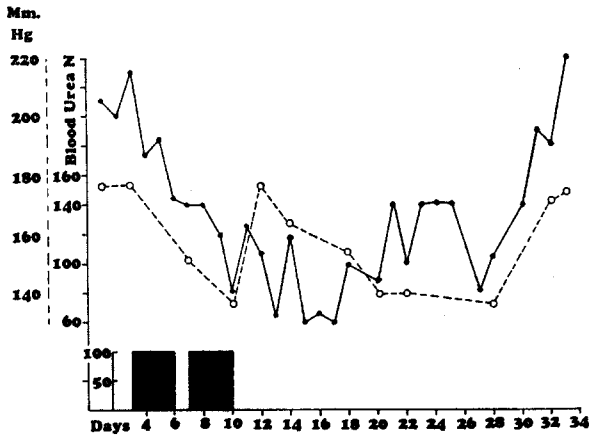


FIG. 1. Effect of renal extract on the blood urea nitrogen and arterial pressure of a dog with malignant hypertension of 3 months' duration. Arterial pressure measured in mm. of Hg on the ordinate and time in days on the abscissa. Blood urea nitrogen also measured on the ordinate in mg. per 100 cc. --o-- = blood urea nitrogen. The height of the shaded area at the bottom of the chart represents the amount of extract in terms of the amount of original whole kidney in grams per kilo of body weight of the dog.

A number of the animals (54) exhibited signs of the malignant syndrome. This was usually ushered in by loss of appetite, weakness, and bloody diarrhea. Shortly the animals became blind, and examination disclosed widely dilated, inactive pupils, detachment of the retinae, papilledema, and often massive hemorrhages in the vitreous and aqueous. Convulsions were

usual. Autopsy confirmed the presence of extensive hemorrhagic, necrotizing arteriolitis. Treatment of these animals with sufficient amounts of renal extract saved the animal's life in 22 cases (Table IV). It appeared of the utmost importance to administer extract early and in large doses. Regression of the eye signs occurs and vision is often restored. It is remarkable to observe a desperately sick animal revive after 24 hours of treatment. The improvement in these animals appears to last only as long

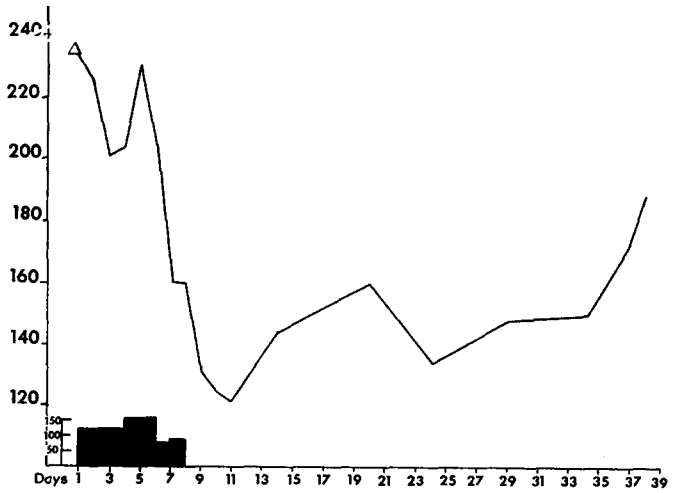


FIG. 2. Dog 7-83, female, weight 8.5 kilos. The effect of an ammonium sulfate renal extract on the arterial pressure. Arterial pressure is expressed in mm. Hg along the ordinate and time in days along the abscissa. Δ represents the average arterial pressure before renal extract was given. The amount of renal extract in grams of kidney administered per kilo of dog per day is expressed by the height of the shaded area along the ordinate. The blood urea nitrogen on the first day on which extract was given was 40 mg. per 100 cc.; on the 5th day was 25 mg. per 100 cc.; on the 7th day 35 mg. per 100 cc.; on the 11th day 75 mg. per 100 cc.; on the 34th day 29 mg. per 100 cc.

as they continue to receive extract. After the signs and symptoms of the malignant syndrome have reappeared, administration of more extract has caused a second regression in four dogs.

*Sample Case History of a Dog with Experimental Malignant Hypertension.*—Dog 5-93, male; weight 9.7 kilos. Cellophane was applied to both kidneys in September, 1939. 2 weeks after the application of cellophane to the second kidney, arterial blood pressure was 130 mm. Hg. 6 weeks later hypertension had been established (average pressure 180 mm. Hg). From Nov. 28 to Dec. 2, 1939, the dog received a renal extract which had been prepared by the glycerol-ammonium sulfate method. 24 hours after the last

injection of this extract, the blood pressure declined from 184 mm. Hg to 154 mm. Hg and in another 48 hours the pressure had increased to 186 mm. Hg.

After an interval of 1 week during which the blood pressure averaged 194 mm. Hg an acetone extract was started. After four injections of this extract the blood pressure declined from 202 mm. Hg to 174 mm. Hg. In the 24 hours after the fifth injection the pressure fell to 120 mm. Hg. From this low level the arterial blood pressure increased

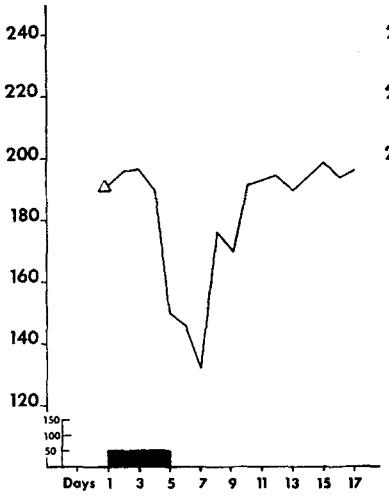


FIG. 3

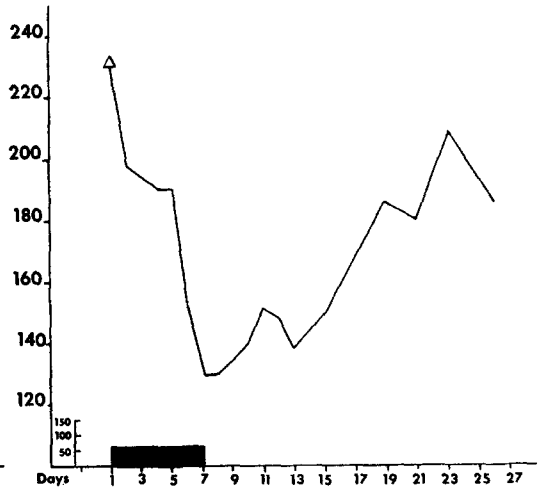


FIG. 4

FIG. 3. Dog 6-17, female, weight 7.5 kilos. The effect of an ammonium sulfate renal extract on the arterial pressure. Arterial pressure is expressed in mm. Hg along the ordinate and time in days along the abscissa. Δ represents the average arterial pressure before renal extract was given. The amount of renal extract in grams of kidney administered per kilo of dog per day is expressed by the height of the shaded area along the ordinate. On the 5th day after extract was started the blood urea nitrogen was 15.7 mg. per 100 cc.

FIG. 4. Dog 4-18, male, weight 11 kilos. The effect of an ammonium sulfate renal extract on the arterial pressure. Arterial pressure is expressed in mm. Hg along the ordinate and time in days along the abscissa. Δ represents the average arterial pressure before renal extract was given. The amount of renal extract in grams of kidney administered per kilo of dog per day is expressed by the height of the shaded area along the ordinate.

and in 5 days it had reached 192 mm. Hg and in 11 more days (Dec. 24, 1939) the blood pressure was 220 mm. Hg.

When the pressure reached 220 mm. Hg the signs of the malignant hypertensive syndrome appeared. Portions of the retina in both eyes were detached; bloody diarrhea was present; and a generalized convulsion occurred. On the first day that these phenomena appeared, another renal extract was started. This extract was administered for 11 days. On the 5th and 6th days the blood pressure was 174 mm. Hg but on the

11th day the pressure was 198 mm. Hg. There were no more convulsions and the bloody diarrhea had stopped.

One week later the dog was given a renal extract orally but this extract did not affect the blood pressure which averaged 196 mm. Hg during this period. The retinal detachment was still present but appeared to be less extensive. The other signs of the malignant syndrome had disappeared.

One week after the oral administration of a renal extract had been completed (Jan. 26, 1940) a laparotomy was done for the purpose of obtaining renal venous blood. This blood was found to contain an increased amount of renin (Page, 1940). Hypertension was not affected by this procedure.

During the next 4 months the dog received five extracts by subcutaneous injection and all failed to reduce the blood pressure. The average blood pressure during this time was 192 mm. Hg. Retinal detachment was unchanged and no other sign of the malignant syndrome was observed during this time.

In May, 1940, a renal extract prepared by the trichloracetic acid process was administered. 24 hours after the eighth injection of this extract, the blood pressure fell from 184 mm. Hg to 150 mm. Hg. No more extract was given but the blood pressure continued to decline, and 3 days after the extract had been stopped the blood pressure was 126 mm. Hg. The pulse rate was 84 per minute when the blood pressure was 126 mm. Hg and there were no signs of shock. The dog walked about and ate its food. The pressure remained below 160 mm. Hg during the next 20 days but at the end of this time the pressure was 188 mm. Hg.

