1-1-1943

# The Relation of renal arteriolar sclerosis to essential hypertension

William Burritt Niehus
*University of Nebraska Medical Center*

This manuscript is historical in nature and may not reflect current medical research and practice. Search PubMed for current research.

THE RELATION OF RENAL ARTERIOLAR SCLEROSIS
TO ESSENTIAL HYPERTENSION


William B. Niehus


SENIOR THESIS

PRESENTED TO

THE COLLEGE OF MEDICINE
UNIVERSITY OF NEBRASKA
OMAHA, NEBRASKA
DECEMBER 1943

# Table of Contents

## Index to Figures and Tables

## Introduction

Richard Bright (1) was probably the first to intimate the renal origin of arterial hypertension. Since Bright lived before the sphygmomanometer had been invented, he had no information concerning the blood pressure of his patients. However, he noted the frequent coexistence of cardiac hypertrophy, thickening of the walls of the arteries, and chronic renal disease. On the basis of these observations he postulated that cardiac hypertrophy resulted from increased peripheral resistance which in turn could be ascribed to renal disease. Inasmuch as blood pressure is elevated by virtue of increased peripheral resistance, it may be said that Bright was the first to consider the renal origin of hypertension. His hypothesis has since been the subject of considerable controversy and extensive experimental investigations which began soon after the appearance of Bright's first report. In 1869, Johnson (2) confirmed Bright's observations and, moreover, made specific reference to hypertension. He quoted Sanderson who wrote: "In cases of chronic Bright's disease with hypertension and hypertrophy of the left ventricle, the sphygmograph affords decided evidence of increased arterial pressure." In addition to the pathological changes reported by Bright, he observed diffuse thickening of the walls of the smallest arteries. It was his conviction that the renal disease was primary. However, as early as 1872 Gull and Sutton (3) founded a school of thought which stressed the non-renal origin of hypertension. These investigators

confirmed Johnson's observations on the changes in the small ar-
teries, which they termed "arteriocapillary fibrosis," and proposed
that "these changes are, or may be, independent of renal disease,and
that the renal change in chronic Bright's disease with contracted
kidneys, when present, is but a part of a general morbid condition."
Thus to them the diffuse vascular disease was the primary patho-
logical state responsible for the increased blood pressure. Mahomed
(4) moreover reported instances of high blood pressure in the ab-
sence of clinical signs of kidney disease and concluded, therefore,
that hypertension was not due to either disease of the kidney or
sclerosis of the arteries but was inevitably followed by definite
renal disease and sclerosis. He therefore regarded hypertension as
the "prealbuminuric stage of Bright's disease."

There were then three conflicting views regarding the patho-
genesis of hypertension, namely: (a) renal disease was primary
(Bright); (b) diffuse vascular disease was primary, the renal dis-
ease being only one manifestation of the generalized vascular dis-
ease (Gull and Sutton); and (c) renal disease and diffuse vascular
disease were each secondary to hypertension (Mahomed).

Some ten years after the report of Gull and Sutton, von Basch
(5) introduced the sphygmomanometer into clinical medicine. As
clinical measurements of blood pressure accumulated, it soon became
apparent that hypertension occurred in the absence of arterio-
sclerosis. Von Basch, for example, wrote: "There are numerous
cases in which examination reveals a high tension of pulse, but the

other characteristics of outspoken arteriosclerosis are either absent or but minimal." He concluded that the elevated blood pressure preceded the arteriosclerosis; hence his term "latent arteriosclerosis" for the hypertensive state. Huchard (6) in France and Allbutt (7) in England, however, are generally credited for having established the fact that the morphological changes in the arteries and arterioles observed in hypertension are not sufficiently widespread to account for the increased peripheral resistance required to produce the elevated blood pressure and therefore could not be considered primary. Huchard termed the hypertensive state "presclerosis" to emphasize that hypertension antedates the sclerotic changes. Thus the theory that diffuse vascular disease was primarily responsible for hypertension fell into disrepute. Allbutt moreover emphasized that hypertension frequently existed in the absence of obvious renal disease and designated such cases with the name "hyperpiesia", after the predominant symptom. However, he also recognized that hypertension usually was present in Bright's disease, i.e., true renal disease. He accordingly differentiated between two hypertensive states: (a) hyperpiesia, in which elevated blood pressure was the principle clinical manifestation with little or no renal involvement; and (b) Bright's disease, in which renal disease was the principle clinical manifestation, with or without elevated blood pressure.

Allbutt's classification was subsequently realized by other investigators. Janeway (8) recognized "primary hypertensive cardio-

vascular disease", probably primarily a disease of the small blood
vessels, in which the hypertension originated insidiously with uri-
nary changes present initially or appearing later in the disease; and
"secondary hypertensive cardiovascular disease" in which the elevated
blood pressure was "engrafted" onto an obvious primary inflammation
of the kidney.  Bell and Clawson (9) stated that "primary" hyperten-
sion is of unknown origin but emphasized that hypertension may re-
sult from renal diseases, particularly those characterized by an
obstruction to the flow of blood, e.g., chronic glomerular nephri-
tis.  Volhard (10) spoke of two types of hypertension, "pale" and
"red".  "Red" hypertension was attributed to a functional derange-
ment unrelated in etiology to the kidney in which the general dis-
tensibility of the small arteries was impaired.  "Pale" hypertension
was considered consequent to renal insufficiency resulting from pri-
mary renal disease (glomerulonephritis, etc. )or the renal vascular
damage secondary to "red" hypertension.  According to this view
"red" hypertension could eventually give place to "pale" hyperten-
sion; however, the two were distinct as regards etiology.

On the basis of these and other observations (11, 12) it is
now generally accepted that hypertension succeeds various affec-
tions of the kidney, e.g., chronic glomerulonephritis, polycystic
kidney, renal panarteritis, severe renal amyloidosis, or obstruc-
tive diseases of the urinary passages.  The hypertensive state be-
lieved to be non-renal in origin has been variously termed the
"prealbuminuric stage of Bright's disease" (Mahomed), "latent

arteriosclerosis" (von Basch), "hyperpiesia"(Allbutt), "prescle-
rosis" (Huchard), "primary cardiovascular disease" (Janeway),
"primary" hypertension (Bell and Clawson), and "red" hypertension
(Volhard). The term however, which has received most general ac-
ceptance was proposed by Frank (13) in 1911, namely, "essential"
hypertension.

The hypertensive state now usually designated essential hyperten-
sion has been defined by Fishberg (11) as an elevation of blood pres-
sure which "neither clinically or anatomically can be demonstrated
to have evolved from antecedent inflammatory diseases of the kidneys
or urinary obstruction." The hypertension resulting from such causes
as obesity, hyperthyroidism, pituitary tumor, toxemia of pregnancy,
increased intracranial pressure, periarteritis nodosa, certain forms
of nephrosis, lead poisoning, adrenal tumor, aortic insufficiency,
coarctation of the aorta, and arteriovenous aneurysm is likewise not
considered as essential hypertension (9,11,14). However, since these
causes of hypertension are relatively uncommon compared to inflamma-
tory diseases of the kidneys and urinary obstruction, they are usually
not listed in the definition of essential hypertension.

Fishberg's definition of essential hypertension merely serves to
emphasize the obscurity surrounding the intrinsic nature of the dis-
ease. It was, however, generally conceded, as is evident from the
foregoing review, to be non-renal in origin. The arguments (12,15)
usually advanced against the renal origin of essential hypertension
have been: (a) the frequent circumstance of an elevated blood

pressure in the absence of any recognizable signs of impairment of renal function (4,7,9,16); (b) failure of many patients ever to develop symptoms of renal insufficiency, death usually resulting from cardiac failure or cerebral hemorrhage (9,17,18; (c) the absence of renal arteriosclerosis in some cases of hypertension (6,9).

