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RENIN SECRETION DURING
RENAL COMPENSATORY HYPERTROPHY

by

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B.Sc., Presidency College (U. Calcutta) 1955

M.Sc., Presidency College (U. Calcutta) 1962

THESIS

Submitted in partial satisfaction of the requirements for the degree of

MASTER OF ARTS

in

ENDOCRINOLOGY

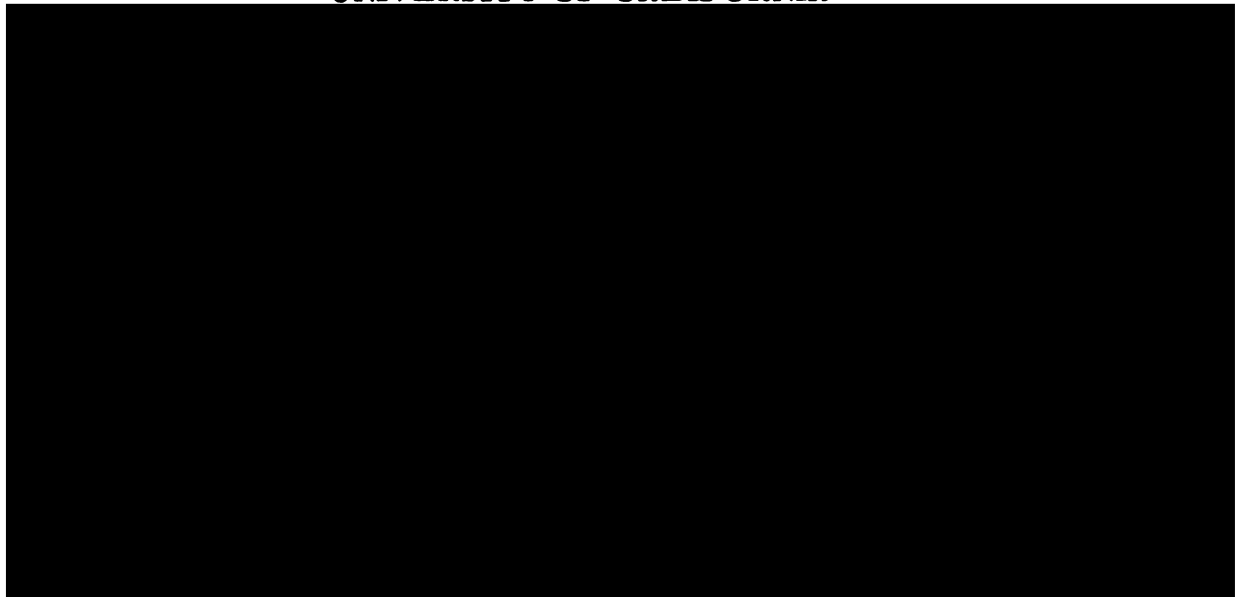
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INTRODUCTION

When renal tissue is lost by disease or surgical removal, the remaining normal renal mass increases in size and weight. This tends to compensate for the loss and has been called compensatory hypertrophy (1).

In 1939 Goormaghtigh suggested that renin might be secreted by the cells of the juxtaglomerular apparatus (2). He (6) and Hartroft (3), Tobian (4) and Gross (5) have shown that the changes in the degree of granulation of the juxtaglomerular cells tend to parallel those in the kidney's renin content in pathological states. They believe that the granules are the stored form of renin and that changes of the granulation of the cells indicate changes in the rate of secretion of renin or a change in the rate of synthesis of renin or both.

In 1960 two new findings suggested the possibility that the renin-angiotensin system is important in the control of aldosterone secretion. First it was observed that an aldosterone-stimulating hormone is secreted by the kidney (7, 8, 9), and secondly it was found that the intravenous infusion of synthetic angiotensin II augments the rate of aldosterone production in man (10). Ganong and Mulrow (9, 11), Davis et al (8), and others have provided evidence for the important role of the renin-angiotensin system in the regulation of aldosterone secretion.

Deane and Masson (12) reported that injection of partially purified solutions of renin produced enlargement of the zona glomerulosa of the adrenal cortex in rats. Hartroft and Hartroft (13, 14) and Hartroft, Newmark and Pitcock (15) have reported that renin has a trophic action on the zona glomerulosa.

The purpose of this investigation was to assess renin content and secretion during compensatory hypertrophy of the kidney. When one kidney is removed, the output of renin from the remaining kidney must double if total renin secretion is to remain unchanged. If it does not double, one might expect the rate of aldosterone secretion to decline. To determine whether renin secretion from the remaining kidney increased, the histology of the juxtaglomerular cells, the renal renin content, and the weight and histology of the adrenal cortex were studied seven days after unilateral nephrectomy in rats.

METHODS

The left kidney was removed from seven male rats of Long Evans strain under ether anesthesia. The rats weighed an average of 275 gm. At the end of the experimental period, seven days after nephrectomy, the right kidney and both adrenals were removed and then the animals were sacrificed. The left kidney was the control kidney and the right kidney was the experimental kidney in this investigation. The change in body weight was noted. Six untreated rats of the same weight, strain, sex, and fed the same diet were used to measure the control weight and width of the zona glomerulosa of the adrenal.

A. The following measurements were made on each kidney separately:

I Weight

II Renin content as determined by bioassay for angiotensin

II equivalents

III Assessment of juxtaglomerular index

In addition, the weights of both adrenal glands and the thickness of the zona glomerulosa of the right adrenal were compared with those of control rats.

I. Kidney weight

The kidneys were blotted free of blood and weighed fresh on a Roller-Smith balance. A piece was then taken out for the assessment of juxtaglomerular index. The remaining parts of the kidney were weighed again. The whole kidney weight was required for the determination of right kidney hypertrophy and the measurement of total renin content.

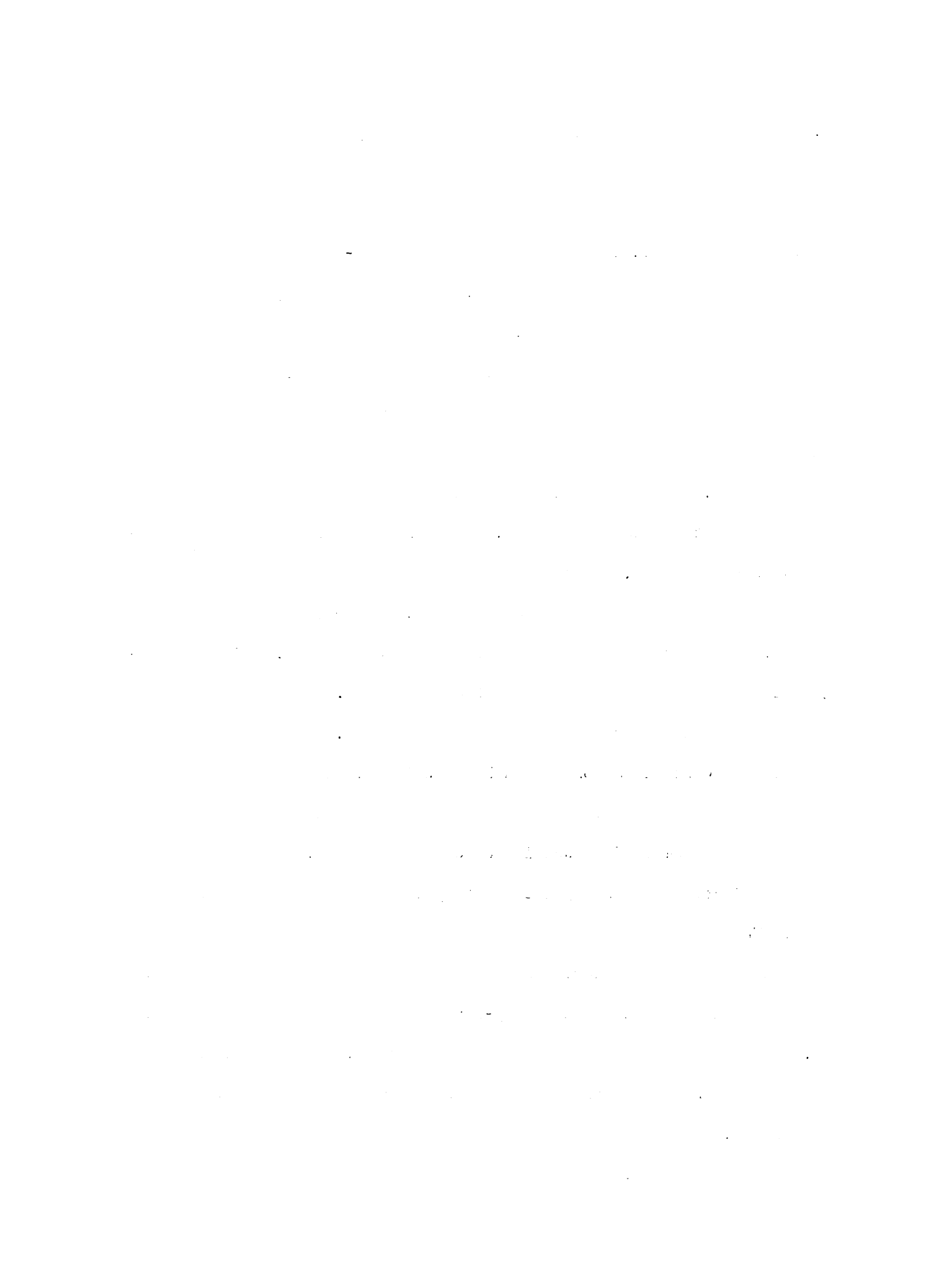
Right kidney hypertrophy was expressed as per cent increase of wet weight of right kidney compared to left kidney (16):