4 days after the arterial blood pressure had reached 188 mm. Hg another renal extract was started. This extract did not alter the blood pressure and the detachment of the retina increased and a bloody diarrhea recurred. The blood urea nitrogen was 82 mg. per 100 cc. In the ensuing 26 days the blood pressure average was more than 180 mm. Hg. On July 26, 1940, (26 days later) the blood pressure was 208 mm. Hg and the blood urea nitrogen was 106 mg. per 100 cc. A renal extract prepared by the ammonium sulfate process was started. Two injections of the extract reduced the blood pressure from 208 mm. Hg to 164 mm. Hg. 24 hours after the third injection of renal extract the blood pressure was 118 mm. Hg. The pulse was 120 per minute. The dog was weak and unable to stand. There was no evidence of blood loss and the weakened condition of the dog appeared to be due to the extremely rapid decline of arterial blood pressure. 2 days later the blood pressure had increased from 118 mm. Hg to 152 mm. Hg. In another 16 days it was 178 mm. Hg. 28 days later the arterial pressure was 206 mm. Hg and blood urea nitrogen was 153 mg. per 100 cc. Fresh retinal hemorrhages and recurrence of bloody diarrhea accompanied the elevation of blood pressure.

A renal extract prepared by the ammonium sulfate process was given during the next 8 days. During the first 3 days of the period of administration of the extract the blood pressure and blood urea nitrogen increased, and on the 3rd day the pressure was 216 mm. Hg and blood urea nitrogen was 155 mg. per 100 cc. On the 4th day blood pressure decreased to 188 mm. Hg. The fall in blood pressure continued and on the 8th day arterial pressure was 160 mm. Hg. Blood urea nitrogen had decreased from 155 mg. to 103 mg. per 100 cc. within the same period. Blood pressure declined in the 24 hours after the eighth dose of extract to 140 mm. Hg and blood urea nitrogen was 80 mg. per 100 cc. 48 hours after extract was stopped the blood pressure increased to 164 mm. Hg and therefore another injection of extract was given. This single injection

was followed by a rapid decline in blood pressure and 3 days later the blood pressure was 128 mm. Hg. When the blood pressure decreased below 140 mm. Hg the blood urea nitrogen did not continue to decrease but, instead, increased from 80 mg. to 123 mg. per 100 cc. As the blood pressure gradually rose from this low level during the next 7 days the blood urea nitrogen decreased to 87 mg. per 100 cc. when the blood pressure reached 150 mm. Hg. Arterial pressure did not rise above 150 mm. Hg for 5 more days and during this entire period of reduced pressure the dog showed no sign of shock, increased weakness, or hemorrhagic phenomena. After 5 days the blood pressure increased slowly and in 15 days was 220 mm. Hg and blood urea nitrogen was 132 mg. per 100 cc.

At this time another renal extract prepared by the ammonium sulfate method was injected. Blood pressure decreased slowly during the 9 days the extract was given. After the extract was stopped the blood pressure continued to decline and 48 hours after the last dose had been given, the blood pressure was 148 mm. Hg. The fall in blood pressure was again accompanied by a decrease in blood urea nitrogen from 148 mg. per 100 cc. to 118 mg. per 100 cc. Pulse rate was 112 per minute when the blood pressure was 148 mm. Hg and the dog ate and walked about in the cage. This period of reduced pressure lasted 4 days, and 5 days after the last dose of renal extract, the pressure was 194 mm. Hg and blood urea nitrogen was 142 mg. per 100 cc. There had been no new hemorrhages in the eyes or from the gastrointestinal tract during the period of administration of this extract.

The syndrome of malignant hypertension, with remissions which followed the injection of renal extracts, had been present for 299 days in this dog. This syndrome usually terminated fatally in from 2 to 7 days in dogs with experimental hypertension produced by uninephrectomy and silk perinephritis.

### *Action of Renal Extracts in Rats*

Much the same clinical phenomena are observed in hypertensive rats as in the dogs (Fig. 5). The malignant syndrome occurred in about the same number as in dogs. Treatment of the rats has been quite as successful as has treatment of the dogs.

### *The Action of Renal Extracts in Human Beings*

It was considered undesirable to reduce the blood pressure of hypertensive patients as fast as had been done in dogs. Extracts equivalent to 800 to 1000 gm. of whole fresh kidney were given intramuscularly daily.

During the early part of the work severe general, as well as local, reactions were observed following injection of extract. As it has been further purified, these have become less frequent. The most usual general reaction consists of pain in the muscles of the back and a feeling of constriction in the chest. This may last for 10 minutes or more and be followed by a rise in temperature to about 102°F. Occasionally a sharp fall in blood pressure occurs a few minutes after injection of extract sufficiently severe to make it

desirable to administer adrenalin. It has been thought that this type of reaction was due to inadvertent injection of extract directly into the blood stream. Local reactions consist simply of reddening, induration, and pain around the site of injection.

The reactions are highly irregular in their appearance. The same extract has been given day after day in patients without reaction, only to be followed by one. Continued administration does not necessarily cause another to occur.[2]


FIG. 5. Rat 117. Ordinate represents average of 5 daily systolic pressures, abscissa time in days, and the shaded area the grams of fresh whole kidney used in preparing the extract which was given subcutaneously.

As in dogs and rats, injection of extract caused no immediate fall in blood pressure, but after several days or a week it was definitely reduced (Fig. 6). Six patients with essential hypertension have been treated and in all of them the blood pressure has been reduced (case histories 6 to 12 and Fig. 6).

When the blood pressure was reduced by extract, headaches disappeared in the patients in whom they had occurred when the blood pressure was high. Dyspnea was lessened. On the whole the patients felt much better, though some of them were not aware of the reduction in the height of their blood pressures. Hemoglobin and plasma proteins were usually unchanged.

The most dramatic changes were observed in the five patients with ad-

[2] Two patients have been successfully desensitized.

vanced malignant hypertension (case histories 1 to 5 and Figs. 11 to 14). Convulsions had occurred in one of them, and two were stuporous (Figs.

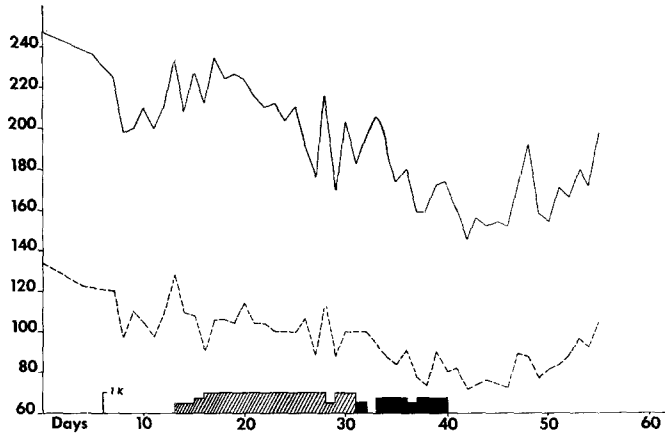


FIG. 6. Patient E-P. Arterial blood pressure of an ambulant patient with essential hypertension treated with renal extract. Ordinate represents average of morning and afternoon systolic and diastolic pressures; cross-hatched areas, dose in kilos of original kidney of a kidney extract which according to tests on dogs was only slightly active; solid shaded areas, dose of a kidney extract which in dogs was highly active.

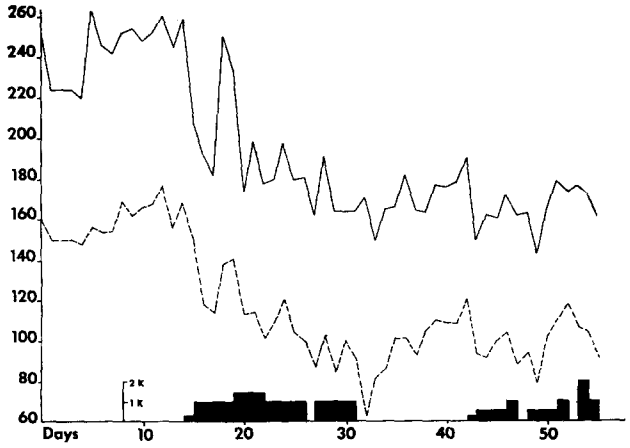


FIG. 7. Patient R-T. Arterial blood pressure of a patient with malignant hypertension treated with renal extract intramuscularly. Ordinate represents average of morning and afternoon systolic and diastolic pressures. Height of shaded areas represents dose of renal extract in terms of original fresh kidney.

7 and 8). 2 days after treatment was initiated the patients were alert and sitting up in bed. Convulsions did not recur during treatment.

Two of the patients were almost blind and the other three had reduction of vision because of hemorrhages, exudates, and papilledema. Vision was partially restored in all. This was accompanied by partial resolution of the morbid changes in the eye grounds. Secondary glaucoma occurred in one patient and concurrently with a fall in arterial pressure due to renal extract, the tension in the eye returned to normal. The size of the cardiac shadow in x-ray photographs was slightly reduced when the blood pressure fell.