The firm conviction that the kidney was not implicated in the pathogenesis of essential hypertension has recently been seriously challenged by the experimental observations of Goldblatt and associates (12,19). Goldblatt succeeded in producing hypertension in dogs similar to essential hypertension by applying a specially designed silver clamp to the renal arteries and producing a desired degree of constriction. He demonstrated that constriction of the renal artery of one kidney produces an elevation in systolic and diastolic pressures which is maintained for weeks or months, whereas narrowing of both renal arteries simultaneously or after an interval results in persistent hypertension which has continued in some animals for six years. Evidently the effect is a result of renal ischemia. The evidence suggests that the hypertension is produced by a pressor substance liberated by the ischemic kidney into the blood. The assumption has therefore been made that renal arteriolar sclerosis, so commonly observed post mortem in essential hypertension (9,14,20), produces a degree of renal ischemia which is comparable to that produced experimentally and which is associated with the liberation of a pressor substance. To illustrate, Goldblatt (12) has stated: "Any method for the experimental deter-

mination of the possible primary part played by renal arteriosclerosis in the origin of essential hypertension should involve the production of at least the physiological effect of renal vascular disease. It is not actually known, but it is at least probable, that the effect is a decrease of the flow of blood to the functioning elements of the kidney and a decrease in the intraglomerular capillary pressure." Mortz and Oldt (14) have suggested that essential hypertension may be "the result of primary renal arteriolar sclerosis either because a generalized reflex spasm of peripheral vessels is initiated in the ischemic kidneys, or because of the retention or elaboration of pressor substances incident to a reduced blood flow through the kidney." Similarly, Scott (15) has concluded unequivocally that "arterial and arteriolar sclerosis of the renal vessels leads to renal ischemia, which by a humoral mechanism produces an increased muscular tone in the peripheral arterioles and thus causes elevation in the systemic blood pressure." Fishberg (11) in the latest edition of his book "Hypertension and Nephritis" has recorded the following: "Experimental production of hypertension by constriction of the renal arteries, coupled with the fact that renal arteriolar sclerosis is almost always found at post mortem, has again raised the question whether essential hypertension is not actually a form of renal hypertension. According to this view, disease of the renal arterioles is primary, and the hypertension is a consequence of the cutting down of renal blood flow." Thus the mechanism by which hypertension is produced in the human

and experimentally in the dog is assumed to be fundamentally the same, and renal arteriolar sclerosis is accepted as the cause of essential hypertension.

It is the purpose of this dissertation to arrive at a reasonable evaluation of the significance of renal arteriolar sclerosis in the pathogenesis of essential hypertension on the basis of the numerous reports in the literature which have been inspired largely by Goldblatt's brilliant observations. The subject matter is conveniently grouped under the following headings: (a) experimental observations on the pathogenesis of essential hypertension; (b) clinical observations in support of the primary role ascribed to renal arteriolar sclerosis in the pathogenesis of essential hypertension; (c) experimental and clinical observations at variance with the primary role ascribed to renal arteriolar sclerosis in the pathogenesis of essential hypertension. For the purpose of completeness and for reference, brief summaries of the clinical picture of essential hypertension and the pathological histology of arteriolar sclerosis are included.

## Clinical Picture of Essential Hypertension

Essential hypertension is a chronic disease which progresses
at a variable rate in different cases. At the onset of the dis-
ease, elevated blood pressure is observed only intermittently,
usually remaining normal except on provocation. This has been
termed the stage of fluctuation. Subsequently the blood pressure
is maintained persistently above 135 mm. Hg systolic and 90 mm. Hg
diastolic if the patient is before or in middle life and above 150
mm. Hg systolic and 100 mm. Hg diastolic if the patient is past
middle life (21). The early symptoms, aside from an elevated
blood pressure, are usually among the following: headache, dyspnea
(especially on exertion), vertigo, nervousness, irritability, in-
somnia, nocturia, poor memory, gastric distress, precordial pain,
weakness, palpitation, blurring of vision, epistaxis, menorrhagia,
cyanotic extremities, occasionally albumin in the urine (9).

The disease may persist for many years with or without im-
portant symptoms. In the majority of cases, however, symptoms
and signs of involvement of the heart, brain, and/or kidneys de-
velop. The symptoms attributable to cardiac disease are dyspnea,
edema, cardiac pains of various kinds, cyanosis, enlargement of the
heart, and heart murmurs (9).

The symptoms ascribed to the brain are headache, vertigo, ner-
vousness, nocturia, fainting, irritability, loss of memory, and
transient or permanent paralysis from cerebral hemorrhage (9).

The symptoms referable to renal damage are progressive renal insufficiency (not evident in the large majority of patients) as determined by urea clearance, urea concentration, phenolsulfonephthalein, and urine concentration and dilution tests, albuminuria, casts in the urine, severe retinal changes, and terminally, clinical signs of uremia (9).

The chief dangers to be feared in essential hypertension are the development of myocardial exhaustion or cerebral accidents and not particularly renal insufficiency. Disability and death most commonly result from cardiac failure, next to which in frequency are cerebral accidents, particularly apoplexy. Renal failure, i.e., uremia, is responsible for death in only a small proportion of cases (11).

At necropsy an individual who suffered with essential hypertension presents a triad of lesions: cardiac hypertrophy, generalized arteriolosclerosis, and so-called arteriolosclerotic kidneys. The various forms of arteriolosclerosis are described in the next section. The renal arteriolosclerosis may be apparent only microscopically but in a large majority of instances the renal arteriolar disease is sufficiently advanced to produce the characteristics of a typical arteriolosclerotic kidney, namely, a granular surface, more or less contraction in size, and an adherent capsule (11).

A small group of patients with essential hypertension (less than 10%) will enter what has been termed the malignant phase of

essential hypertension (11). The phase is characterized by the usual symptoms of essential hypertension and in addition a persistent and marked elevation of diastolic pressure (at least above 130 mm. Hg), necrosis and endarteritis of the renal arterioles,and increased intracranial pressure. The endarteritis and necrosis of the renal arterioles lead to rapidly progressive impairment of renal function so that the death usually results from uremia.

Along with the marked elevation of diastolic pressure, the malignant phase is usually signaled by headache, less frequently by uremic symptoms, visual disturbances due to retinal changes, or convulsions or other manifestations of hypertensive encephalopathy. The entire clinical course is seldom more than two years following the appearance of hypertensive neuro-retinopathy, an indication which proves to the clinician that essential hypertension has entered the malignant phase.

## Pathological Histology of Arteriolar Sclerosis

Moritz and Oldt (14) have recently reported an extensive study of arteriolar sclerosis in 100 hypertensive and 100 non-hypertensive individuals. The spleen, pancreas, adrenals, gastro-intestinal tract, brain, skeletal muscle, liver, and kidney were each examined for arteriolar changes. The authors were unable to distinguish satisfactorily between the "arteriole" and a "small artery" on the basis of the usual criteria and therefore employed the two terms interchangeably. The investigation included only arteries with an external diameter of 100 microns or less. The tissues were sectioned in uninterrupted series and were stained in rotation with hematoxylin-eosin, and according to Weigert's method for elastic tissue, van Gieson's method for connective tissue, Wilder's method for reticulum, and Mallory-Heidenhain's azancarmine method for connective tissue. Nine uninterrupted series numbering between 100 and 400 sections in each were pre-pared from various tissues in order to determine the longitudinal extent and distribution of the different types of arteriolar le-sions. Chronic rather than acute arteriolar changes were studied. Acute primary degenerative and inflammatory arterial and arteriolar disease were not included in the investigation.

Three distinctly different forms of chronic arteriolar scle-rosis were observed: intimal hyalinization, medial hypertrophy and degeneration, and endothelial hyperplasia.

Intimal hyalinization was observed most commonly and was characterized by an accumulation of a homogeneous, acidophilic material (hyalin) between the smooth muscle of the media and the endothelium (Fig.2). The distribution of the hyalin varied considerably, appearing diversely as a subendothelial collar of uniform thickness, a subendothelial collar of irregular thickness which displaced the lumen to an eccentric position, or circumscribed subendothelial placques. The longitudinal distribution of hyalin along any given vessel was also variable, normal segments appearing interspersed between diseased segments. The arterioles with intimal hyalinization usually had narrowed lumens; however, some actually appeared to be dilated. Although the major portion of the accumulation of hyalin was usually inside the internal elastic lamella, the hyalin actually enveloped the elastic lamella which in many vessels lay near the center of the hyalin mass. In these instances elastic degeneration as manifested by swelling, disruption and dispersion, and subsequent complete disappearance of the fibrils occurred.