$$\frac{(\text{Right kidney wet weight} - \text{Left kidney wet weight})}{\text{Left kidney wet weight}} \times 100$$

II. Measurement of total renin content of kidney

(a) Extraction of renin

Renin was prepared according to the method of Haas and Goldblatt (17). The kidneys that had been stored in a deep-freeze cabinet at about -20°C were thawed at room temperature. The renal pelvis, peripelvic fat and fibrous tissues were removed. Care was taken to save renal cortex and tissue juice as far as possible. The tissue was cut into small pieces and homogenized in a Waring blender for seven minutes, cooling it with ice when necessary to keep the temperature of the homogenate between 10°C and 20°C . The homogenate was centrifuged for an hour at 1600g, and the supernatant was then collected. The same extraction process was repeated on the residue, and the two supernatants were combined. All further steps were performed in an ice bath. The extract was acidified to pH 2.6 by addition of 5N H_2SO_4 with constant stirring. After 10 minutes it was neutralized by slow addition of 5N KOH. The above mentioned two steps were to denature the nonspecific protein. The precipitate was separated by centrifugation for an hour at 1600g. The pH of the supernatant was adjusted to 4.5 by adding 2N H_2SO_4 . The renin was precipitated by adding ammonium sulfate until a concentration of 2.2M was reached. The precipitate was then separated out by centrifugation for an hour at 1600g. The supernatant was discarded, and the precipitate was suspended in ice cold distilled water. The suspension was dialyzed against cold distilled water for at least twenty-four hours in a cold room at about 4°C . The distilled water was changed three times. The resultant renin solution, which was clarified by centrifugation and filtration, was lyophilized. The dry powder of renin was dissolved in 4 ml of distilled water before bioassay.



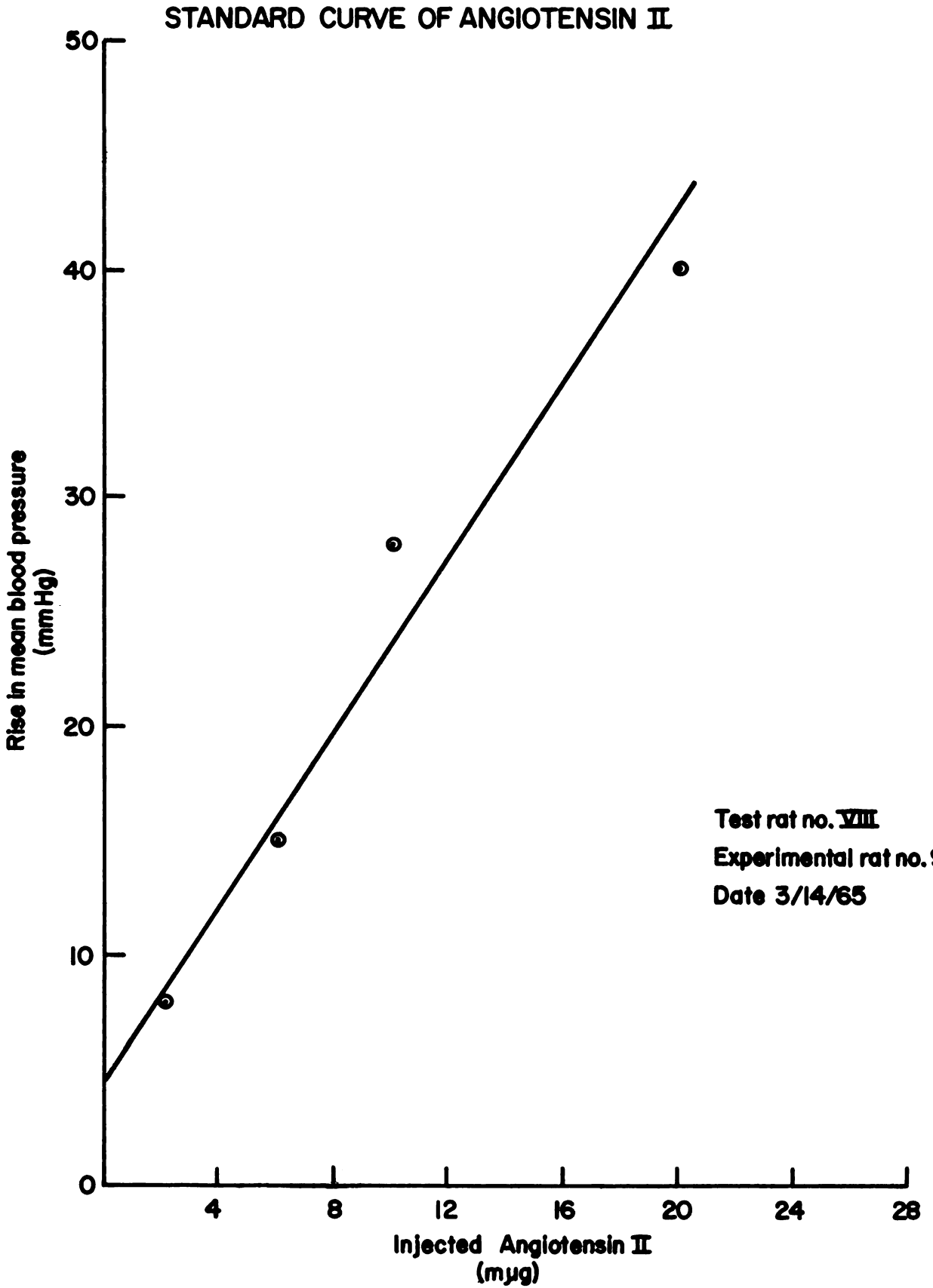


Figure I

(b) Bioassay of the prepared renin

The prepared renin solution was bioassayed by Peart's direct method (18), that is, by the pressor response produced in rats. Eight male rats of Long Evans strain weighing about 350 gm to 500 gm were used for bioassay. The animals were anesthetized with sodium pentobarbital (40 mg/kg body weight) intraperitoneally. The blood pressure was lowered by 1-methyl pyrrolidinium bitartrate (Ansolsen tartrate) (25 mg/kg body weight) subcutaneously. The mean blood pressure was measured directly from the carotid artery, with the aid of a Statham pressure transducer and a Grass Model 5 polygraph, using electrical damping. The external jugular vein was also cannulated and was used for giving renin and angiotensin II. All doses were given from similar tuberculin syringes. The maximum volume which can be injected without any change in mean pressure was checked by injecting heparinized saline. It was found to be 0.35 ml. The volume of renin solution injected varied from 0.2 to 0.35 ml. After each injection the cannula was washed with 0.35 ml heparinized saline. The mean blood pressure was noted for each dose of renin injected.