It is of interest that after treatment of patients with malignant hypertension with renal extracts the electrocardiogram demonstrates improve-

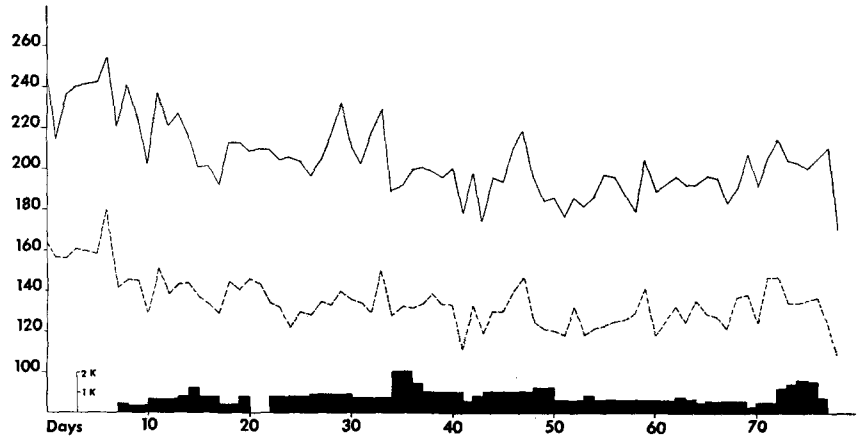


FIG. 8. Patient J-C. Arterial pressure of a patient with malignant hypertension treated with kidney extract injected intramuscularly. Ordinate represents average of morning and afternoon systolic and diastolic arterial pressures; abscissa, days in the hospital; and height of shaded areas, the dose of kidney extract in terms of original fresh kidney.

ment of the state of the myocardium. This is indicated in the records by the T waves becoming upright when they have been inverted (Figs. 9, 10).

Hemoglobin has tended to fall even after what appeared to be sufficient amounts of extract. It is not improbable that the anemia of malignant hypertension may require treatment in addition to that with renal extract.

Two of the patients with malignant hypertension are dead. One died in the hospital with congestive failure due, we believe, to the fact that his renal function as measured by urea clearance was only 5 per cent of normal on admission and we were unable to prepare enough potent extract to cope with his condition. The second patient voluntarily discontinued treatment because of his desire to go home. He died at home. The other three patients are ambulant and one is now being treated as an outpatient.


FIG. 9. Part 1. Feb. 28, 1940.

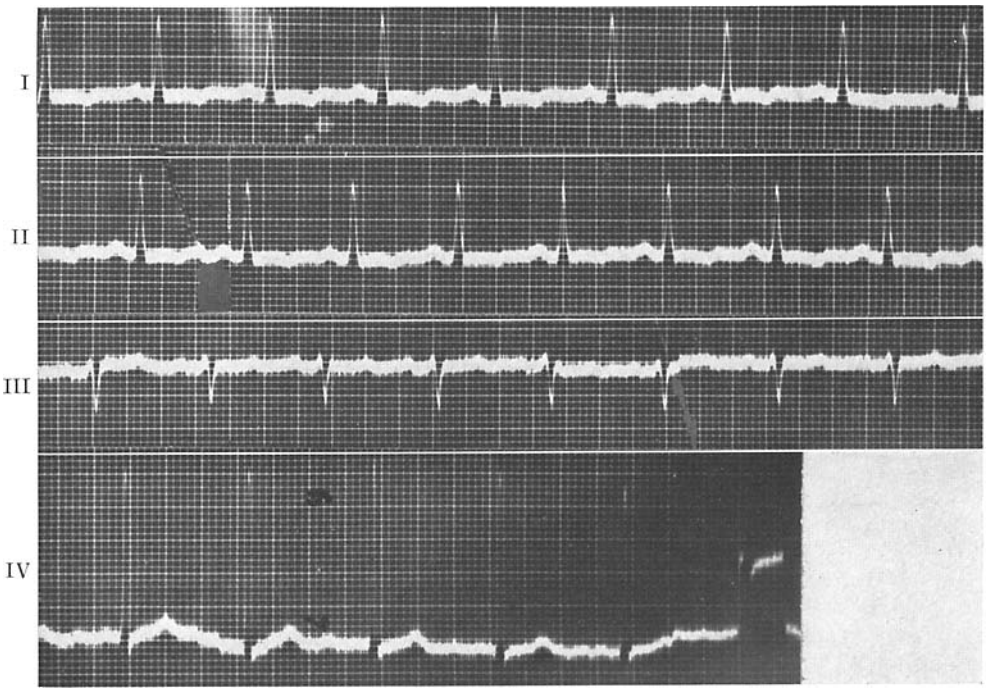


FIG. 9. Part 2. Mar. 7, 1940.

FIG. 9. Electrocardiograms of patient C-R 671 taken on Feb. 28, 1940, and Mar. 7, 1940, before treatment and on Oct. 9, 1940, after treatment.

The renal efficiency as measured by urea clearance tends to rise slightly even when it is below the uremic level of 20 per cent of normal. It is not possible to predict on the basis of the present evidence whether lasting

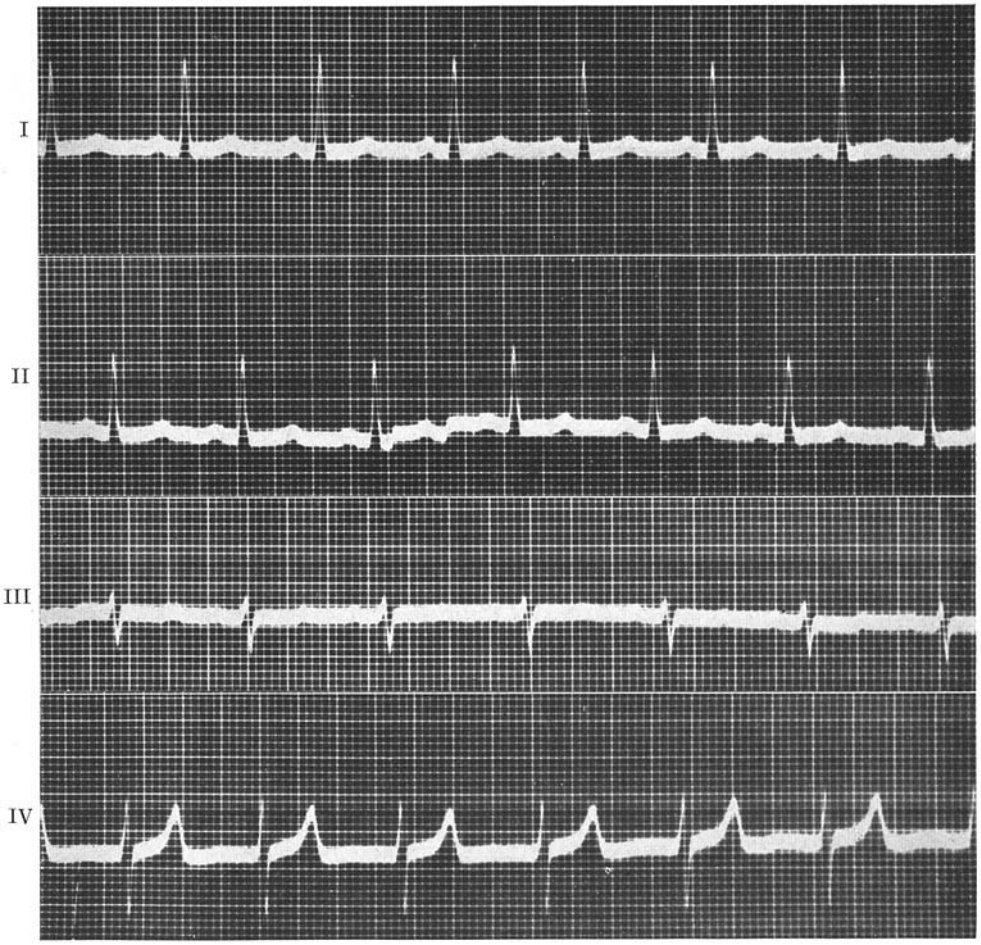


FIG. 9. Part 3. Oct. 9, 1940.

improvement in renal function will occur. Corcoran and Page (1940) have studied the changes by means of the diodrast, phenol red, and inulin clearances. When arterial pressure was reduced both in dogs with experimental hypertension and in patients, an increase of diodrast clearance and a decrease in the ratio inulin/diodrast clearance occurred. These changes are interpreted as due to increased renal blood flow and a decrease in the