Medial hypertrophy and degeneration were the two types of pathological changes observed in the media in arteriolosclerosis. The former was characterized by an increase in the thickness of the media occasioned by an increase in the number and size of the smooth muscle cells (Fig. 3) and the latter by a relative increase in the amount of intercellular collagen throughout the media (Fig. 4). True hypertrophy could be positively identified when

the internal elastic lamella did not exhibit the degree of undulation noted in normal vessels (Fig. 1). Medial degeneration was more pronounced in the inner than in the outer half of the media and was occasionally associated with atrophy rather than hypertrophy of the smooth muscle cells. As was the case with intimal hyalinization, a longitudinal segmental distribution of the medial degeneration was observed.

Endothelial hyperplasia was characterized by a piling up of endothelial cells layer on layer (Fig. 5). New elastic fibers usually developed between the hyperplastic endothelial cells. These fibers either formed an irregular intercellular mesh or were organized into essentially concentric lamellas which were separated from each other by newly formed endothelial cells. In rare instances the hyperplasia was superimposed on a relatively unaltered internal elastic lamella. As observed in intimal hyalinization, the elastic fibers, both new and old, exhibited a pronounced tendency to degenerate as revealed by swelling, disruption and dispersion of the fibrils. Endothelial hyperplasia produced a reduction in the caliber of the lumen and was observed most frequently in vessels above 50 microns in diameter, rarely in arterioles below 30 microns in diameter.

The distribution of the various histological types of arteriolar sclerosis is summarized in another section.
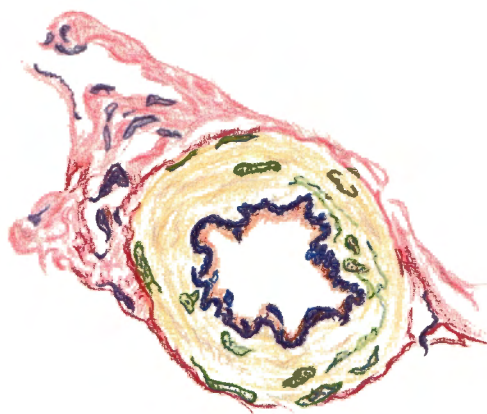
Fig. 1
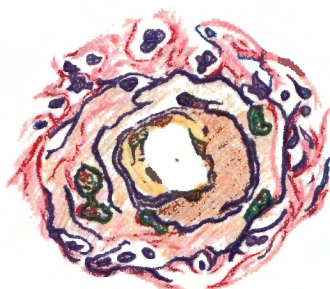


Fig. 2

Fig. 1.  Normal arteriole showing increased wall thickness as the result of pronounced post-mortem contraction. (Combination of van Gieson's and Weigert's elastic methods on same section, x 500.)

Fig. 2.  Arteriole showing plaque of intimal hyalin.  (Combination of van Gieson's and Weigert's elastic methods on the same section, x 500.)
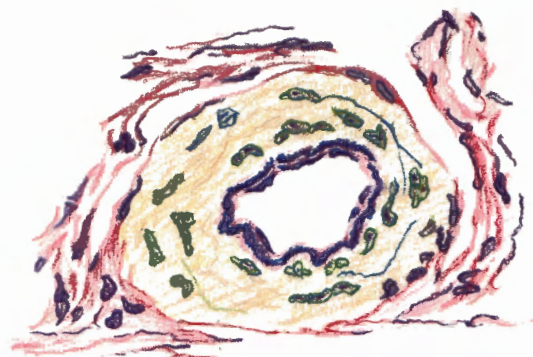
Fig. 3
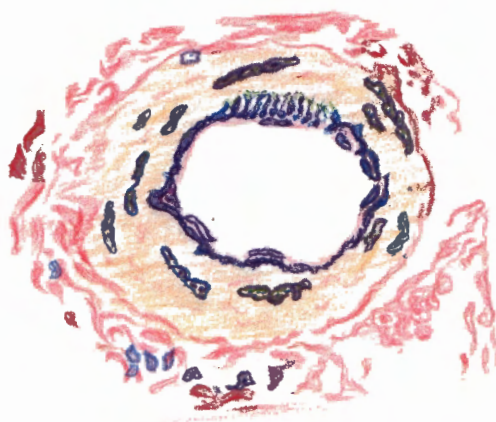


Fig. 4

Fig. 3.  Arteriole showing medial  hypertrophy.  (Combination of van Gieson's and Weigert's elastic methods on same section, x 500.)

Fig. 4.  Arteriole showing collagenous degeneration and medial  hypertrophy. (Combination of van Gieson's and Weigert's elastic methods on same section, x 500.)
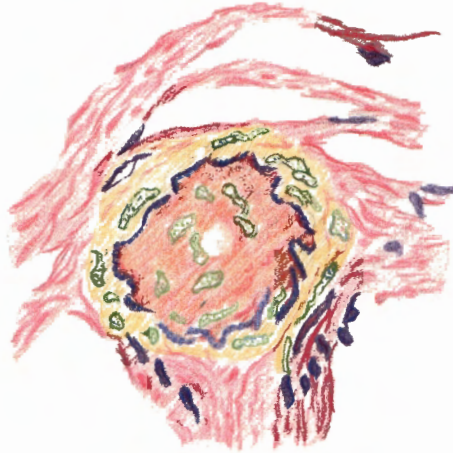
Fig. 5

Fig. 5. Arteriole showing endothelial hyperplasia
within an intact internal elastic lamella with pro-
nounced intimal thickening and reduction in lumen
caliber. (Combination of van Gieson's and Weigert's
elastic methods on same section, x 500.)

Experimental Observations on the Pathogenesis
of Essential Hypertension

The elucidation of the cause and cure of a disease process
in humans is invariably expedited by experimental reproduction
of the disease in laboratory animals. Essential hypertension is
the leading cause of death (22) but nevertheless has remained one
of man's most enigmatic diseases. It is not surprising, there-
fore, that investigators have painstakingly endeavored for many
years to reproduce the disease in experimental animals (12). It
was not until 1934, however, that Goldblatt and associates (23)
successfully produced persistent hypertension experimentally in
dogs which in many respects appeared to be the counterpart of es-
sential hypertension. The most striking similarity to essential
hypertension observed in experimental hypertension was an elevated
arterial pressure without a concomitant reduction of peripheral
blood flow (24,25), in which respect the hypertensive state dif-
fered from that elicited by most know pressor agents such as pit-
ressin, adrenalin, etc. (22). Goldblatt's accomplishment has
tremendously facilitated the study of the pathogenesis of essen-
tial hypertension.

Goldblatt, impressed by the constancy with which renal ar-
teriolosclerosis is observed post-mortem in essential hyperten-
sion (9,20), had as his working hypothesis that arteriolar neph-
rosclerosis is the initiating factor in the pathogenesis of es-
sential hypertension. Therefore, any experimental method for the

production of hypertension must duplicate the physiological effect of renal vascular disease. Conceivably, the effect is a decrease in the blood flow through the parenchyma of the kidney, i.e., renal ischemia. Accordingly, renal ischemia induced by constriction of the main renal arteries should be followed by an elevation of blood pressure.

Goldblatt was able to verify these theoretical considerations experimentally. The constriction of the main artery of one kidney of a dog by means of a special silver clamp designed to permit a reduction of the lumen to any desired caliber resulted in an elevation of blood pressure which persisted for weeks or months but usually returned to the normal level after one month. The degree of hypertension obtained was approximately proportional to the amount of constriction. Failure to maintain an elevated blood pressure was attributed to the development of collateral circulation, thereby thwarting the experimental renal ischema. Persistent hypertension was established by the constriction of both main renal arteries simultaneously or with an interval between clampings. A permanent elevation of blood pressure likewise resulted from constriction of the main renal artery of one kidney and subsequently removing the other kidney. Even in animals with both renal arteries constricted, the elevated blood pressure tended eventually to decline, probably in like manner because of the development of collateral circulation. The decline, however, was readily prevented by further constricting the main renal arteries.