The number of samples of renin assayed in each assay animal varied from 1 to 3. For each assay a standard curve using pure synthetic angiotensin II was prepared. At the beginning of the experiment a series of angiotensin II standards were administered and the corresponding rise of mean blood pressure was noted. The doses of angiotensin II given for the calibration curve were between 2 and 20 μ g. The line drawn through these assay points (by eye estimation) was used for computing the angiotensin II equivalent of each renin extract (shown in Fig. I). In three test experiments at the end of the assay another standard curve

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2. The second part of the document focuses on the implementation of robust risk management strategies. It outlines the process of identifying, assessing, and mitigating various risks that could impact the organization's operations and financial stability. This includes the development of risk registers, the establishment of risk appetite, and the implementation of control measures to reduce the likelihood and impact of adverse events. The document also discusses the importance of communication and reporting in risk management, ensuring that all stakeholders are aware of the organization's risk profile and the actions being taken to address it.

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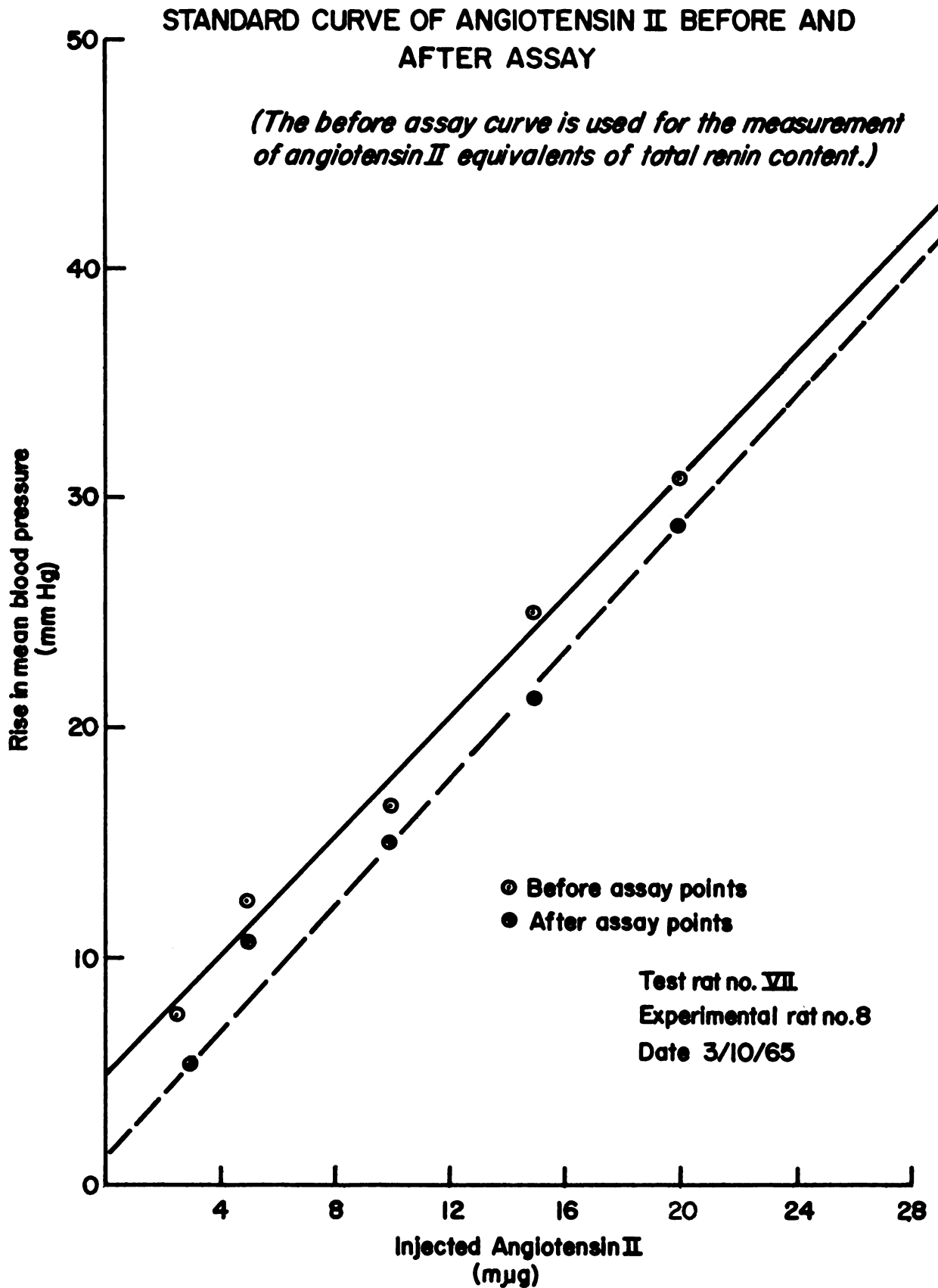


Figure II

was obtained to test the reproducibility of the assay method and reveal any change or deterioration of the preparation (shown in Fig. II). This after assay curve was not used for computing the angiotensin II equivalents of the unknown renin extract.

III. Assessment of indices of granulation of the juxtaglomerular cells

(a) Fixation of kidney

Slices of kidney (approximately 3 mm in thickness) were taken from the middle of each kidney in a transverse plane at a right angle to the superior-inferior longitudinal axis. These were fixed in Helly's fluid (Zenker's solution without acetic acid but with addition of 5 ml of formalin per 100 ml immediately before use) and embedded in paraffin in the usual manner. Sections were no more than 4 micra in thickness. Albumen was used as an adhesive, and care was taken to avoid excessive amounts, as albumen may interfere with the staining procedure.

(b) Staining procedure

The sections were stained according to the Bowie technique as described by Cowdry (19) and modified by Hartroft and Pitcock (13, 20). The paraffin sections were taken rapidly through xylols and alcohols to alcoholic iodine. The sections were immersed not more than three minutes in iodine and sodium thiosulfate respectively and washed in running water for five minutes. 2.5% potassium dichromate was used as mordant overnight at approximately 40°C.

The sections were rinsed with distilled water and immersed overnight in 20% ethyl alcohol containing 10 to 15 drops of Bowie's stock solution per 100 ml. The sections were blotted with bibulous paper, dipped quickly 2-3 times in two changes of acetone to remove excess stain,



and differentiated in a 1:1 mixture of xylol and clove oil until they appeared red or reddish purple. The sections were stained until the renal parenchyma was red (or magenta) in contrast to the bluish purple of the elastic tissue of vessels. Juxtaglomerular cell granules, where present, were the same color as elastic tissues. The latter provided a convenient criterion for determining completion of differentiation. Red blood cells were usually amber because of previous bichromate mordanting. The sections were mounted in benzene-balsam or Permount. The whole cortex of the sections from each kidney was examined for juxtaglomerular cells systematically under the "high dry" magnification of the microscope at an approximate magnification of 200 diameters. All glomeruli encountered were examined regardless of plane of section. The number of glomeruli examined per kidney was between 80 and 280. Units of juxtaglomerular cells, that is, a group of granular cells found together in the same arteriole at the pole of the same glomerulus, were recorded and each unit was assessed for degree of granulation as follows:

One plus -- Cells with only few granules accumulated around the nuclei

Two plus -- A few cells (1 to 3) containing more granules than one plus classification; granules scattered throughout the cytoplasm but not completely covering the cells

Three plus- A few cells (1 to 3) so densely packed with granules that the matrix of the cytoplasm could hardly be seen and the cells appeared swollen

Four plus - More than three cells distended with granules

The totals recorded under one, two, three and four plus were multiplied by the factors 1, 2, 4, and 8 respectively, since, at a very conservative estimate, at least eight times as many granules were present in groups of cells classified as four plus as were present in those classified as one plus. The weighted totals were then expressed per 100 glomeruli to obtain the indices of granulation of juxtaglomerular cells (13).