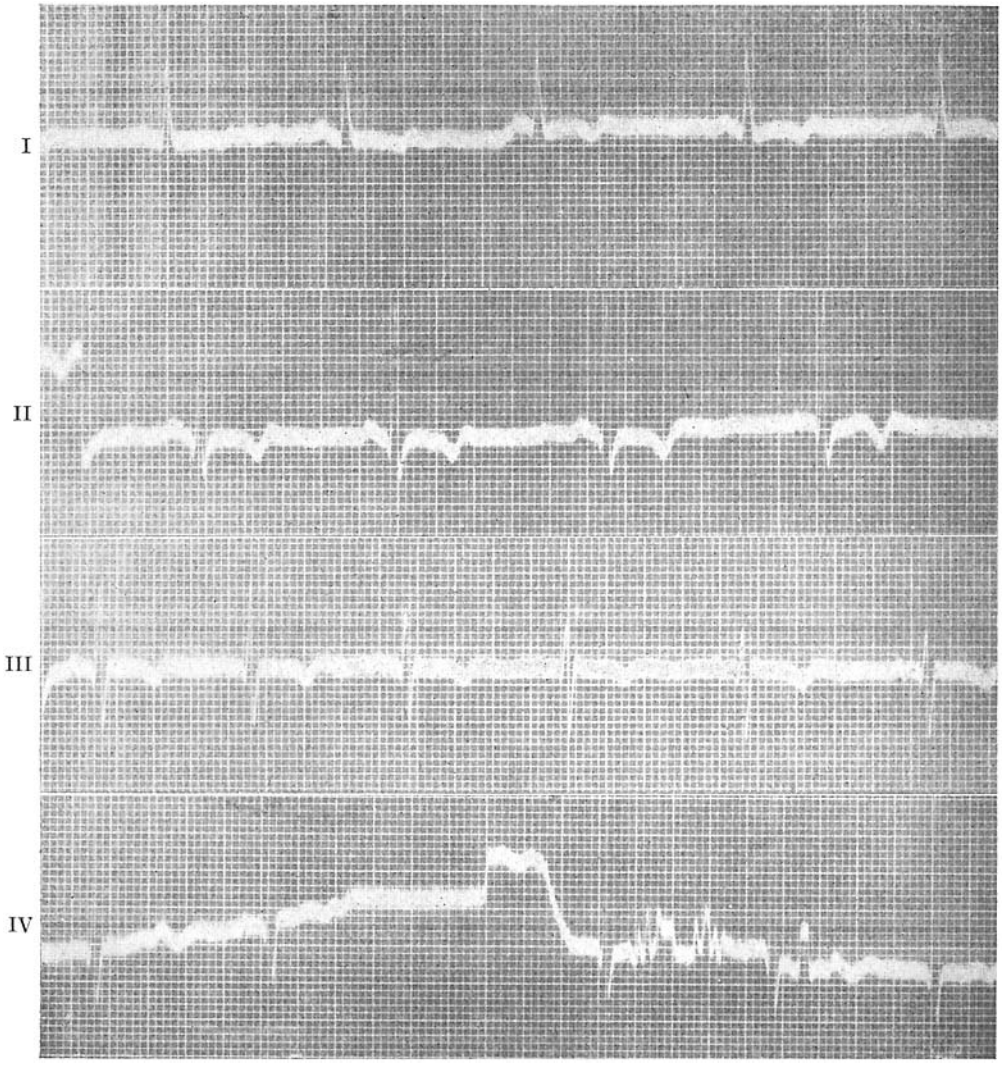


FIG. 10. Part 1. July 12, 1940.

FIG. 10. The electrocardiographic records of patient R-T 703 taken on July 12, 1940, before treatment, and Aug. 6, 1940, and Oct. 14, 1940, after treatment with renal extract.

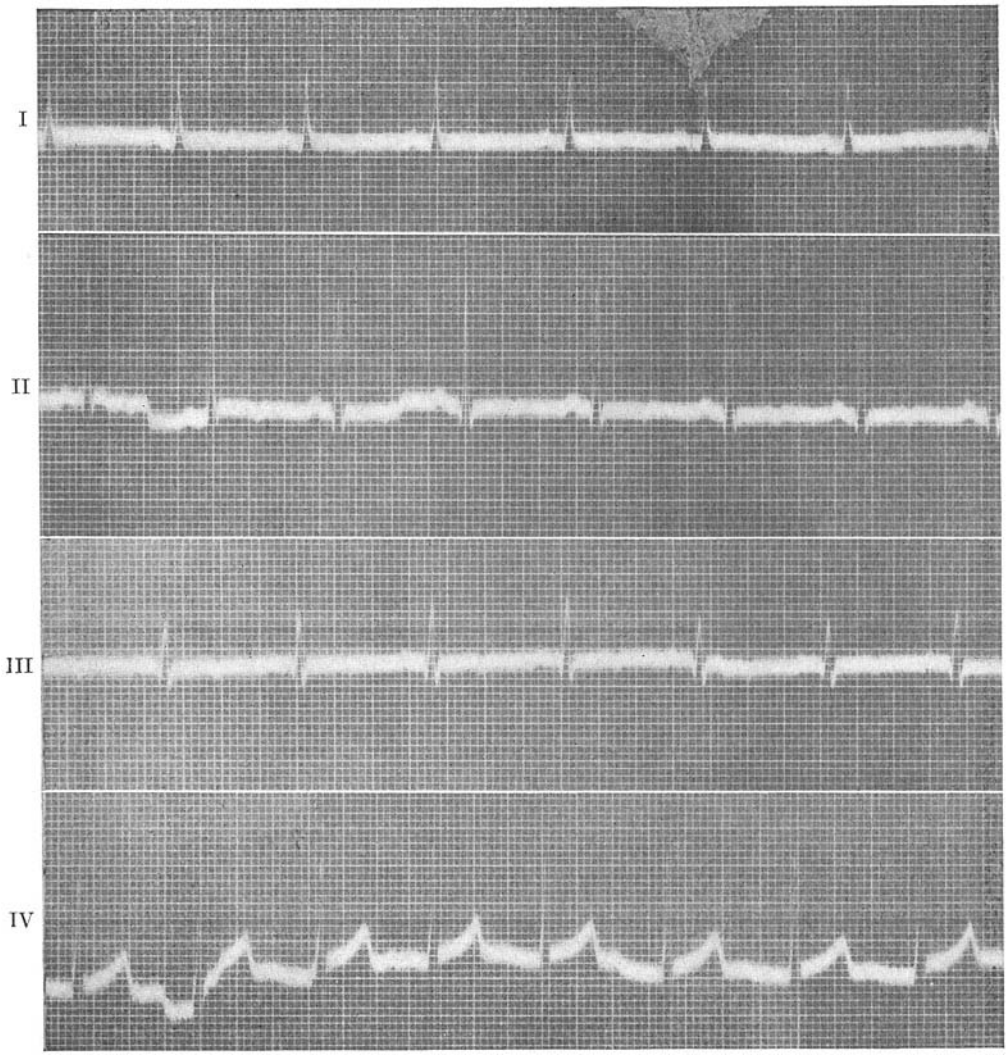


FIG. 10. Part 2. Aug. 6, 1940.

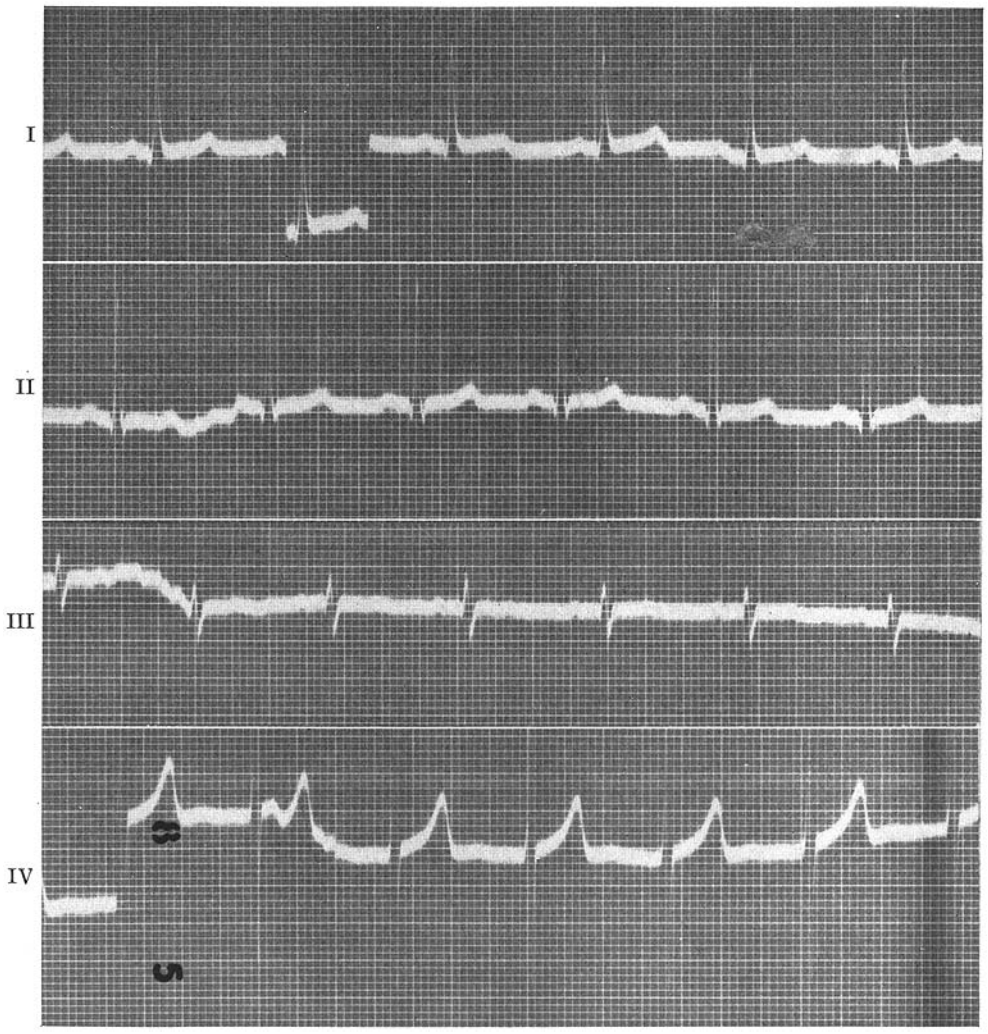


FIG. 10. Part 3. Oct. 14, 1940.

proportion of water removed from the plasma by glomerular filtration. It was suggested that these changes are due chiefly to relaxation of the tone of the efferent arterioles.

### *Histories of Patients Treated with Renal Extract*

R-T 703 (Fig. 11), malignant hypertension.

This 24 year old man complained of severe headache and blurring of vision. At 12 years of age he had scarlet fever. During the preceding winter he had headaches regularly. 2 weeks before admission he fell and hit the back of his head. A severe headache immediately occurred and persisted. At this time his blood pressure was found to be elevated. Vision in the left eye rather suddenly became so poor that he was unable to read and the vision in the right one seemed to be deteriorating.