The hypertension produced consisted of both increased diastolic and systolic pressures. Typical results obtained with eleven dogs are presented in Table I (23). The mean systolic blood pressure for the periods before and after constriction of both main renal arteries are recorded for each dog. In one instance (dog 8-7) the mean systolic blood pressure rose from 152 mm. Hg for the control period to 262 mm. Hg for the four-day period immediately following constriction of the arteries. Hypertension has now been successfully produced by the same method in the monkey (26), rat (27), rabbit (28), goat, and sheep (29).

Mild compression of the main renal arteries had no effect on renal function as determined by urea and creatinine clearance tests, the phenolsulfonephthalein test, and analyses of blood and urine (26,30,31). However, if the renal arterial occlusion were nearly complete, disturbance of renal function usually accompanied the elevated blood pressure and fatal uremia developed (23,30). Apparently the malignant phase of essential hypertension is reproduced by severe compression of the main renal arteries.

Another method for the experimental production of hypertension in dogs has been developed by Page et al. (32). In this method, the kidney is exposed and without removing the capsule cellophane or preferably silk is applied to the surface of the kidney and the wrapping secured by a string tied loosely around the pedicle. In four weeks a marked aseptic perinephritis usually develops which is accompanied by an exudate of white cells and

## TABLE I

Mean daily systolic blood pressure during the control
period before clamping either renal artery and during
the entire period after the initial constriction of
both main renal arteries

| Dog No. | Control Period | | Period after initial constriction of both renal arteries | |
|---|---|---|---|---|
| | Mean systolic blood press. | No. of days | Mean systolic blood press. | No. of days |
| | mm. Hg | | mm. Hg | |
| 2-5 | 146 | 62 | 174 | 21 |
| 3-8 | 160 | 63 | 252 | 454 |
| 4-9 | 159 | 63 | 215 | 363 |
| 5-5 | 161 | 161 | 202 | 138 |
| 5-6 | 154 | 76 | 205 | 201 |
| 5-8 | 150 | 83 | 214 | 294 |
| 5-9 | 169 | 148 | 232 | 274 |
| 6-0 | 185 | 134 | 224 | 227 |
| 6-1 | 191 | 182 | 221 | 161 |
| 8-7 | 152 | 86 | 262 | 4 |
| 8-9 | 173 | 72 | 212 | 98 |

plasma covering the surface of the kidney. The exudate ultimately organizes through growth of fibroblasts and finally forms a leathery capsule which encloses and slightly compresses the entire kidney. The slight compression apparently is responsible for the altered intrarenal hemodynamic condition which elicits the hypertension.

Goldblatt has demonstrated by ingenious devices that the ischemic kidneys are in some manner directly responsible for the development of experimental hypertension. Thus, if the main renal artery is constricted and the ischemic kidney subsequently excised, when the blood pressure is still elevated, the blood pressure falls promptly to the normal level (30). Or if, instead of nephrectomy, the clamp on the ischemic kidney is released, the blood pressure likewise returns to the normal level (30). Moreover, if persistent, hypertension is produced by constriction of both main renal arteries and one clamp subsequently released, the blood pressure declines slowly to the original level as is ultimately the case when only one main renal artery is clamped initially; but if both clamps are released at the same time, the blood pressure returns immediately to the normal level (30). Blalock and Levey (33) and Glenn, Child and Heuer (34) independently performed an experiment in which one kidney of a dog was transplanted to the neck or inguinal region and the other removed. Constriction of the arterial blood supply to the transplanted kidney produced an elevation of blood pressure. It has also been demonstrated that constriction

of femoral or splenic arteries (23, 35), splanchnic arteries (36), or the aorta immediately below the origin of both renal arteries (37) fails to produce a rise in blood pressure. Bilateral nephrectomy, likewise, does not result in a persistent hypertension (30). These results are evidence that the kidney is primarily implicated in the development of experimental hypertension.

In dogs with experimental hypertension, as in essential hypertension, the blood pressure is elevated by virtue of increased peripheral resistance and an augmentation of the force of the heart beat (22). The increased peripheral resistance in experimental animals cannot be attributed to structural changes in the arterioles because of the rapidity with which it becomes established. Therefore, functional constriction of the arterioles must be responsible and could conceivably be induced either by a generalized reflex stimulation of the vasomotor system initiated by the ischemic kidney or through the elaboration of a pressor agent in the ischemic kidney, which transported in the blood stream, produces an increased muscular tone in the peripheral arterioles, i.e., through a humoral mechanism.

The former possibility is excluded on the basis of several observations. In dogs denervation of the renal pedicle failed to prevent or alleviate hypertension produced by constriction of the renal arteries (38). Resection of the splanchnic nerves and excision of the lower four thoracic sympathetic ganglia (39), section of the anterior nerve roots from the sixth dorsal to the second

lumbar spinal nerves inclusive (40), and total sympathectomy in
the thorax and abdomen including denervation of the heart (41,
42) had no effect on the course of experimental hypertension.
Moreover, as previously described, in a dog with one kidney re-
moved and the other kidney transplanted to the neck or inguinal
region and made ischemic by clamping the arterial supply, hyper-
tension developed even though there was no possible connection
between the kidney and the nervous system in such an animal
(33,34).  In view of these results, it is improbable that
ischemic kidneys evoke hypertension by virtue of a nervous reflex.

Attention has therefore centered upon a possible humoral
mechanism in the etiology of experimental hypertension (19,22).
Investigations have yielded results entirely consonant with this
hypothesis.  For instance, if the renal veins are obstructed at
the same time that the renal arteries are compressed, no increase
in blood pressure occurs (43).  The demonstration that, when one
kidney of a dog is removed and the other transplanted to the neck
or groin devoid of any nervous connections with the host, a rise
in blood pressure still results when the main artery to the trans-
planted kidney is constricted, not only eliminates the possi-
bility of a nervous reflex from the ischemic kidney but indicates
a humoral mechanism (33,34).  Moreover, if the arterial supply of
the transplanted kidney is not clamped, the blood pressure re-
mains at the normal level.  Finally, the demonstration that venous
blood collected from kidneys with constricted arteries is ac-

tively vasopressor whereas venous blood from kidneys under normal circumstances is without effect, affords incontrovertible evidence for the existence of a humoral mechanism in the pathogenesis of experimental hypertension (44,45).

The intrinsic nature of the humoral mechanism has been elucidated largely through the efforts of Page and collaborators (22) and independently and coincidentally by Munoz and coworkers in South America (46). Inasmuch as it is not within the scope of this thesis to present a critical review of the numerous experiments which have been performed to establish the intimate nature of the humoral mechanism, only the essential aspects of the evidence are presented.

In 1898, Tigerstedt and Bergman (47) found that a saline extract of rabbit kidneys exerted a prolonged pressor effect when injected into another rabbit. The active ingredient, named renin, apparently was a protein, not dialyzable and heat labile. The experimental production of hypertension by constriction of the main renal arteries immediately prompted renewed interest in renin and methods of purification were soon developed (48,49). The various fractions obtained in the course of purification were assayed on both intact animals and isolated organs (rabbits' ears or dogs' tails) perfused with Ringer's solution (50). The interesting fact emerged that fractions which were extremely active in the intact animal possessed little or no activity in isolated organs perfused with Ringer's solution. Evidently purification had removed a sub-

stance necessary for the activation of renin. However, if blood, plasma, or the pseudoglobulins of plasma were added to renin in Ringer's solution prior to perfusion, a marked vasopressor effect occurred in isolated organs which were perfused. The pseudoglobulin in blood apparently required for the activation of renin was termed renin-activator, which merely signified that renin remained inactive as a pressor substance in its absence. Renin-activator has also been termed preangiotonin (19). Subsequent investigation disclosed that if renin and renin-activator were mixed in a test tube and allowed to incubate for ten or fifteen minutes followed by boiling the mixture to precipitate the renin and renin-activator, the supernatant solution contained a substance, angiotonin, which was strongly pressor (51). Angiotonin, unlike renin and renin-activator, is not a protein but is thermostabile and dialyzable. Certain crystalline derivatives have been prepared. The reaction between renin and renin-activator seems to be enzymatic in nature (53). Renin apparently is the enzyme and so called renin-activator the substrate. In view of this relationship the term preangiotonin is preferable to renin-activator.