Therefore, the Juxtaglomerular Granulation Index (JGI) =

$$\frac{\text{Weighted rating of juxtaglomerular cells}}{\text{Number of glomeruli}} \times 100$$

The Juxtaglomerular Granulation Index is only a comparative index, but the relative difference in the number of glomerular granules between the removed kidney and the hypertrophied kidney can be estimated by calculating this index from the histological data.

B. Measurement of the width of the zona glomerulosa of the adrenal cortex

The adrenals were fixed and stored in neutral formol and embedded in paraffin. Sections were made about seven micra thick. Care was taken to cut the sections as closely as possible through the center of the gland to prevent errors due to tangential cutting. The sections were stained with hematoxylin and eosin.

The width of the zona glomerulosa was determined microscopically by taking the average of four measurements per section. For each animal three sections were examined. The values were expressed in micra. The zona glomerulosa was measured with an eye-piece micrometer under 10X magnification. The micrometer was standardized with a graduated stage micrometer at 10X magnification. The following is the calibration:

15 divisions of ocular micrometer = 100 micra of stage micrometer
at 10X magnification

Therefore, 1 division = 6.667 micra at 10X magnification. The reading of the eye piece micrometer obtained from the measurement of the zona glomerulosa of the adrenal cortex was multiplied by 6.667 to transform eye piece reading to micra.

V. Statistical evaluation of data

The following equation was used for computing the standard deviation and standard error of mean (47):

$$SD = \sqrt{\frac{\sum x^2 - \left(\frac{\sum x}{n}\right)^2}{n-1}}$$

$$SE = \frac{SD}{\sqrt{n}}$$

Here, $\sum x^2$ is the sum of the squares of the individual values and $(\sum x)^2$ is the square of the sum of the items, i.e., the items added together and then squared. SD and SE are standard deviation and standard error respectively. n is the number of individual values in the series.

The following formula was used for evaluating the significance of the difference between two means. "Student's" t test was used for computing 'P' value.

$$t = \frac{M_a - M_b}{\sqrt{(SE_a)^2 + (SE_b)^2}}$$

M_a and M_b represent the mean of two series and SE_a and SE_b the standard error of two series. By using Fisher's table (48) the 'P' value was computed from the 't' value.



TABLE I

Pre- and postoperative body weight, weight of normal left kidney and of hypertrophied right kidney seven days after left nephrectomy

Rat no.	Left kidney wet weight (gm)	Right kidney wet weight (gm)	% increase in wet weight of right kidney**	Preoperative body weight (gm)	Postoperative body weight (gm)	Body weight change (gm)	% change in body weight
4	1.032	1.444	39.9	265	265	0	0
5	0.820	0.966	17.8	245	235	-10	-4.1
6	1.120	1.460	30.4	285	310	25	8.8
7	1.162	1.500	29.1	310	320	10	3.2
8	1.042	1.502	44.1	280	300	20	7.1
9	1.042	1.496	43.6	275	300	25	9.1
10	0.982	1.423	44.9	250	275	25	10.0
Mean	1.029	1.399	35.7	273	286	14	4.9
SE	± 0.04	± 0.07	± 3.8	± 8.0	± 11.2	± 5.3	± 2.0

** $\frac{\text{Right kidney weight} - \text{left kidney weight}}{\text{left kidney weight}} \times 100$

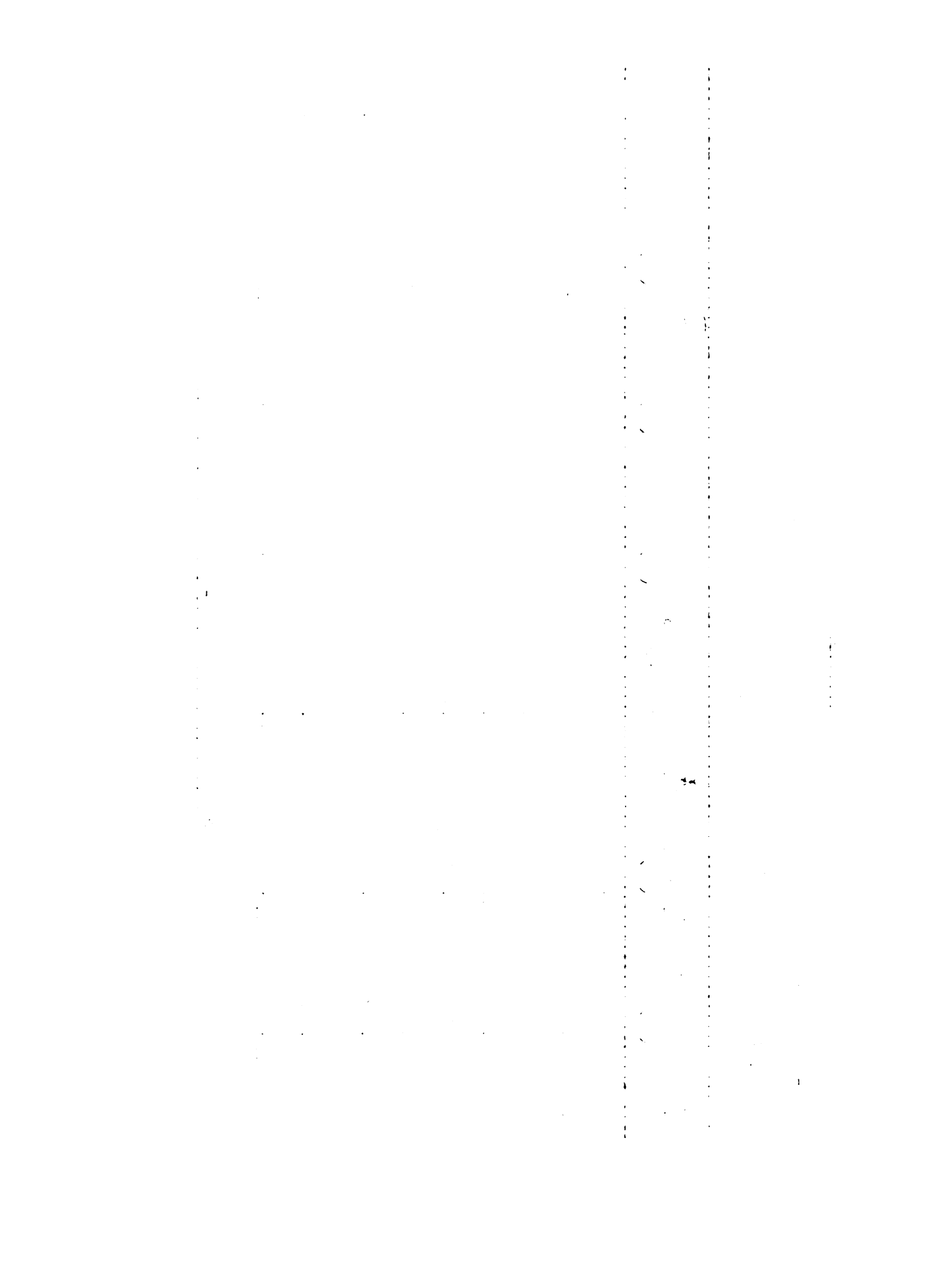


TABLE IIA

Determination by bioassay technique of total renin content of
left (control) kidney seven days after left nephrectomy

Rat no.	Volume of extract in- jected in assay rat (ml)	Mean blood pressure rise (mm Hg)	Equivalent of angioten- sin II (from standard curve μg)	Renin content of part of kidney extracted (angio- tensin II equiva- lents; μg)		Renin content of whole kidney
				Values	Mean	
4	0.2	7	1.0	20		
	0.2	10	3.0	60	67	78
	0.2	15	6.0	120		
5	0.35	10	3.0	34		
	0.35	10	3.0	34	44	55
	0.3	15	6.0	80		
	0.3	8	2.0	27		
6	0.2	8	1.8	36		
	0.3	8	1.8	24	28	32
	0.3	8	1.8	24		
7	0.3	15	7.6	101	85	111
	0.3	10	5.1	68		
8	0.3	8	4.0	53		
	0.3	15	9.0	120	99	127
	0.3	20	12.7	169		
	0.3	8	4.0	53		
9	0.3	23	9.6	128		
	0.3	40	18.4	245	197	259
	0.3	36	16.4	219		
10	0.3	15	9.0	120		
	0.3	20	12.7	169	114	139
	0.3	8	4.0	53		