The patient appeared acutely ill; his face was drawn and anxious. The right side of his face twitched. A subconjunctival hemorrhage was seen in the right eye. Grade 3 papilledema, grade 4 exudates, grade 2 hemorrhages, and grade 3 constriction were observed in the eyegrounds. The heart was slightly enlarged (+5 per cent deviation[3]). Venous pressure was 22 cm. in terms of normal salt. The electrocardiogram showed inversion of the T waves in leads 1, 2, 3, and 4.

The remainder of the results of laboratory examinations are recorded in Fig. 11.

The clinical improvement in this man was remarkable. Shortly after admission acute glaucoma occurred. Reduction of the blood pressure by kidney extract appeared to aid in resolution of the process.

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*Description of Figs. 11 to 15.*—Arterial blood pressure is recorded as the weekly average of the measurements made daily in the morning and evening. Fundus changes are indicated under the following headings, employing a semi-quantitative scale of + to ++++ to grade them: (1) arteriolar constriction, (2) arteriolar sclerosis, (3) exudates, (4) retinal hemorrhages, and (5) papilledema. Urea clearance, as determined by the modification described by Van Slyke, Page, Hiller, and Kirk (1935) of the original method, is expressed as average per cent of normal. The ability to concentrate urine maximally is ascertained by withholding water from the patient for 24 hours and measuring the specific gravity of the urine passed after the last 12 hours. Correction is made for the gravity contributed by protein in the urine. Hematuria is determined by counting the red cells in the urine according to the technique of Addis (1926). Values above 500,000 in a 12 hour specimen are considered abnormal. Plasma proteins were determined by the method of Howe (1921). The black areas representing edema have the following significance: Height of black area in quarters of total space (1) trace, (2) moderate pithing, (3) marked pithing, (4) general edema with ascites. The transverse cardiac diameter is recorded as the per cent deviation from normal according to the table of Ungerleider and Clark. The circulation time was determined by intravenous injection of 2.25 gm. of soluble saccharin in 5 cc. of distilled water. The arm-to-tongue time is measured in seconds. The normal range is considered from 7 to 10 seconds and borderline normal from 10 to 20 seconds. Venous pressure is recorded in centimeters of blood. The thiocyanate content of the blood was ascertained by the method of Crandall and Anderson (1934), and recorded as mg. in 100 cc. of blood.

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[3] Ungerleider-Clark tables of theoretical transverse diameter of the heart.

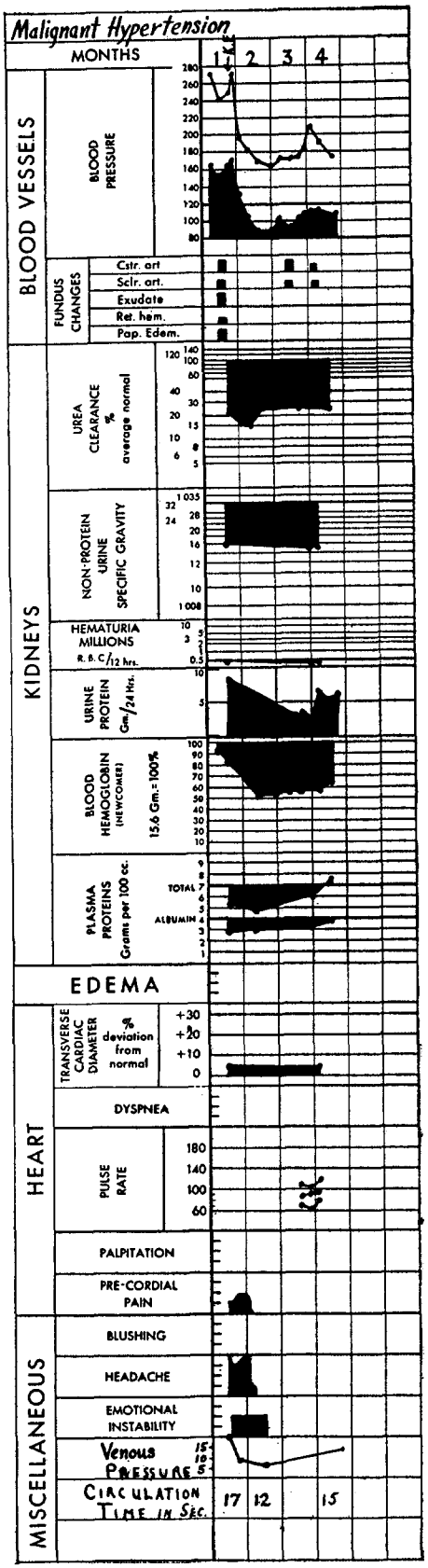



FIG. 11. R-T 703. Male, 24 years, height 167½ cm., weight 53.8 kilos.

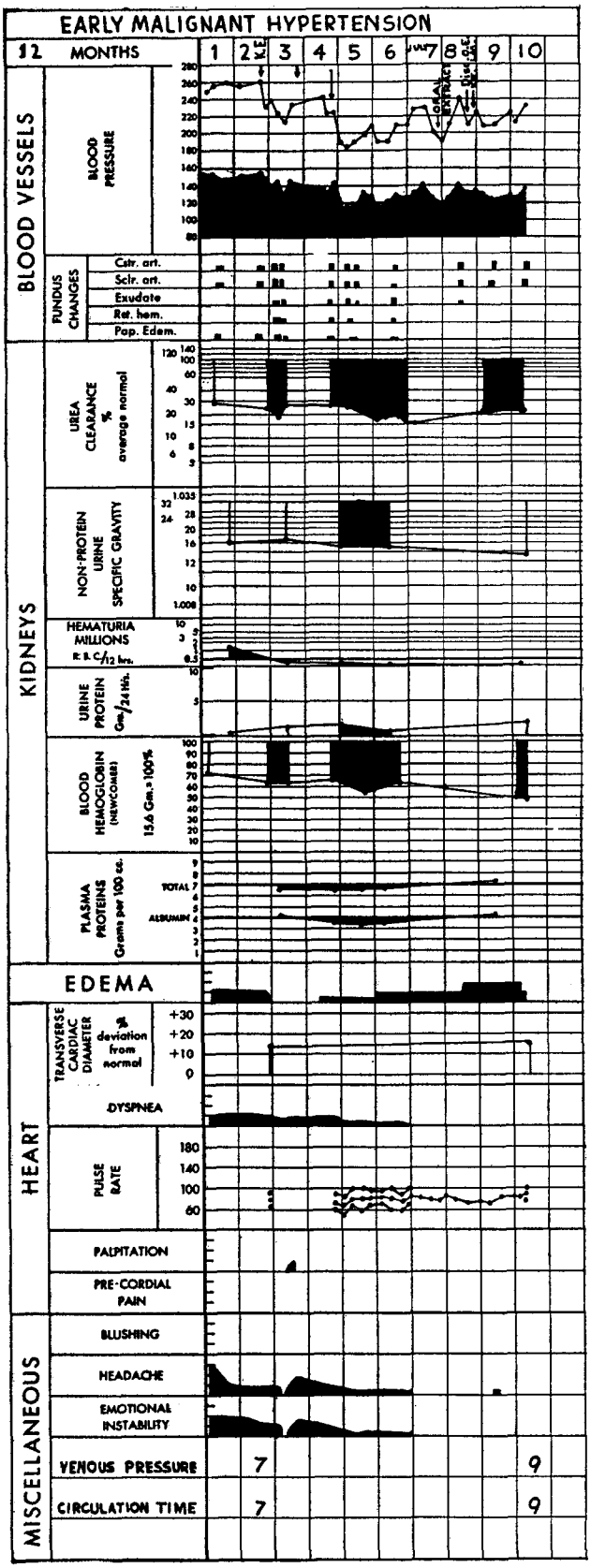



FIG. 12. C-R 671. Female, 37 years, height 165 cm., weight 67.9 kilos.

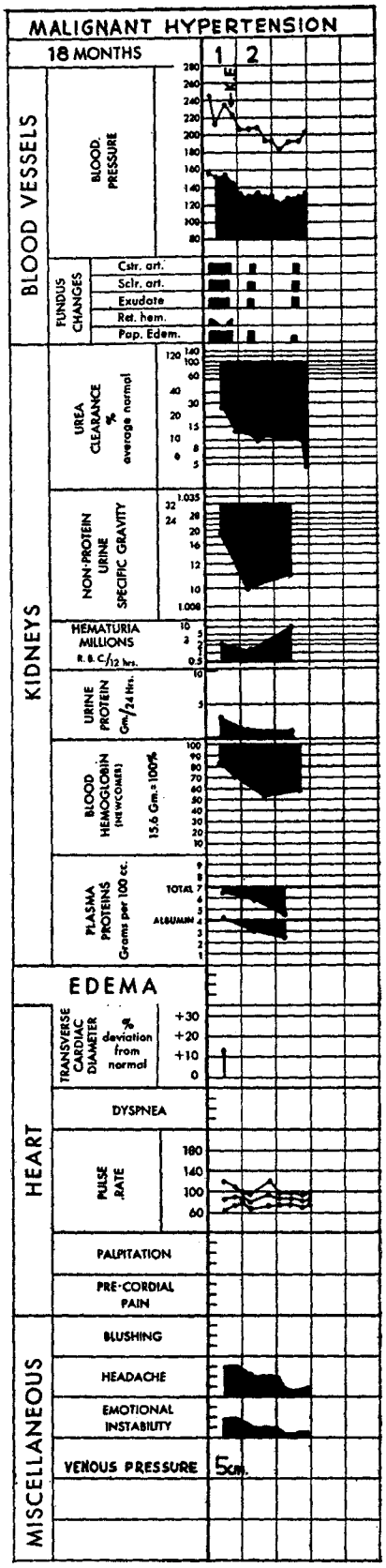



FIG. 13. J-C 683. Male, 30 years, height 171.4 cm., weight 60 kilos.