Angiotonin apparently is the effector substance in the renin-renin-activator vasopressor system. When angiotonin is injected into normal animals, experimental hypertension is simulated in that among other effects the blood pressure is markedly elevated without a reduction in peripheral blood flow and the force of the heart beat is augumented (22,52).

Repeated injections of angiotonin into normal animals re-
sulted in a loss of pressor responsiveness (tachyphylaxis). How-
ever, bilaterally nephrectomized animals failed to develop tachy-
phylaxis to angiotonin (54). From this and other observations
(19,55), evidence has accumulated which indicated the presence
in normal blood and normal kidneys of a substance, termed angio-
tonin inhibitor or angiotoninase, which inhibits the action of
angiotonin. The angiotonin inhibitor has been successfully ex-
tracted from kidneys and produces a lowering of the blood pres-
sure when injected into animals with experimental hypertension
(56,57).

To summarize, the pressor mechanism apparently originates
in renin, which, when liberated by the kidneys into the blood
stream, combines with renin-activator to form angiotonin. Angio-
tonin elicits the rise in blood pressure. The kidney contains a
substance which opposes or balances the action of angiotonin, i.e.,
angiotonin inhibitor. The South American investigators have ar-
rived at the identical conclusions (19, 46), Renin-activator has
been termed by them hypertensinogen; angiotonin, hypertensin; and
angiotonin inhibitor, hypertensinase.

Hypertension produced by compression of the renal arteries or
of the renal parenchyma has been generally regarded as the result
of renal ischemia (12, 15, 23). This belief is founded largely on
original observations reported by Goldblatt et al. (23), which
were subsequently corroborated and extended by Levy, Light, and

Blalock (58). Goldblatt measured the blood flow from the renal vein of a dog following various degrees of constriction of the main renal artery. For this purpose a "T" cannula was inserted in the main renal vein which permitted a continuous flow of blood through the vein or shunting of the stream to permit collection of blood for the purpose of measurement of rate of flow. The blood was collected for a standard period of three minutes, measured, and immediately returned to the body through a cannula in the jugular vein to avoid possible effects of loss of blood on blood pressure and blood flow. Table II (23) illustrates the data obtained in four successive determinations of renal outflow in a dog under ether anesthesia following moderate, severe, and very severe constriction of the main renal artery. The average outflow with no constriction, moderate, severe, and very severe constriction was 1.3, 0.8, 0.4, and 0.1 cc., per second, respectively. Thus a direct demonstration of renal ischemia under the conditions of the experiment was achieved. The experiment, however, as Goldblatt realized (12), did not determine whether the decreased blood flow persisted after hypertension had developed. That such actually appeared to be the case is evidenced in the experiments of Levy, Light, and Blalock. These investigators measured renal blood flow in ten dogs approximately one week before and once or twice at varying intervals following constriction of the main renal arteries when a well marked, sustained hypertension had developed. When necessary, the clamps were tightened in order to maintain

TABLE II

Effect of various degrees of constriction of the
main renal artery on the outflow of blood from
the renal vein

| Degree of constriction of renal artery | | | |
|---|---|---|---|
| None | Moderate | Severe | Very severe |
| Outflow of blood from renal vein in 10 sec. | | | |
| cc. | cc. | cc. | cc. |
| 13.0 | 8.5 | 4.5 | 1.3 |
| 14.5 | 7.5 | 4.8 | 1.0 |
| 12.5 | 8.0 | 3.6 | 1.2 |
| 13.0 | 8.0 | 4.0 | 1.0 |
| Average outflow per sec. | | | |
| 1.3 | 0.8 | 0.4 | 0.1 |

the elevation in blood pressure. The blood flow was determined
without anesthesia by means of a cannula devised by Blalock et al.
inserted in the renal vein (59). The results indicated a marked
reduction in renal blood flow after the renal arteries had been
constricted for from 6 to 73 days, averaging 41% of the control
flow. Thus renal ischemia existed even in the face of elevated
arterial pressure. Some of the animals after the determination
of renal blood flow were anesthetized with ether, the abdomen
opened, and the blood pressure in the renal arteries distal to the
clamp measured by inserting into the artery a needle connected to
a mercury manometer. The blood pressure was reduced in all deter-
minations.

Page and coworkers (22) questioned the validity of the hy-
pothesis that renal ischemia per se is the cause of experimental
hypertension on the basis of the observation that urea clearance
was occasionally normal in hypertensive animals (23). Inasmuch
as urea clearance in normal dogs has been shown by Van Slyke et al.
(60) to parallel the rate of renal blood flow, the kidneys in
those hypertensive dogs with normal urea clearance were probably
not ischemic. Moreover, Page (61) demonstrated that renal clear-
ance of phenol red, inulin, creatinine, and urea in some instances
remained normal in uninephrectomized dogs with hypertension due
to compression of the main renal artery. It was inferred from
these measurements that no marked decrease in renal blood flow
had occurred. To confirm this view, measurements of femoral

arterial pressure and indirect determinations of renal blood flow,
based on phenol red and inulin clearances (62), were made in
uninephrectomized dogs with single subcutaneously explanted kid-
neys (63) before and after compression of the renal artery (64).
The arterial pressure in the renal artery distal to the point of
clamping was also measured. The results indicated that constriction
of the renal artery will reduce renal blood flow only if the mean
arterial pressure has been reduced distal to the point of clamping,
thus corroborating Blalock et al.(58). However, if the clamp is
only tightened enough to dampen the pulse, and if the systemic ar-
terial pressure is increased somewhat in consequence, intrarenal
arterial pressure may remain unchanged and renal blood flow there-
fore maintained at a normal level. This result was achieved in
only five dogs and is well illustrated in the case of dog 2-50 in
Fig. 6 (65). The considerable variations in renal blood flow ob-
served over a period of more than a year in this instance are ex-
plained by the repeated adjustments of the degree of arterial con-
striction which were made. However, it is apparent that normal
blood flow persisted during moderate hypertension. Blalock (66)
more recently has likewise observed that the renal arterial pres-
sure in some experimentally hypertensive dogs distal to the point
of clamping is normal. It is quite improbable that the renal blood
flow would be affected by clamping if the arterial pressure were
not. Blalock and coworkers (67) have also observed that, follow-
ing clamping of the renal artery, there is a tendency for renal
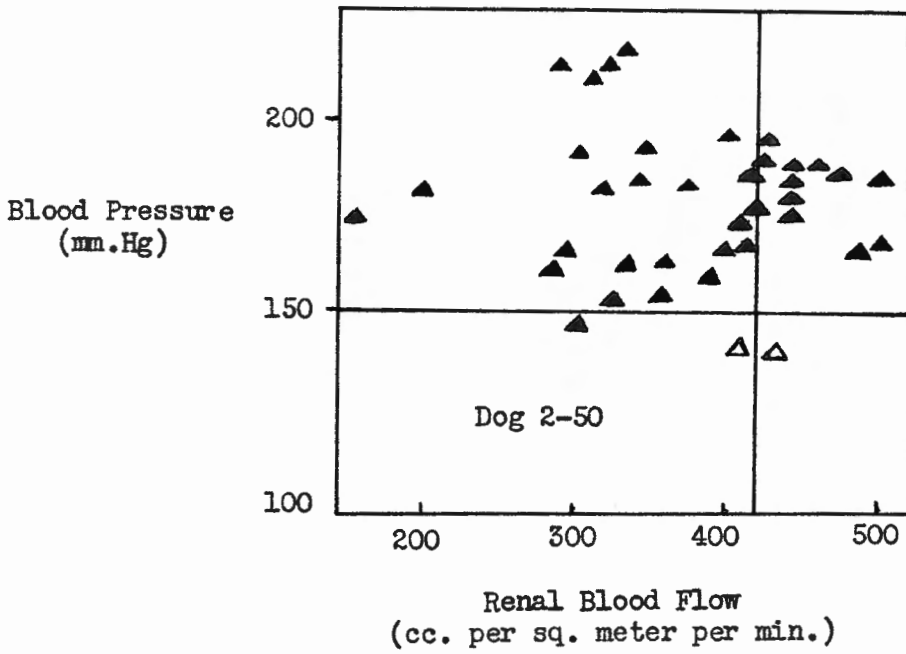
Fig. 6. Relation of mean femoral arterial pressure to total renal blood flow in a uninephrectomized dog before (△) and after (▲) application of a Goldblatt clamp to the main renal artery.