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TABLE IIB

Determination by bioassay technique of total renin content of hypertrophied right kidney seven days after left nephrectomy

Rat no.	Volume of extract injected in assay rat (ml)	Mean blood pressure rise (mm Hg)	Equivalents of angiotensin II (from standard curve μg)	Renin content of part of kidney extracted (angiotensin II equivalents; μg)		Renin content of whole kidney
				Values	Mean	
4	0.3	10	3.0	40	33	39
	0.3	8	2.0	27		
5	0.3	15	6.0	80	68	84
	0.3	13	4.5	60		
	0.3	13	4.5	60		
	0.3	18	7.6	101		
	0.15	8	1.4	37		
6	0.3	13	4.8	64	61	67
	0.3	8	1.8	24		
	0.2	13	4.8	96		
7	0.3	18	8.9	119	110	141
	0.3	15	7.6	101		
8	0.3	40	26.6	355	360	464
	0.3	44	29.4	392		
	0.3	33	21.8	291		
	0.3	45	30.1	401		
9	0.3	38	17.6	235	217	293
	0.3	30	13.7	182		
	0.3	38	17.6	235		
10	0.3	28	18.5	247	184	227
	0.3	15	9.0	120		

TABLE III

Summary of Table IIA and IIB and paired comparison of total renin content
of kidney seven days after unilateral nephrectomy

Rat no.	Total renin content of kidney (angiotensin II equivalents; μg) Left (control) (from Table IIA)	Right (hypertrophied) (from Table IIB)	Difference in total renin contents in left and right kidney (angiotensin II equivalents; μg)	% increase or decrease
4	78	39	-39	-50
5	55	84	29	53
6	32	67	35	109
7	111	141	30	27
8	127	464	337	265
9	259	293	34	13
10	139	227	88	63
Mean	115	188	--	69
SE	± 28.1	± 57.4	--	± 37.5

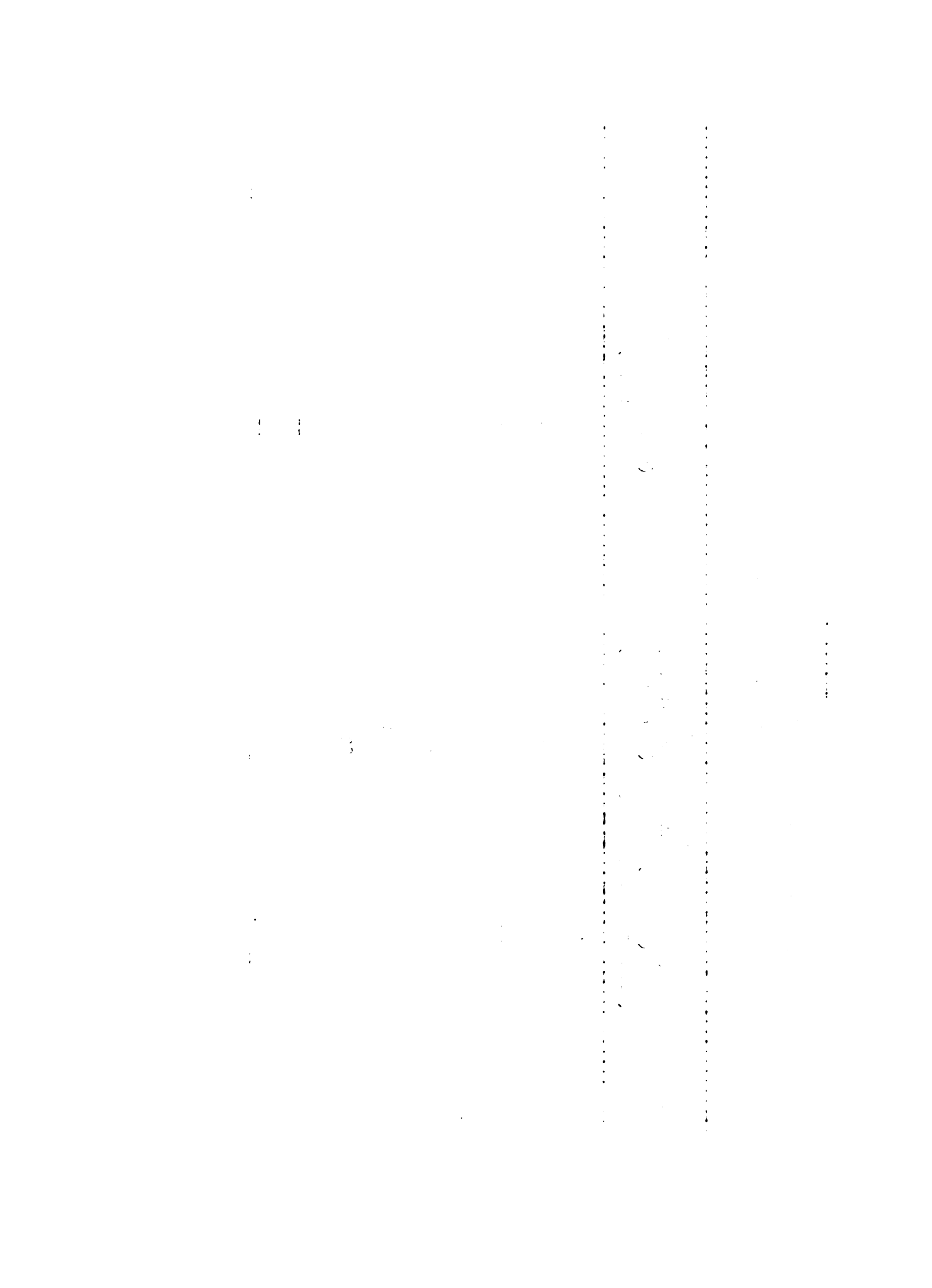


TABLE IV

Change in juxtaglomerular granulation index during compensatory
hypertrophy

Rat no.	Kidney	Number of glomeruli counted	Units of juxta- glomerular cells				Weighted total	Juxta- glomerular index
			+	++	+++	++++		
4	Left	257	9	4	1	0	21	8.2
	Right	214	14	4	2	0	30	14.0
5	Left	84	5	0	0	0	5	6.0
	Right	254	9	5	1	0	23	9.1
6	Left	282	8	3	1	0	18	6.4
	Right	288	16	3	3	0	34	11.8
7	Left	249	5	3	1	0	15	6.0
	Right	224	12	3	4	0	34	15.1
8	Left	232	7	3	1	0	17	7.3
	Right	170	5	4	1	1	25	14.7
9	Left	209	10	2	0	0	14	6.7
	Right	170	6	1	1	1	20	11.8
10	Left	175	4	0	1	0	8	4.6
	Right	109	5	4	0	0	13	11.9



TABLE V

Weight of adrenal and width of zona glomerulosa of adrenal cortex
of normal rats and unilaterally nephrectomized rats

Rat no.	Weight of adrenal (mg)		Width of zona glomerulosa (micron) of right adrenal
	Left	Right	
<u>Unilaterally nephrectomized</u>			
4	23	22	47.6
5	26	24	41.3
6	25	25	37.3
7	27	24	46.0
8	29	26	40.3
9	27	--	**
10	27	26	51.1
Mean	26	25	43.9
SE	± 0.7	± 0.6	± 2.2
<u>Normal</u>			
1	28	26	40.0
2	25	23	42.0
11	24	27	47.0
12	23	24	40.0
13	21	23	43.0
14	22	24	48.0
Mean	24	25	43.3
SE	± 1.0	± 0.7	± 1.4