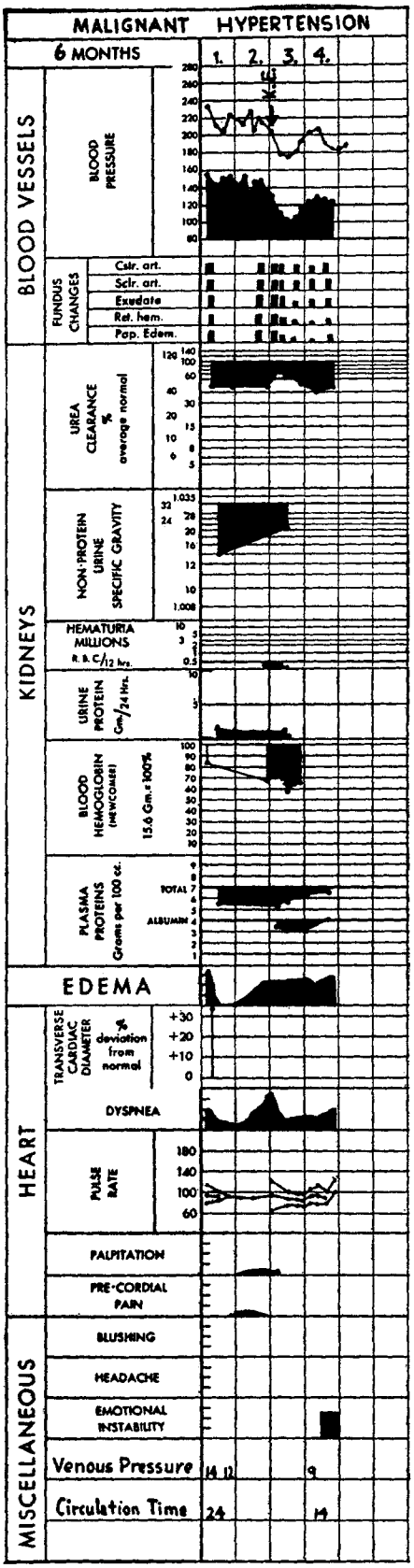



FIG. 14. L-S 662. Male, 41 years, height 173.9 cm., weight 89.8 kilos.

The extract was given by rectum to this patient with apparent success after the blood pressure had been reduced following intramuscular injection. Despite the fact that extracts prepared by a number of different methods were employed, the blood pressure has been kept at a relatively low level (Fig. 7).

The patient is now up and about, is able to read and the headaches have disappeared. The T waves became upright in leads 1 and 4 after 2 weeks of treatment and 2 months later the electrocardiogram was even more nearly normal (Fig. 10). He has now been treated for 6 months.

C-R 671 (Fig. 12), malignant hypertension.

A colored female, aged 36, complained of headaches, failing vision, and nocturia of about 10 months' duration. These symptoms progressed until she was unable to read.

Grade 2 arteriosclerosis and constriction of the retinal arterioles were found and grade 2 papilledema. Blood pressure was 256/152 mm. Hg. Grade 1 edema was present. Urea clearance had already fallen to 30 per cent of normal and was continuing to fall. The Addis count revealed a marked increase over normal of the red blood cells in the urine. The cardiac diameter showed +14 per cent deviation from normal. The electrocardiogram exhibited isoelectric T waves in leads 1 and 2 (Feb. 28, 1940), which 8 days later became inverted.

While resting in bed the blood pressure averaged 233/140 mm. Hg. Retinal hemorrhages were appearing in crops. Beef muscle extract was administered intramuscularly and the blood pressure fell to 188/118 mm. Hg. After discontinuing this extract the pressure rose to 237/143. The patient was discharged from the clinic and readmitted a month later. The blood pressure average was 224/130 mm. Hg. Kidney extract was administered and the blood pressure fell within 2 days to an average of 195/124 and continued down to 185/117. The remainder of the blood pressure averages are shown in Fig. 12.

Urea clearance was low (16 per cent) and did not change significantly during treatment. It is of interest that the T waves which were inverted in leads 1 and 2 became upright (Fig. 9). Retinal hemorrhages, exudates, and papilledema disappeared.

J-C 683 (Fig. 13), malignant hypertension.

This white male, aged 34, complained of headaches, failing vision of about 18 months' duration. Vision became suddenly diminished. The headaches became so severe that it was necessary to give large amounts of codeine.

The patient appeared very ill. He was unable to read. Examination of the eyegrounds showed grade 3 constriction and sclerosis of the arterioles, grade 3 papilledema and exudates, and grade 2 hemorrhages. The heart was slightly enlarged (+ 14 per cent deviation). The S-T segments in leads 1, 2, and 3 were depressed and the Q.R.S. complex was splintered in lead 3.

Shortly after admission the patient had a series of four convulsions. The arterial blood pressure was 278/170 and spinal fluid pressure 200 mm. of water. Severe vomiting then began and all fluids had to be given by rectum. The patient became irrational. Since the outlook seemed so poor, kidney extract was administered. The blood pressure fell progressively (Fig. 8). Without extract the diastolic pressure was seldom below 158 mm. Hg and often much higher, while with it, it was seldom above 130 mm. Hg. Hemorrhages disappeared from his eyegrounds and the papilledema regressed so that he was able to read. Urea clearance was 13 per cent of normal when treatment was started and did not appear affected by it. Headaches were much reduced in severity.

Since we did not believe that the extremely low renal function was reversible, we could not conscientiously advise him to continue treatment. When it was discontinued and the patient allowed to go home, the blood pressure rose sharply and he died within 2 weeks.

E-P 722, malignant hypertension.

This 46 year old colored patient noticed that 2 years ago she became short of breath on slight exertion, and 1 year ago swelling of her feet and ankles occurred. Exertion brought on attacks of a smothering feeling in her chest and severe palpitation. 10 days before admission mild apoplexy occurred followed by moderate left hemiplegia. Nocturia became persistent. Anginal pains also occurred on even slight exertion.

The patient is obese. Eyegrounds showed grade 3 constriction, sclerosis, exudates, papilledema, and hemorrhages, both fresh and old. Blood pressure on admission was 310/124 mm. Hg. The heart was enlarged (27+ per cent deviation). The T waves in leads 1, 2, 3, and 4 were inverted, the P wave in lead 3 isoelectric. Urea clearance was 70 per cent of normal. Vital capacity was reduced to 40 per cent of normal. Retrograde pyelograms show that there was bilateral hydronephrosis but cultures of the urine were negative.

Kidney extract was administered after the blood pressure had been stabilized at an average level of 260/136. During the next week it had fallen to an average of 216/103, the 2nd week 205/100, the 3rd week 202/100, and the 4th week 202/97 mm. Hg (Fig. 6). Marked regression of the eyeground changes occurred. There was less exudate and only a small amount of hemorrhage. Proteinuria diminished from 3 gm. in 24 hours to less than 0.1 gm. Hemoglobin was not changed significantly (70 per cent). The electrocardiogram, taken 3 weeks after treatment was initiated, showed inversion of the T waves in leads 1, 2, and 3 but not in lead 4.

L-S 662 (Fig. 14), malignant hypertension.

This 41 year old man complained of dyspnea, headache, insomnia, nausea and vomiting, edema of the legs, and swelling of the abdomen. He knew that he had hypertension for 4 years, but 2 years before admission dyspnea and fatigability became pronounced. On admission he exhibited cyanosis of the extremities, orthopnea, grade 4 edema, and ascites. The eyegrounds showed grade 3 sclerosis and constriction of the vessels, grade 3 hemorrhages, exudates, and papilledema. The heart was markedly enlarged (+39 per cent deviation), the rate was rapid and gallop rhythm was present. The venous pressure was elevated (12 cm. of blood) and many moist râles were heard in the chest. The results of laboratory examinations are charted in Fig. 14. The electrocardiogram demonstrated numerous extrasystoles, depression of the S-T segment in leads 1, 2, and 3; inverted, splintered Q.R.S. in lead 3 and biphasic Q.R.S. in lead 4.