blood flow which initially had decreased to return to or approach normal levels. Of significance, too, are the demonstrations (68,69) that renin and angiotonin cause a marked decrease in renal blood flow in normal animals. From these results it may be inferred that renin and angiotonin elicit a vasoconstriction in the kidneys. Therefore, Page (65) has suggested that the rate of renal blood flow depends in each instance on the balance achieved between the increased systemic arterial pressure and the increase in renal resistance due primarily to clamping of the renal artery and secondarily to the renal vasoconstriction induced by the renin liberated when the renal artery is clamped. Thus, if with increased resistance, there is a corresponding increase of arterial pressure, no reduction in blood flow will occur. It is obviously difficult to attain this point of balance with the application of metal clamps. Therefore renal ischemia will usually occur and normal rates of renal blood flow will only exceptionally be observed in experimentally hypertensive animals. However, the fact that hypertension of a moderate degree may occasionally be induced experimentally without a significant change in renal blood flow would eliminate renal ischemia as the anomalous hemodynamic condition responsible for the elevated blood pressure in experimental hypertension.

The most obvious circulatory change, other than ischemia, which might result from compression of the main renal artery is reduction of pulse pressure distal to the clamp (64). Kohlstaedt

and Page (70) demonstrated that renin is not liberated from iso-
lated dogs' kidneys perfused with blood at normal blood pressure
and flow. In a similar experiment the renal arteries were gradu-
ally compressed to a point where pulse pressure was greatly re-
duced while renal blood flow was either unaffected or slightly
decreased. Arterial pressure was then sufficiently increased
proximal to the compression so that both the mean arterial pres-
sure in the renal artery and renal blood flow were maintained
within normal limits. Under these conditions the perfused kid-
neys liberated considerable quantities of renin into the renal
venous blood. It thus appears that the stimulus for the libera-
tion of renin from the kidneys, and therefore the initiating fac-
tor in the genesis of experimental hypertension, is a reduction in
intrarenal pulse pressure, or more simply stated, a partial conver-
sion of pulsatile to continuous flow of blood.

The mechanism by which reduction of pulse pressure provokes
hypertension has not been established. Organs perfused in the
absence of pulsatile flow quickly become edematous and the cells
do not exhibit normal permeabilities to vital dyes (71). It is
therefore conceivable that renin, a protein with a relatively
large molecular size, is contained in the renal tubular cells
which are normally impermeable to it. This is evidenced by the
absence of renin from normal venous blood. However, reduction of
pulse pressure increases renal cellular permeability thus permit-
ting renin to escape as evidenced by the presence of renin in

renal venous blood of experimentally hypertensive animals.

On the basis of the foregoing observations Page (72) has formulated a reasonable concept of the pathogenesis of experimental hypertension. Reduction of pulse pressure by compression of the main renal arteries or renal parenchyma initiates the liberation of renin by increasing the permeability of the tubular cells. The renin combines, probably enzymatically, with the renin-activator in the blood to form angiotonin. Hence blood issuing from the renal vein contains a mixture of renin and some angiotonin. As the renin circulates, ever increasing amounts of it are converted to antiotonin. When the blood reaches the heart and arterioles, most of the renin has been converted to angiotonin. The angiotonin causes peripheral arteriolar constriction and cardiac augmentation resulting in arterial hypertension.

In view of the marked similarity between experimental hypertension and essential hypertension (22), it is possible that a like sequence of events functions in the pathogenesis of essential hypertension. However, the cause of the reduction in pulse pressure, which presumably must be the initiating factor in the genesis of essential hypertension as well, remains to be determined.

### Clinical Observations in Support of the Primary Role Ascribed to Renal Arteriolar Sclerosis in the Pathogenesis of Essential Hypertension

Various pathological states have been recognized in humans which effectively produce a constriction of the renal arteries and are therefore clinical analogues to the Goldblatt experimental method (23) for the production of hypertension in animals. Hypertension often occurs in these instances. Thus Leiter (73) described a case of chronic hypertension which at autopsy revealed arteriosclerotic occlusion of the main renal arteries. Another similar case reported by Leiter apparently resulted from thromboarteritis obliterans of the small renal arteries. Freeman and Hartley (74) observed a case in which hypertension developed following removal of a ruptured kidney. It was found subsequently that the opposite renal artery was occluded by an atheromatous plaque. Other cases of a similar nature have been reported by Moritz and Oldt (14).

Perhaps a more striking illustration of the human counterpart of Goldblatt's experimental method is afforded by a case in which renal torsion of from 45 to 60 degrees effectively created a compression of the renal artery by a twisting tendency (75). The observed blood pressure was 240 mm. Hg systolic and 120 mm. Hg diastolic. A corset was devised to support the kidney in a more normal position. When the patient wore the corset, the blood pressure invariably remained near normal; but without it, the blood pressure rose. Constriction of the renal artery by

bending may also occur in nephroptosis (76). In some instances of nephroptosis, assuming the erect posture results in an elevation of blood pressure which is nullified when the patient lies down. Hypertension is also often associated with coarctation of the aorta (77,78,79). In this condition the stricture of the aorta apparently produces the same effect on renal blood flow as compression of the main renal artery.

Emboli of the renal arteries likewise give rise to hypertension. Fishberg (80) observed four cases in which embolism of one or both renal arteries was followed by a pronounced increase in arterial pressure. Prinzmetal, Hiat, and Tragerman (81) reported an interesting case of a patient suffering with rheumatic heart disease. The patient suddenly became hypertensive within the space of a few days following an attack of severe abdominal pain. The elevation of blood pressure was accompanied by increasing suppression of urine, and death occurred in uremia. Post-morten examination revealed a thrombus in both main renal arteries.

Page (82) has reported an instance in which lymphosarcoma constricted both renal arteries and both ureters to some extent. The blood pressure rose from 150 to 204 mm. Hg in seven months.

It is thus apparent that pathological circumstances are encountered in humans which obviously duplicate the effect of the renal arterial clamp in experimental hypertension and which are associated with hypertension. The fact that hypertension in humans can be produced in this manner lends credence to the

hypothesis that renal arteriolar sclerosis is the cause of essential hypertension. In renal arteriolar sclerosis "myriads of little clamps" (65) are effectively applied to the some 1,250,000 afferent arterioles (15,83) in each kidney. If clamping of the main renal arteries in animals and "effectively clamping" the main renal arteries or the small renal arteries in man evokes hypertension, it is at least conceivable that the clamping of the renal arterioles actually inherent in arteriolar nephrosclerosis should likewise give rise to hypertension.

Moreover, in Page's method (32) for the experimental production of hypertension, compression of the renal parenchyma, and therefore undoubtedly of the renal arterioles as well, occurs. This method apparently has its clinical counterpart in an unusual case (84). A boy, 18 years of age, sustained an injury at 6 years of age. The injury resulted in the formation of a hemorrhagic cyst which enveloped the kidney parenchyma. The walls of the cyst thickened and appeared to have compressed the kidney. The associated blood pressure was 154 mm. Hg systolic and 102 mm. Hg. diastolic. Following removal of the cyst to relieve the compression, the blood pressure decreased to around 104 mm. Hg systolic and 62 mm. Hg diastolic. Thus an experimental procedure in animals and a pathological circumstance in man, both of which very probably effect a degree of constriction of the renal arterioles, lead to an elevation of blood pressure. In like manner, the constriction of renal arterioles inherent in renal arteriolar sclerosis should

conceivably produce hypertension.