** Left adrenal -- 39.0

TABLE VI

Summary of Tables --- I, III, IV and V

Rat No.	Body weight gain (gm)	% increase of right kidney weight over left kidney	Total renin content (angiotensin II equivalents; μ g)		Juxtaglomerular granulation index		Width of zona glomerulosa of right adrenal (micron) of uni-laterally nephrectomized rat
			Left (control)	Right (hypertrophied)	Left (control)	Right (hypertrophied)	
4	0	39.9	78	39	8.2	14.0	47.6
5	-10	17.8	55	84	6.0	9.1	41.3
6	25	30.4	32	67	6.4	11.8	37.3
7	10	29.1	111	142	6.0	15.1	46.0
8	20	44.1	127	464	7.3	14.7	40.3
9	25	43.6	259	293	6.7	11.8	**
10	25	44.9	139	227	4.6	11.9	51.1
Mean	14	35.7	115	188	6.5	12.6	43.9
SE	± 5.3	± 3.8	± 28.1	± 57.4	± 0.4	± 0.9	± 2.2

** Left adrenal -- 39.0

RESULTS

The differences between the postoperative and preoperative body weights of the rats varied from -10 gm to +25 gm with an average of $+14 \pm 5.3$ gm (Mean \pm standard error). The per cent body weight change averaged 4.9 ± 2.0 . The increase in body weight is not statistically significant ($P < 0.4$) (Table I).

The kidneys removed seven days after left unilateral nephrectomy were heavier than the normal kidneys removed at the start of the experiment. The weight of the control left kidney averaged 1.03 ± 0.04 gm and that of the hypertrophied right kidney averaged 1.399 ± 0.07 gm. The weight of the hypertrophied kidney is significantly greater than that of the control kidney ($P < 0.01$) (Table I).

Total renin content expressed in angiotensin II equivalents as determined by the bioassay averaged 115 ± 28.1 in the control left kidney and 188 ± 57.4 in the hypertrophied right kidney. The renin content of the hypertrophied kidney decreased in one animal, but in the rest of the animals it rose when compared to the control kidney. There was considerable variability from rat to rat in the total renin content in control and hypertrophied kidneys (Table IIA, IIB); consequently the standard errors of the means (Table III) were very large. The difference between the renin content of the hypertrophied kidneys and the control kidneys is not statistically significant ($0.2 < P < 0.3$) (Table III). The per cent increase or decrease of total renin content averaged 69 ± 37.5 . After expressing each experimental value as per cent change from its paired control in the same animal, the 't' test did not show a significant increase ($0.1 < P < 0.2$) (Table III).

The juxtaglomerular granulation index of the control left kidney averaged 6.5 ± 0.4 and that of the hypertrophied right kidney averaged 12.6 ± 0.9 (Table IV). The juxtaglomerular granulation index of the hypertrophied kidney is significantly greater than that of the control ($P < 0.01$) (Table VI). The juxtaglomerular granulation index of the hypertrophied kidney is twice that of the removed kidney. In one animal (rat #4) in which the assay showed a decrease in the total renin content of the hypertrophied kidney, the juxtaglomerular index was doubled.

The width of the zona glomerulosa of the adrenal cortex averaged 43.9 ± 2.2 micra in the unilaterally nephrectomized animals and that of the untreated animals of the same weight and strain averaged 43.3 ± 1.4 micra. The average weight of the left and right adrenal was 26 ± 0.7 mg and 25 ± 0.6 mg respectively and that of the untreated rats 24 ± 0.1 mg and 25 ± 0.7 mg respectively (Table V). Thus during compensatory hypertrophy of the kidney, there was no change in the weight of the adrenal or in the width of the zona glomerulosa.

DISCUSSION

In discussing the results of this investigation, the present knowledge of the factors regulating compensatory renal hypertrophy, the functional changes that occur during this process, the relation between renin and this process and renin content and secretion during this process are considered.

Nephrectomy leads to a decrease in the amount of kidney tissue present, and this deficiency is reduced very quickly by an anatomical hypertrophy of the remaining renal mass (1). The sequence of events during compensatory hypertrophy of the kidney following unilateral nephrectomy is not well defined. Many factors controlling the process have been suggested, and many have been ruled out. An increase in the weight of an organ may result from an increase in intracellular substance (hypertrophy), or an increase in cell number (hyperplasia), or a combination of these. Rollanson (21) and Sulkin (22) found an increase in the number of mitotic figures in the kidneys between 2 and 24 hours after the removal of one kidney. Thomas (23) reported increased incorporation of thymidine into renal DNA after unilateral nephrectomy. Simpson (24), using P^{32} uptake in DNA as an index of mitosis also reported that more incorporation took place in the unilaterally nephrectomized animals. However, on the whole, hypertrophy quantitatively overshadows hyperplasia (25).

The mechanism regulating such cell division and growth is poorly understood. Unilateral nephrectomy produces two outstanding changes in the excretory apparatus. First, the total number of kidney cells and therefore the kidney mass is halved. Second, if the composition of the

1. Introduction

The purpose of this report is to analyze the impact of the COVID-19 pandemic on the global economy and to provide recommendations for recovery. The report is structured as follows:

- 2. Methodology
- 3. Results
- 4. Discussion
- 5. Conclusion

2. Methodology

The data for this report was collected from various sources, including government reports, academic journals, and news articles. The data was analyzed using statistical methods and economic models.

3. Results

The results of the analysis show that the COVID-19 pandemic has had a significant negative impact on the global economy. The global GDP has declined, and unemployment rates have risen. The impact has been particularly severe in emerging markets and developing countries.

4. Discussion

The discussion of the results highlights the need for coordinated international efforts to address the economic challenges posed by the pandemic. Key areas for discussion include the impact of the pandemic on different sectors of the economy, the role of government intervention, and the potential for long-term economic recovery.

5. Conclusion

The conclusion of the report is that the COVID-19 pandemic has had a profound impact on the global economy. The results of the analysis suggest that a coordinated international response is needed to address the economic challenges posed by the pandemic. The report provides recommendations for recovery, including the need for government intervention and the potential for long-term economic recovery.

body fluids is maintained the remaining kidney must excrete twice as much salts, wastes, and water as formerly and hence its excretory load is doubled. Stimulation of cell division after unilateral nephrectomy might be related either to the decrease in cell number or to the increase in work load of the remaining cells. Simpson (24) showed that the increased work load is not responsible for stimulation of cell division. Thus, renal hyperplasia failed to occur in conditions such as drainage of one ureter into the peritoneal cavity in rats (24), transplantation of the ureter of the kidney into the duodenum in hypophysectomized dogs (26) and increasing endogenous protein metabolism (27). From the above it seems clear that increased excretory work load is not the stimulus to hypertrophy.

Though the attempt to demonstrate that the increased work load initiates the hypertrophy in the excretory part of the kidney has failed, Hartroft and Hartroft (13, 28) showed that conditions which demand increased secretion from the juxtaglomerular cells lead to hypergranulation or degranulation, hyperplasia and vacuolation in the juxtaglomerular apparatus.

White (29), Goodkind (30), Winternitz and Water (31), Bojs (32), and Mcqueen-Williams and Thompson (33) have established the influence of the anterior pituitary on kidney function, size and weight during compensatory hypertrophy. It is not clear how such influence is brought about. Among other possibilities the idea of a pituitary hormone with a specific effect on the kidney, "renotrophin", has been suggested. Each of the pituitary hormones was tested in hypophysectomized and unilaterally nephrectomized animals. After hypophysectomy rats lose weight and fail to grow normally. It is therefore difficult to assess whether the

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6. The sixth part of the document explores the benefits of data-driven decision-making and how it can lead to improved organizational performance. It provides examples of successful data-driven initiatives and the impact they have had on the organization.

7. The seventh part of the document discusses the future of data management and the emerging trends in the field. It highlights the importance of staying up-to-date with the latest developments and technologies to maintain a competitive edge.

8. The eighth part of the document provides a summary of the key points discussed throughout the document. It reiterates the importance of data management and the need for a comprehensive and integrated approach to data collection, analysis, and governance.