During the first 4 weeks after admission the blood pressure averaged 215/150 mm. Hg. The week following administration of kidney extract the pressure averaged 178/110. He complained of less dyspnea and the rhythm of the heart became regular. The papilledema receded. Extract was discontinued and the blood pressure rose to near its former level, the pulse became irregular and rapid, and dyspnea returned. Urea clearance began to fall and retinal hemorrhages appeared along with papilledema. A more purified but evidently weaker extract was again administered. The patient, however, became stuporous and complained of severe joint pains. Urea clearance continued to fall and massive hemorrhages occurred from the bowel. The latter con-

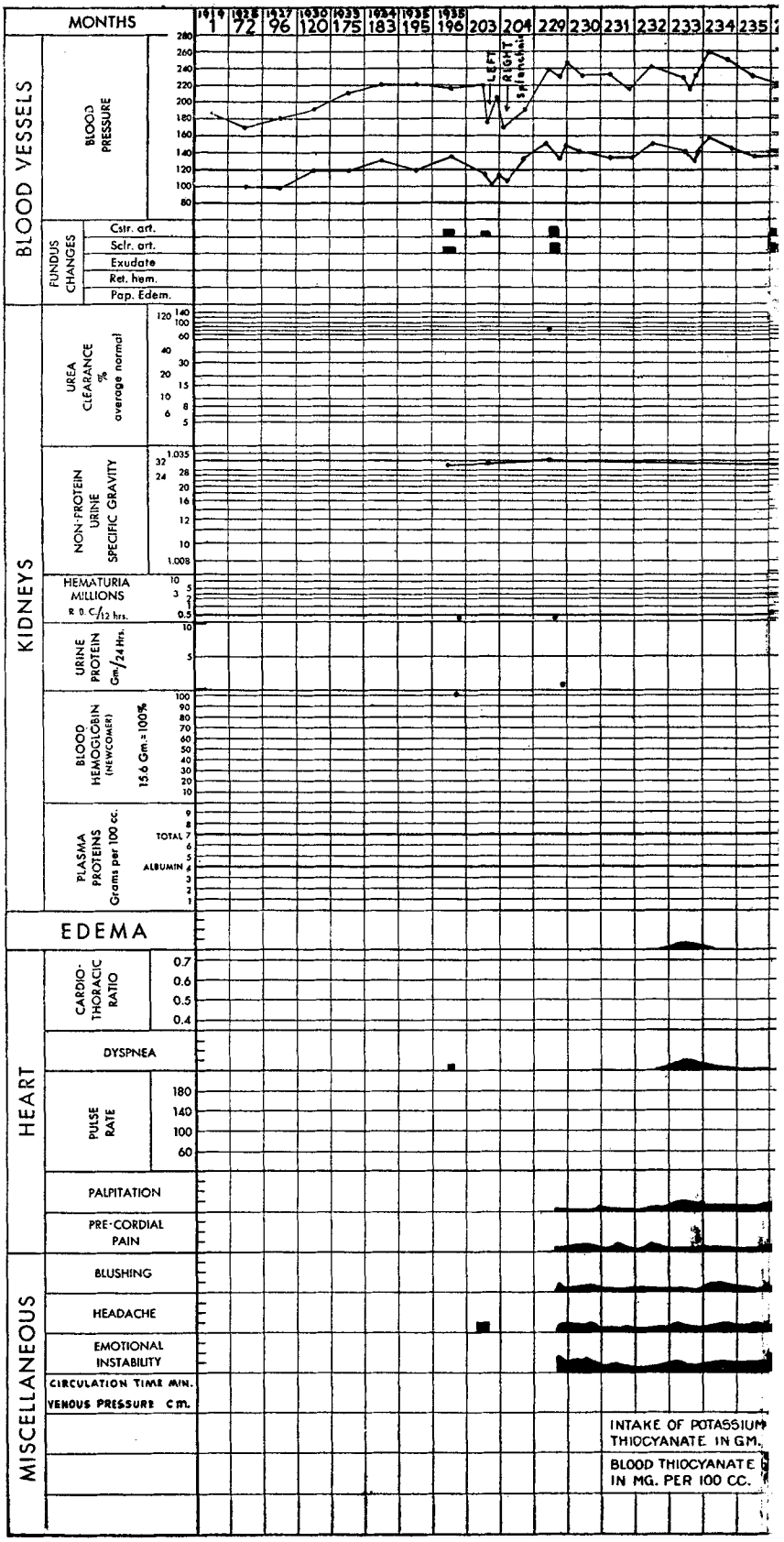
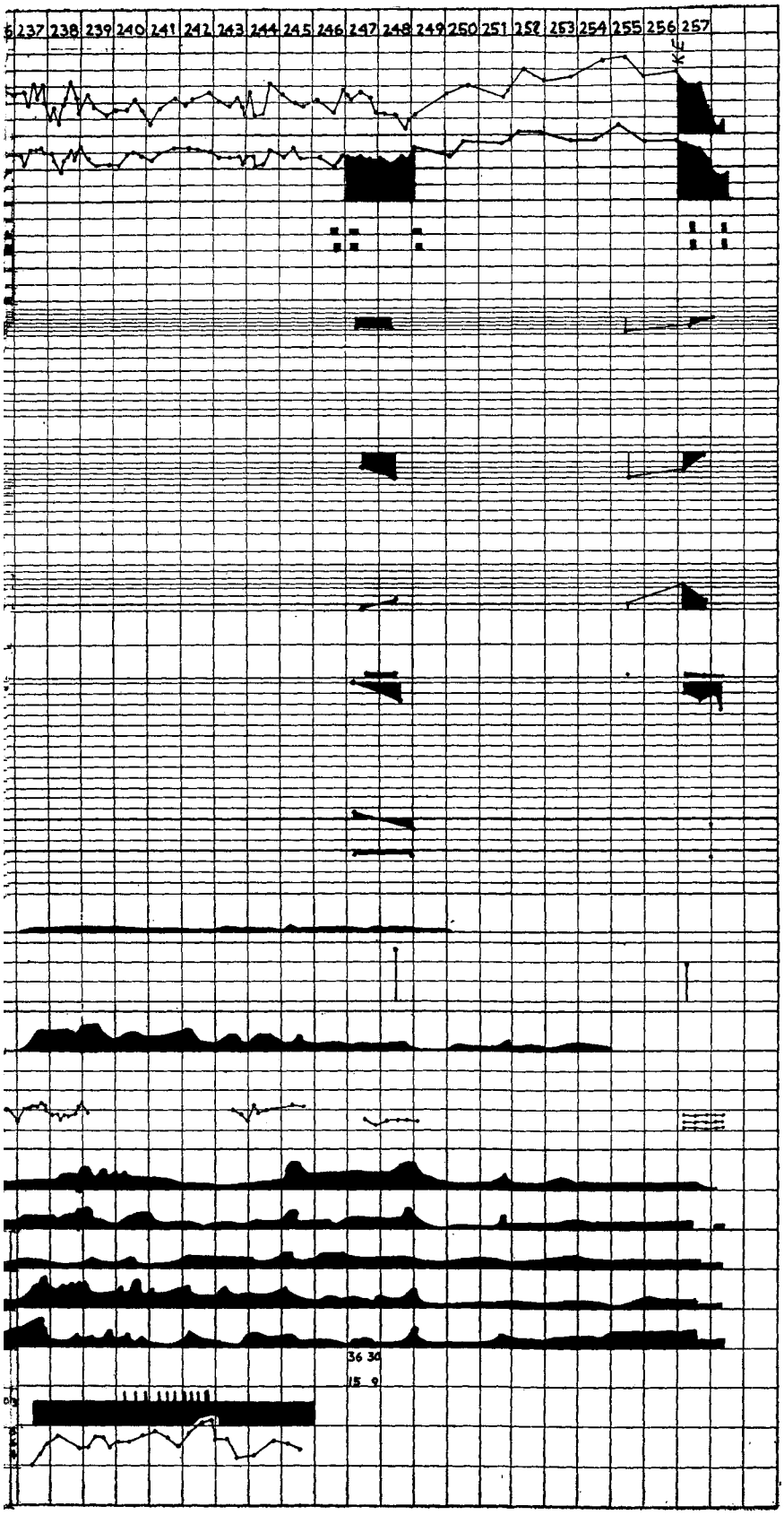



FIG. 15. L-K 553. Female, 40 yea




rs, height 161 cm., weight 75 kilos.

tinued and apparently were the immediate cause of death. The diagnosis of malignant hypertension was confirmed at autopsy. The bleeding was coming from ulcers in the large bowel.

J-B 724, essential hypertension.

This 37 year old negro complained of occipital headaches for the past 3 years. 4 years ago his blood pressure was normal but 2 years ago it was 170/100. Several members of his family are hypertensive.

On admission the blood pressure was 220/130 mm. Hg and, except for grade 1 constriction of the retinal arterioles, the physical examination was negative. Retrograde pyelograms showed no abnormalities. Electrocardiogram was normal as were the other laboratory examinations. The cold pressor test caused the blood pressure to rise from 186/130 to 256/180, and the seconal[3] test a fall from 230/138 to 130/100.

Renal extract was administered after the average pressure was established at 182/123 while the patient was in bed. After 4 days the patient was discharged from the clinic and received the injections daily as an outpatient. Since the patient was ambulant the pressures would probably have been lower had he been confined to bed as during the control period. The first week the average was reduced to 155/106, the next week 160/107, the 3rd week 157/109, and the 4th week 148/103 mm. Hg.

L-K 553 (Fig. 15), essential hypertension.

A white female, aged 38 years, complained of palpitation, headaches, insomnia, and precordial pain. Hypertension was discovered 21 years ago. In 1936, because of the severity of the hypertension, both splanchnic nerves were resected but within 2 weeks the pressure had risen to 190/135 mm. Hg. On admission to the Lilly Clinic in 1938 the blood pressure was 248/148 mm. Hg. Maintenance doses of digitalis were being given before her admission because, on discontinuing it, decompensation occurred. Despite the long continued hypertension, the renal function was good.

Administration of thiocyanate for a period of 10 months brought no significant reduction of blood pressure.

Kidney extract administration was started 6 months ago. At first the extracts were not so potent as those now employed and the fall in blood pressure was correspondingly smaller. The average blood pressure over several years before administration of extract was 230/134 mm. Hg and after extract it had fallen to 172/104.

R-G 701, essential hypertension.

This 33 year old white female complained of severe headaches, weakness, and dimness of vision. Hypertension was found during the last pregnancy 2 years ago when she had the typical signs and symptoms of toxemia.