More direct evidence in support of renal arteriolar scle-
rosis as the primary causal factor in essential hypertension is
presented in a report by Moritz and Oldt (14).  These investiga-
tors conjectured that a comprehensive and purely objective post-mor-
tem study of the pathological histology, distribution, and relative
severity of arteriolar sclerosis in the various organs and tis-
sues in a large number of hypertensive and non-hypertensive indi-
viduals should throw considerable light on the relationship of
arteriolar disease to essential hypertension.  The report presents
the results obtained in such a study.

The investigation included 200 autopsies.  One hundred of the
cases had no history of hypertension whereas the other 100 were
known to have had chronic hypertension.   A case was regarded as
non-hypertensive if two criteria were fulfilled, namely: first, a
previous record of repeated blood pressure determinations none of
which exceeded 140 mm. Hg systolic and 90 mm. Hg diastolic; and
secondly, heart weights in males less than 400 grams and in fe-
males less than 300 grams.  Moreover, cases with records of normal
blood pressures and heart weights which exhibited histological
evidence of cardiac hypertrophy were excluded.  Conversely, a
case was regarded as hypertensive if there was a previous record
of blood pressure determinations consistently higher than 160 mm.
Hg systolic and 90 mm. Hg diastolic or 150 mm. Hg systolic and
100 mm. Hg diastolic and if the heart weights in males were

greater than 450 grams and in females greater than 350 grams.
Cases of inflammatory heart disease were excluded, and a heart
weight greater than 500 grams was stipulated if severe coronary
arteriosclerosis was encountered. The two groups were comparable
as to age, sex, and color. Approximately one-third of the indi-
viduals in each group were between 31 and 45 years of age, one-
third between 46 and 60 years, and one-third 61 years of age or
over.

The spleen, pancreas, adrenals, gastrointestinal tract, brain,
skeletal muscle, liver, and kidney were examined for arteriolar
changes in every case. All sections of each organ or tissue in
each individual were examined objectively with no knowledge of
the history of the case. The severity of the arteriolar changes
were recorded as mild, moderate, or severe. Focal arteriolar
sclerosis was not considered in the general evaluation of the
severity of arteriolar disease in a given tissue. Diffuse vascu-
lar disease must have been present in any given organ or tissue
before it was graded as mild, moderate, or severe. In many cases
of mild and occasionally in instances of moderate or severe scle-
rosis not all the arterioles were affected, but invariably enough
were diseased to constitute a generalized rather than a confined
disease process. The classifications of mild, moderate, or
severe arteriolosclerosis were not comparable between organs or
tissues, i.e., severe arteriolar sclerosis in skeletal muscle was
not of the same degree of severity or even the same type of ar-

teriolar disease as observed in severe arteriolar sclerosis in
the pancreas. Thus any one of the three grades into which a par-
ticular organ or tissue may have been classified acquired signi-
ficance only when compared to the other two grades for that organ
or tissue. The size of vessels studied and the methods of inves-
tigation employed by Moritz and Oldt is reviewed in the section
on Pathological Histology of Arteriolar Sclerosis.

Correlation of the relative severity of arteriolar sclerosis
in each organ or tissue of hypertensive and non-hypertensive
individuals revealed an extremely high incidence of renal arterio-
lar sclerosis in essential hypertension, whereas in non-hyperten-
sive individuals renal arterioles were less frequently diseased
than in any other organ or tissue. These results are well exemp-
lified in Fig. 7 (14). Thus, renal arteriolar sclerosis was ob-
served in 109 of the 200 cases studied. Ninety-seven of the 109
cases of nephrosclerosis had essential hypertension during life.
Therefore, 97 per cent of the hypertensive individuals and only
12 per cent of the non-hypertensive individuals had renal arteri-
olar sclerosis, and of the latter, only 2 per cent revealed more
than mild renal vascular disease. The import of the kidney be-
comes particularly apparent in view of the fact that even though
the other organs and tissues likewise exhibited an increase in
both incidence and severity of arteriolar disease in hypertension,
a sequence of these organs and tissues arranged in the order of
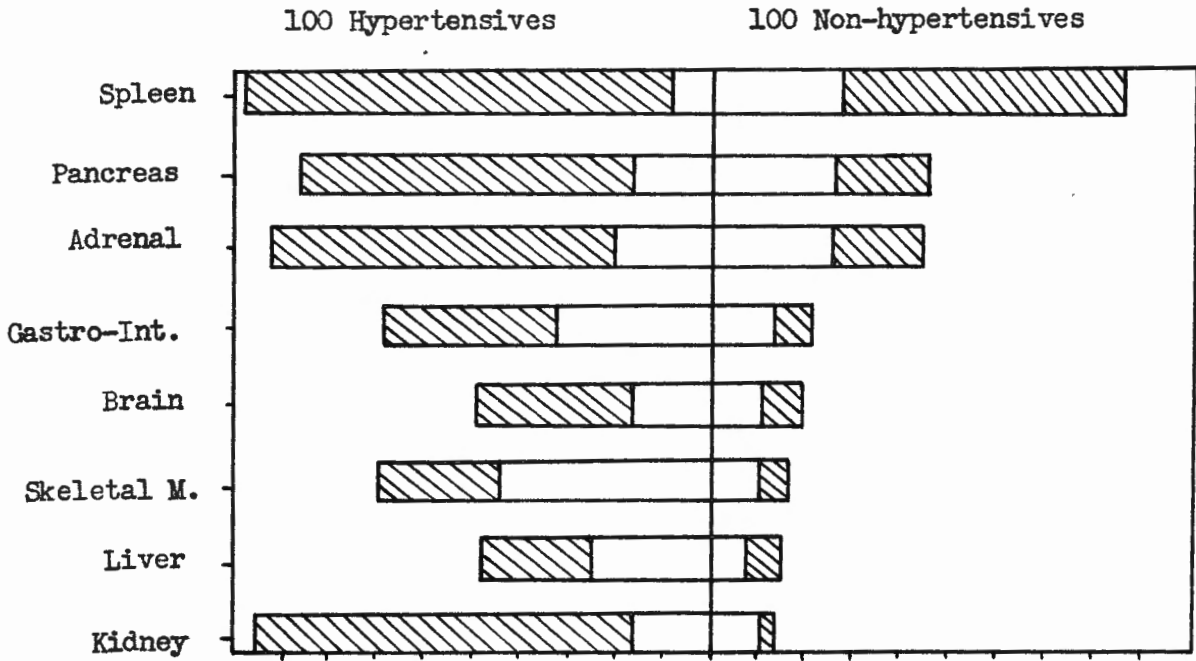increasing incidence of arteriolar sclerosis was approximately

Fig. 7. A comparison of the occurrence of arteriolar sclerosis in the various organs and tissues of 100 hypertensive and 100 non-hypertensive individuals

Mild ☐ .        Severe ▨

the same in the hypertensive and non-hypertensive groups. There-
fore, the correlation demonstrated in the case of the kidney was
unique. For instance, arteriolar disease was present in the spleens
in 98 per cent of the cases with hypertension, an incidence equal
to that observed in the kidneys of hypertensive individuals, but
the arterioles in 87 per cent of the spleens in individuals with-
out hypertension were also diseased. Thus the generalized increase
in the degree of arteriolar sclerosis in hypertension is by far
most profound in the kidney.