9. The ninth part of the document includes a list of references and resources for further reading. It provides links to relevant articles, books, and industry reports that can provide additional insights into the topics discussed in the document.

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11. The eleventh part of the document discusses the importance of data literacy and the need for training and development programs. It outlines the key skills and knowledge required for effective data management and analysis.

12. The twelfth part of the document provides a list of key performance indicators (KPIs) that can be used to measure the success of data management initiatives. It includes a brief description of each KPI and how it can be tracked and reported.

13. The thirteenth part of the document discusses the importance of data ethics and the need for a strong ethical framework. It outlines the key principles and best practices for ensuring that data is collected, stored, and used in a responsible and ethical manner.

14. The fourteenth part of the document provides a list of resources and tools that can be used to support data management and analysis. It includes a brief description of each resource and how it can be used to improve data management practices.

15. The fifteenth part of the document concludes with a final summary and a call to action, encouraging the organization to take the steps necessary to implement the best practices and strategies outlined in the document. It emphasizes the need for ongoing monitoring and evaluation to ensure continued success.

failure of the remaining kidney to hypertrophy is due to a non-specific effect or the deficiency of a particular hormone or hormones. Bearing this in mind, Astarabadi (34) studied the effect of growth hormone (36), ACTH (35) and prolactin (36) on renal compensatory hypertrophy. He saw no change in the weight and size of the kidney when the hypophysectomized and unilaterally nephrectomized animals were treated with purified ACTH and prolactin. ACTH neither influences directly nor indirectly through its target organ. This is consistent with the report by Simpson et al (37) on the failure of ACTH to increase the size of the kidney in normal rats, but inconsistent with Hay et al (39) who found some increase in size of the kidney in hypophysectomized rats following ACTH administration. Astarabadi (36) reported significant hypertrophy of the remaining kidney in growth hormone-treated, hypophysectomized nephrectomized rats, but growth hormone failed to restore the kidney weight to normal, although it was effective in increasing body weight. Astarabadi suggested that the growth hormone preparation was contaminated with an unidentified "renotrophin" (29) or that probably the pituitary is the source for another principle with a specific renotrophic activity. Bullough (38) hypothesized that compensatory hypertrophy occurs because of the removal of "mitosis inhibitor." However, this theory does not take into account the failure of compensatory renal hypertrophy in the absence of a pituitary. Zeckwar (40) reported that thyroidectomy did not prevent the occurrence of compensatory renal hypertrophy. Cortisone (41) and estrogen (42) have an inhibitory effect on renal compensatory hypertrophy.

Vasilenko (43) studied the functional changes during compensatory hypertrophy of kidney. He reported that during six months following unilateral nephrectomy both renal blood flow and glomerular filtration



rate increased by about 50% in the remaining kidney. Filtration fraction tended to fall insignificantly. He pointed out that glomerular function in the remaining kidney increased rapidly, suggesting vasodilation, while the changes in tubular function developed gradually and in several cases more than compensated for the absent kidney.

Two hormonal theories, both based on the existence of hypothetical blood-borne renotrophic agent or agents have dominated the experimental work in this area. The first proposes that a temporary decrease in renal excretory function results in increased blood levels of renotrophic material. The second proposes a reciprocal relationship between the blood levels of renotrophic material and renin; a decrease in kidney weight but no decrease in renal excretory function results in increased renotrophin blood levels. The second hypothesis is supported by Schaffenburg (16). He showed that renin inhibits compensatory hypertrophy of the kidney.

The special function, that is, non-excretory function of the juxtaglomerular cells during compensatory hypertrophy has not been systematically studied. Goormaghtigh (44) observed some hypertrophy in the juxtaglomerular cells in the kidney when one kidney had been taken out and the remaining one was ischemic. Hartroft and Hartroft (45) during their study of juxtaglomerular cells in the rat showed that in the unilaterally nephrectomized rat the average juxtaglomerular index of the remaining kidney was not different from that of the kidneys in the sham operated control rats. The remaining kidney weighed 30% more than the control (sham operated) rats. They concluded that uncomplicated compensatory hypertrophy does not affect the juxtaglomerular cells. Tverdy (46) got

different results. Working in Goormaghtigh's laboratory he studied the condition of the granular cells in juxtaglomerular apparatus and how these cells react during compensatory hypertrophy in mice. He kept the animals after nephrectomy for seven to sixty-one days. In his experiments 76% of the observed animals for varying periods showed an increase in juxtaglomerular index in the hypertrophic kidney. Not only the granules changed but there were mitotic figures in those cells indicating hyperplasia. The difference between the findings of Tverdy and those of the Hartrofts can be explained. Tverdy compared the degree of granulation of the juxtaglomerular cells of the hypertrophied kidney with that of the kidney removed from the same animal. The Hartrofts compared the index of granulation of the remaining kidney with the corresponding kidney in the control (sham operated) rats, rather than to the removed kidney.

My findings on the changes in juxtaglomerular index of hypertrophied kidney in this investigation on rats agree very well with those of Tverdy (46) but not with the results of Hartroft and Hartroft (45). As mentioned before, the Hartrofts used kidneys of sham operated rats as controls, rather than the removed kidney. The amount of stored hormone will naturally depend on the previous history and nutritional condition of the animal at the time of study. This may account for the tremendous variation in the total renin content found by bioassay of kidney in the control used in this investigation. The use of the removed kidney as the control overcomes somewhat the difficulty of individual variability and permits determination of directional changes of total renin content in the same animal. The juxtaglomerular index is not quantitative but is only a comparative index. It only estimates the relative difference in the

number of juxtaglomerular granules, which are thought to be stored renin. There are some inherent limitations to the use of the index as a guide to renin secretion. The subjective influence can hardly be eliminated. The classification of cells according to granularity will be influenced very much by the personal choice of the investigator. The evaluations which the Hartrofts designated plus one, plus two, etc., may or may not be the same as mine.

To interpret the results it is necessary to elucidate the significance of variation of the juxtaglomerular index. Secretory cells may both synthesize and store their product. The number of granules within the cell represents the result of a difference between the rate of synthesis and rate of secretion. No conclusion can be drawn about the secretion or synthesis of renin from the juxtaglomerular index alone, but Hartroft and Hartroft (13) interpreted the high juxtaglomerular index in their experiments to mean both accumulation and increased secretion of renin. Before the Hartrofts, Goormaghtigh (6) correlated hyperactivity of juxtaglomerular cells with increased granulation of juxtaglomerular cells.

The juxtaglomerular index of the hypertrophied kidney increased significantly ($P < 0.01$) from the control kidney during compensatory hypertrophy. If one accepts the Hartrofts' interpretation of juxtaglomerular index, it can be said that both renin content and secretion increased significantly.

Due to some unknown reasons the variation in mean blood pressure rise in the same test animal following the same dose of renin extract was enormous, while the changes in mean blood pressure responses to the

same doses of angiotensin II did not vary more than 10% to 20% (Fig. 2). It might be noted that angiotensin II acts directly on the vascular smooth muscle with a short half life, whereas renin acts on angiotensinogen, producing angiotensin I, which is again acted upon by the converting enzyme producing angiotensin II. Thus, any response to renin will not only depend on the total amount injected but also on the concentration of angiotensinogen and the availability and activity of the converting enzyme. The renin extract used in the present investigation was not pure, whereas the angiotensin II used was pure and synthetic, so the impurities of renin might have affected the change in mean blood pressure after renin injection.