Physical examination revealed grade 2 constriction and sclerosis of the retinal arterioles. A grade 3 systolic murmur was heard at the apex of the heart. There was no cardiac enlargement.

The blood hemoglobin was 65 per cent of normal, urea clearance 52 per cent, maximum specific gravity of urine 1.032, and Addis count was normal.

During a 3 week period of observation with the patient in bed the twice daily blood

[3] Seconal (sodium propyl-methyl-carbinyl allyl barbiturate, Lilly).

pressure estimations averaged 200/129 mm. Hg. Kidney extract was administered daily and the following 2 weeks it fell to an average of 173/118 mm. Hg.

On discharge the patient felt much improved. Headaches had all but disappeared and she was emotionally more stable than before treatment.

She was then followed in the outpatient clinic. Without treatment 1 week after discharge the blood pressure average was 182/122, 2 weeks after 193/125, 3 weeks after 200/127, 4 weeks after 199/133, and 5 weeks after 214/142. The headaches and excessive nervousness reappeared.

A-K 681, essential hypertension.

This white female, aged 46 years, complained of headaches, nervousness, pain over the heart, edema of the legs, and cramping in the feet and legs of a year's duration. 5 years ago she passed through the menopause. Shortly before admission, vision in her left eye suddenly became blurred and she was unable to see with her right eye.

Physical examination revealed grade 2 constriction and sclerosis of the retinal arterioles. In the right retina there was a circular hemorrhagic area with a small patch of exudate. The heart was enlarged (+27 per cent deviation). Grade 1 edema was present over the ankles.

Urea clearance averaged 70 per cent of normal and maximal ability to concentrate urine was 1.029. Some white blood cells were seen in the urine. A retrograde pyelogram revealed normal kidneys; urine culture was negative. The T waves in leads 1, 2, and 3 were inverted and the S-T segment was depressed.

During the 16 day control period, the blood pressure averaged 237/130. Renal extract was then administered and during the next 4 days the average was 183/100. A second extract was then employed for 4 days and the blood pressure averaged 189/107. The average while receiving a third extract was 189/109. Still a fourth extract was used and the average pressure was 189/102. Extract was then discontinued and the blood pressure rose to an average of 248/132 during a control period of 26 days.

M-J 586, essential hypertension.

This patient, a colored female, aged 44 years, complained of headaches, vertigo, and dyspnea occasionally. Hypertension is believed to have occurred for the first time during her seventh pregnancy 11 years ago, and 8 years ago her blood pressure was found to be 150/88. 3 years ago it had risen to 200/140.

On admission to the Lilly Clinic grade 2 constriction and grade 1 sclerosis of the retinal arteries were observed. The thyroid gland was diffusely enlarged (grade 1). The electrocardiogram showed left axis deviation. Urea clearance varied from 82 to 93 per cent of normal. Maximal ability to concentrate urine was 1.026. The Addis count was normal as were the plasma proteins. The heart was slightly enlarged (+13 deviation). The retrograde pyelogram was normal except for slight dilatation of the calyx on the left side. The blood pressure during her stay of 50 days averaged 213/123. As an outpatient the pressure average was 220/130.

The patient was readmitted 10 months later. Sclerosis of the retinal arterioles was now grade 2 and constriction grade 3. The liver was palpable below the costal margin. The maximum ability to concentrate urine was reduced (1.018 to 1.021). Urea clearance was 103 per cent. The deviation from normal cardiac size was +15 per cent.

Blood pressure during the control period averaged 190/114. The first kidney extract,

given for a period of 7 days, caused no significant fall in pressure (191/110). The second extract, given for 4 days, was associated with a fall (170/106 average). Extract was discontinued and the pressure rose to 200/114.

The patient was again readmitted a month later. This time, during the control period of 1 week, the arterial pressure average was 210/125. Renal extract was started and for the next 8 days the pressure fell to an average of 169/110, at times being as low as 140/90. During the next 3 weeks 5 different batches of extract were given. The blood pressure average was 175/99, occasionally falling to low levels (132/84). The patient felt well throughout the period she received extract, except for relatively slight pain around the site of the injections.

Extract was discontinued and the patient treated in the outpatient clinic. The blood pressure rose to an average level of 209/129 for 10 days.

E-P 471, essential hypertension.

This 49 year old colored woman complained of headaches, dizziness, and dyspnea on exertion for the past 7 years. Hypertension was found at that time. Since then the blood pressure has remained elevated, ranging from 200 to 270 systolic and 120 to 180 diastolic.

Physical examination showed grade 2 constriction and sclerosis of the retinal arteries. The heart was enlarged (+15 deviation) and there was a diastolic blow heard at the base. The electrocardiogram showed left axis deviation, slight inversion of the T wave in lead 1, and an S wave was present in lead 2. She is known to have had syphilis since 1935 and received sufficient treatment to alter the Wassermann reaction from positive to negative. The gold curve of the spinal fluid was that of paresis. Retrograde pyelograms were negative. The patient was treated in the outpatient clinic and was not confined to bed.

During the control period the blood pressure averaged 229/119. The first 2 weeks after injection of kidney extract the pressure average was 196/98, the following 2 weeks 182/90, and the next week 157/78. The site of the injection in the buttocks became swollen and an abscess developed. Hence the extract was given in five times the dosage by mouth. The blood pressure averages for each succeeding week were 168/85, 177/91, 178/91, and 184/96. Extract was discontinued and the average for the week was 210/104. For the next 2 weeks injections of extract were given at irregular intervals and the blood pressure average was 186/92.

## DISCUSSION

Renal extracts have now been prepared of sufficient potency that the yield from 400 to 1000 gm. of original fresh kidney will reduce the mean blood pressure of experimentally hypertensive dogs from levels of 200 mm. Hg or more to normal levels in the course of 6 to 8 days. The results in rats are similar. Such treatment has been adopted as a routine method for assaying the potency of the extracts.

We have not observed any toxic effects of these renal extracts when injected parenterally into dogs except when large overdoses are given, which result in a precipitate fall in arterial pressure to levels below normal. On

the contrary, several times animals which have been either apathetic or comatose have been restored to normal vigor by treatment within 1 to 6 days. Equally impressive have been the results in human beings with malignant hypertension. Williams, Grollman, and Harrison (1940) find treatment of dogs by mouth far more satisfactory than by injection. In their hands renal extracts administered parenterally gave toxic symptoms and signs, but they attribute this largely to impurities.

The effect of renal extracts on arterial pressure is unlike any known depressor substance. Instead of a prompt fall in pressure, such as occurs when histamine, choline, adenylic acid, etc., are injected, these preparations produce at first a marked rise. This is due to the renin contained in them. The gradual fall is not evident until after several days of treatment, suggesting that not only is the active principle slow acting, but a sufficient amount must be injected to fill emptied stores of the material in the hypertensive before it becomes effective.

We are unable to explain the large differences in the time required for the return of the pressure to hypertensive levels after discontinuing treatment. Of the 60 dogs successfully treated, several have shown no return of hypertension after treatment. This may have been a spontaneous fall in blood pressure and need not indicate alleviation of it.

Dramatic results have been observed in the five patients with malignant hypertension. These cases are impressive because one is accustomed to anticipate early death (see comparable charts published by Page (1939*c*) of instances in which no extract was given). The response of the blood pressure in patients with essential hypertension is often as striking, but since many of the patients had few symptoms before treatment was started it is not surprising that the reduced blood pressure seems a mere academic achievement to the uninitiated.

Had early cases of hypertension been chosen for treatment, reduction of blood pressure might have been more easily accomplished. We have chosen those with the so called "fixed" hypertension because there is much less danger of misinterpretation of the results due to spontaneous changes in blood pressure.

## SUMMARY

1. Extracts of kidneys have been prepared containing a substance which lowers arterial blood pressure for prolonged periods in patients with essential and malignant hypertension, and in hypertensive dogs and rats.

2. Several different chemical procedures are proposed for the preparation of the extract. The best one has not been decided upon.

3. The quantity of original fresh whole kidney required to yield enough extract to lower blood pressure from hypertensive levels (200 mm. Hg mean pressure) to normal levels is roughly 600 to 900 gm. in dogs within 4 to 8 days. In hypertensive patients the yield from 700 to 1000 gm. daily for several weeks may be necessary.

4. Lowering of the blood pressure too rapidly in animals results in a shock syndrome which may be fatal. If overdosage is avoided, no appreciable rise in blood urea nitrogen occurs, nor do other signs of toxicity appear.

5. Lowering of blood pressure to nearly normal levels has been accomplished in 60 hypertensive dogs, and in some of these it has been allowed to rise and was again reduced as many as five times. Similar results have been obtained with hypertensive rats.

6. Six patients with essential hypertension have been treated resulting in prolonged reduction of blood pressure. Clinically the patients appear improved.

7. Five patients with malignant hypertension have been treated, with reduction of the blood pressure in all instances. One patient was treated despite urea clearance of 5 per cent of normal. His blood pressure was sharply reduced, but death in uremia occurred. The second patient also exhibited sharp reduction of pressure and died after treatment was discontinued. The other three are much improved after treatment, as indicated by increase in vision and mental activity, loss of dyspnea, improvement in the electrocardiogram, etc.

8. The length of time the blood pressure remains lowered varies greatly in both animals and man. The trend is usually upwards after discontinuing treatment for 4 to 6 days.

9. Increasing experience with this treatment suggests that it is of value in the management of hypertension, but it is yet in the experimental stage.

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