After being corrected for the observed increases in body weight during seven days, the values of the control and hypertrophied kidneys come out to be 124 μg of angiotensin II equivalents and 189 μg of angiotensin II respectively. The renin content per gram of kidney was 113 μg of angiotensin II equivalents of control and that of hypertrophied kidney 135 μg of angiotensin II equivalents. The control and experimental values of the total renin content of kidney are quite variable, consequently the mean of the experimental values did not differ significantly ($0.2 < P < 0.3$) from the mean of the control values. Even after expressing each experimental value as per cent change from its paired control in the same animal, the 't' test shows no significant increase ($0.1 < P < 0.2$). The left and right kidney sample of rat #9 and the right kidney sample of rat #8 are off the calibration curve of angiotensin II (Table IIA and IIB). The angiotensin II equivalents of those samples were computed by extending the calibration curve. The

values of the above samples might not be as accurate as the other samples. Thus an increase in renal renin content has not been proven by these experiments, since there remains an appreciable chance that the observed increases might have been due to random sampling. Nevertheless, the probabilities are in favor (88 to 90 chances out of 100) of there being a real increase in renal renin under these circumstances. The lack of complete statistical proof is attributable to the presence in the series of two rats (Numbers 4 and 8) whose values (-39 and +337) differed markedly from the values obtained from the other five rats which were all between +30 and +88 angiotensin II equivalents (μg). The reasons for these two aberrant bioassay results are unknown.

The measurement of the width of the zona glomerulosa of the adrenal cortex can serve as an index to the rate of production or secretion of renin, because Hartroft and Hartroft (28) have shown that renin has a trophic action on the zona glomerulosa of the adrenal. Degranulation of juxtaglomerular cells was associated with atrophy of the zona glomerulosa and hypergranulation with hypertrophy of the zona glomerulosa. Therefore, there is usually a direct relationship between juxtaglomerular index and the width of the zona glomerulosa. In the present investigation the data show no significant change ($P < 0.05$) in the width of the zona glomerulosa after the loss of the left kidney. This suggests that the remaining hypertrophied kidney is secreting the amount of renin that was previously secreted by both kidneys, or at least an amount sufficient to maintain production of aldosterone at a constant rate.

Therefore, though the results of the bioassay demonstrate no significant change in renal renin content, the significant increase in

juxtaglomerular index and the constancy of the zona glomerulosa indicate that the renal renin content and its secretion increased during the compensatory hypertrophy of the kidney.

Himman and Mendes (1) reported that it takes about 32 days for the structural hypertrophy of kidney to be completed. It is interesting to note that the results of the present investigation show that an adequate functional hypertrophy with respect to renin secretion took place within only seven days, before the anatomical compensation was completed. This point should be further investigated, and the time course of the change of renin secretion following unilateral nephrectomy should be followed.

The present investigation could be expanded in the following way: if under physiological conditions aldosterone secretion is continually being controlled by renin and if it can be postulated that the doubling of renin secretion from the single kidney in unilaterally nephrectomized animals maintains the normal drive for aldosterone secretion, then this should be demonstrable by finding that the initial low level of aldosterone in the adrenal venous effluent after removal of one kidney gradually returns to normal. The amount of aldosterone in the venous effluent should be correlated with renin secretion as a function of time after unilateral nephrectomy.

SUMMARY

The left kidney was removed from seven rats and the following procedures were carried out one week later when the animals were sacrificed. The change in body weight was noted and the two kidneys compared for (1) weight, (2) renin content as determinable by bioassay for angiotensin II and (3) histological examination of the granule content of the juxtaglomerular cells (juxtaglomerular granulation index). In addition, the weights of the adrenal glands and thicknesses of their zona glomerulosa were compared with those of similar healthy rats. At the end of a week after nephrectomy, the remaining kidney of each rat had increased in weight appreciably. Although the bioassays failed to show statistically significant increases in the renal renin contents, the juxtaglomerular granulation indices were significantly increased in the hypertrophied kidneys. This, together with the fact that there was no reduction in the amount of tissue in the zona glomerulosa of the adrenals, suggests that the renin output of the hypertrophied kidneys was sufficient to replace that of their absent partners within a week after operation insofar as the control of aldosterone secretion is concerned.

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7. The seventh part of the document includes a list of references and sources used in the research. It provides a comprehensive overview of the literature and resources that informed the study, ensuring the credibility and accuracy of the findings.

8. The eighth part of the document contains a list of appendices and supplementary materials. These materials provide additional details and data that support the main findings of the study, offering a more in-depth look at the research process and results.

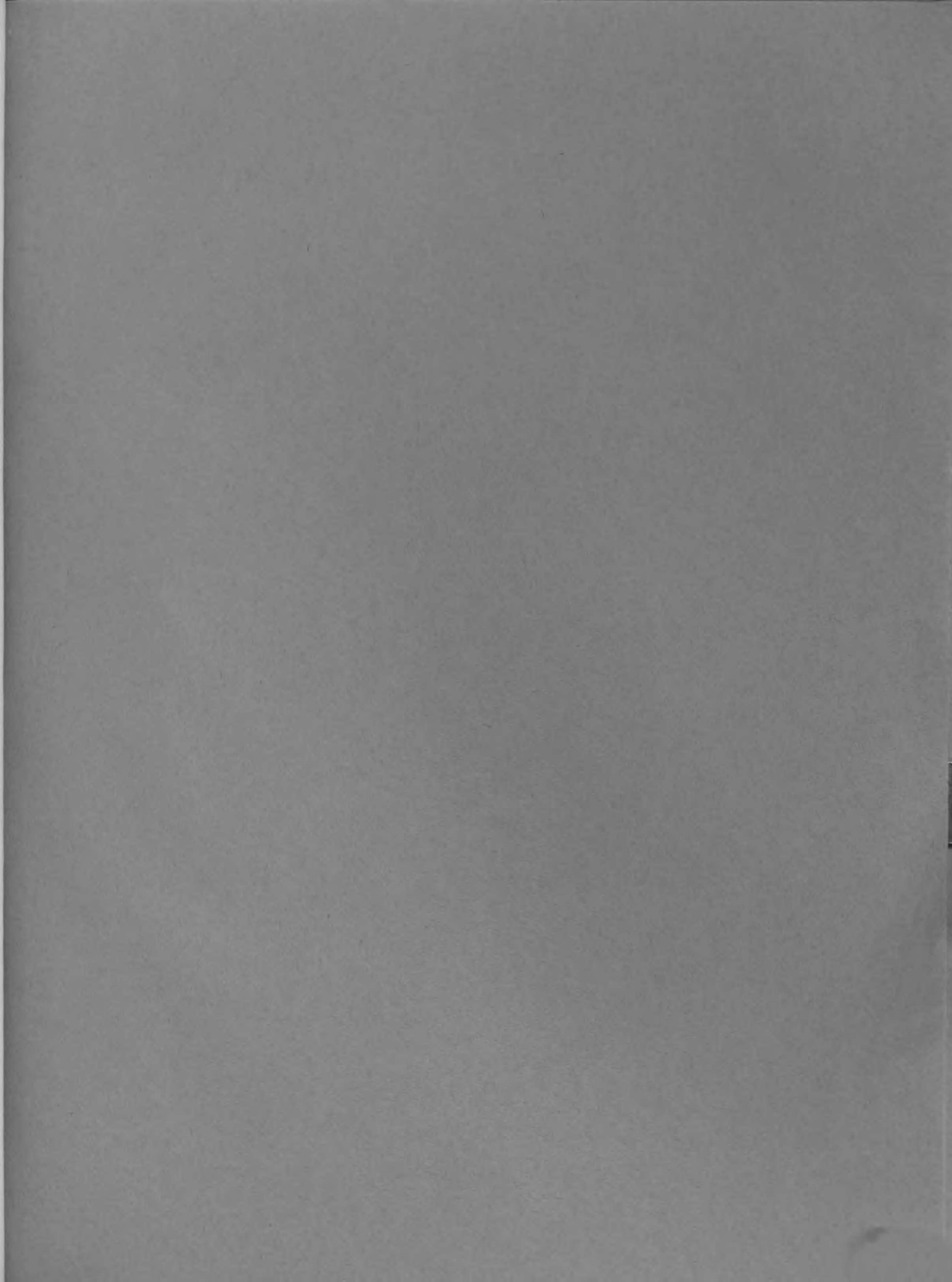
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12. The twelfth part of the document contains a list of footnotes and endnotes. These notes provide additional context and details for specific points mentioned in the main text, ensuring that the information is accurate and well-supported by evidence.

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