The most reasonable interpretation of this observation is
that renal arteriolar sclerosis is primarily responsible for hyper-
tension. The other possibility, namely, that hypertension causes
renal arteriolar sclerosis demands the assumption that the renal
arterioles possess an extremely high degree of selective vulnera-
bility to high blood pressure, since renal arteriolar disease was
present in almost every case of hypertension but was rarely ob-
served in any other circumstances. At the same time, it would be
necessary to attribute to the renal arterioles a high degree of
resistance to every other sclerosing process since renal vascular
disease was observed only very infrequently in the control group.
That two so diametrically opposed characteristics should be essen-
tial in one organ seems unlikely. Thus by exclusion, the view that
renal arteriolar sclerosis antedates hypertension is given credence.
Moreover, it seems more tenable to assume that arteriolar sclerosis
is a primary pathological change which may affect the renal arteri-

oles as well as those in the spleen, pancreas, adrenals, and other tissues. When the renal arterioles become sufficiently sclerotic to alter the intrarenal hemodynamics in the manner of the Goldblatt clamp or the fibrocollagenous perinephritis induced by cellophane, hypertension ensues. The fact that renal arteriolar sclerosis in a few instances occurs without an associated hypertension does not necessarily detract from the major hypothesis. Since it is not possible to accurately predict the functional effect of a structural change, what may morphologically appear to be a mild form of arteriolar disease may in reality account for a considerable modification in intrarenal hemodynamics; and the converse is equally true. Therefore, the circumstance of renal arteriolar sclerosis without an associated hypertension merely signifies that the hemodynamic state of the kidneys has not been appreciably affected by the disease process. The three cases of chronic hypertension in which there was no significant degree of arteriolar disease in the kidneys disclosed marked renal arteriosclerosis and therefore do not controvert the foregoing arguments.

Other investigators have similarly observed renal vascular disease in a high percentage of cases of essential hypertension. Fishberg (20) in a study of 72 cases observed renal arteriolar sclerosis in 100 per cent. Bell and Clawson (9) found renal arterial disease within the parenchyma of the kidney in 97.6 per cent and sclerosis of the afferent glomerular arterioles in 89.4 per cent of 420 cases of hypertension. The failure of these

authors to observe arteriolar disease in all instances of hyper-
tension may be due to the possibility of severe sclerosis in some
portion of the main renal arteries in the negative cases. Formerly
lesions of this type were probably overlooked and the cases classi-
fied as essential hypertension without renal vascular disease (12).

The study of the pathological histology of arteriolar sclerosis
reported by Moritz and Oldt revealed that no type of chronic ar-
teriolar disease, separately or in combination, was pathognomonic
of hypertension. Intimal hyalinization appeared to be a simple
"wear and tear" type of tissue reaction, since it was observed
with greater frequency and severity as age advanced in the non-hy-
pertensive group, and was most frequently found in the abdominal
organs supplied by relatively large short branches of the aorta
(spleen, kidney, pancreas, and adrenals) in the control group. In
hypertensive individuals it was similarly distributed but was seen
with greater frequency and severity and even extended into vascular
beds (liver and gastro-intestinal tract) where it seldom appeared
in non-hypertensive cases. Assuming that hypertension might aug-
ment arteriolar "wear and tear" and since intimal hyalinization
appeared to be a simple "wear and tear" type of tissue reaction,
it is not unreasonable to expect the lesion to be more widely dis-
trubuted and of greater severity in hypertension than in its ab-
sence.

Endothelial hyperplasia was generally observed in the control
group only in association with inflammatory or involutional changes

in the various organs and tissues. In hypertension it was observed most frequently in the kidneys and occasionally in other tissues, apparently as a primary morbid process.

Medial hypertrophy and degeneration were seen with greater frequency and severity in hypertensive than in non-hypertensive individuals and resembled the changes following distension of any hollow muscular structure. In hypertension it was observed most frequently in skeletal muscle where it was very widespread. In non-hypertensive individuals it was observed occasionally in skeletal muscle and the gastro-intestinal tract.

It is therefore apparent that the three types of chronic arteriolar disease were observed separately and in combination in hypertensive as well as in non-hypertensive cases. Therefore none could be considered as pathognomonic of hypertension. If the arteriolar sclerosis observed in essential hypertension were entirely secondary to the elevated blood pressure, it is reasonable to suppose that a characteristic type or pattern of arteriolar disease peculiar to hypertension would be observed. However, actually, arteriolar disease in hypertension is merely more severe and widespread than in non-hypertensive cases and does not represent a deviation in histological characteristics. Thus it would appear that arteriolar sclerosis assumes a primary role.

In the study of the incidence of renal vascular disease in hypertensive and non-hypertensive individuals, Moritz and Oldt (14) observed instances of unilateral nephrosclerosis in the hyper-

tensive group. If the diagnosis in these cases could have been achieved in life, removal of the diseased kidney might have resulted in a return of blood pressure to normal and thus afforded positive evidence for the primary role imputed to renal arteriolar sclerosis in the genesis of hypertension. Actually, such evidence has been obtained. Leadbetter and Burkland (89) and Boyd and Lewis (90) have reported two cases of essential hypertension associated with unilateral renal vascular disease in which the removal of the diseased kidney resulted in a prompt return of the blood pressure to normal. If the unilateral renal vascular disease in these cases had not been primarily responsible for the hypertension, removal of the diseased kidney should not have effected a cure.

In summary, renal arteriolar sclerosis is probably primarily implicated in the pathogenesis of essential hypertension on the basis of the following evidence. First, pathological states in humans which create a reduction of the lumen of the main renal arteries or small renal arteries, for one reason or another, are associated with hypertension. It is reasonable to suppose that the narrowed lumen of the arterioles in renal arteriolar disease presents a deviation in intrarenal hemodynamics similar to that effected by reduction in lumen of the main renal arteries and should therefore, likewise, evoke hypertension. Secondly, significant arteriolar sclerosis is observed only rarely in non-hypertensive individuals at autopsy; whereas, in essential hypertension it is almost a constant finding. The significance of this result becomes particu-

larly apparent in view of the observation that the relative fre-
quency of arteriolosclerosis in other organs and tissues in hyper-
tensive and non-hypertensive cases is very nearly the same.
Thirdly, no type of vascular disease is in or by itself indicative
of essential hypertension. On this basis arteriolar sclerosis rea-
sonably becomes a primary morbid process. Finally, unilateral
nephrectomy in cases of unilateral renal disease associated with
essential hypertension produces a prompt return of the blood pres-
sure to normal. Such a situation is only rationalized by attribu-
ting to renal arteriolar disease a causal relationship to essential
hypertension.

Experimental and Clinical Observations at Variance with the
Primary Role Ascribed to Renal Arteriolar Sclerosis in the
Pathogenesis of Essential Hypertension

The usual tests of renal function reveal that a large ma-
jority of patients with essential hypertension have no significant
abnormality of renal function (11). Van Slyke's urea clearance is
usually within normal limits and concentration tests reveal that
the great majority of patients with essential hypertension are able
to excrete urine with a specific gravity of approximately 1.025.
Mac Lean's urea concentration test also yields satisfactory re-
sults. The determinations of the phenolsulfonephthalein test may
frequently be subnormal. This, however, is usually the result of
cardiac weakness rather than of impairment of renal function. If
a normal concentration test is observed along with a subnormal
phenolsulfonephthalein test, the latter result is generally con-
sidered to be of cardiac orign. Renal integrity in essential hy-
pertension is also indicated by a normal non-protein nitrogen
level in blood and the absence of proteinuria. However, with the
advent of the ingenious renal clearance procedures devised by
Smith (85,86,87) it became apparent that definite abnormalities in
renal function in patients with essential hypertension could be
demonstrated. These methods have aided considerably in expound-
ing the relationship between renal arteriolar sclerosis and essen-
tial hypertension.

Smith and co-workers (85,87) have established that plasma

diodrast clearance is a measure of the physiologically effective

renal plasma flow in cubic centimeters per minute. Diodrast is

excreted largely by tubular secretion, i.e., by discharge of dio-

drast from the plasma of the peritubular capillaries through the

cells of the proximal convoluted tubules into the tubule lumen, and

also by glomerular filtration. Smith has observed that the extrac-

tion of diodrast from blood by the kidney is virtually complete at

low plasma concentrations of diodrast. Therefore it follows that

diodrast clearance at lowplasma levels is nearly equivalent to renal

plasma flow, or, at least, to the rate of flow of plasma to intact,

functioning renal parenchyma (effective renal plasma flow). The

renal blood flow may be calculated by dividing the fraction of

plasma in the blood, as measured with the hematocrit, into the plas-

ma diodrast clearance.

Smith et al. (88) in a study of 60 patients with well-

established essential hypertension demonstrated that, with the

exception of three subjects, the kidneys of the hypertensive pa-

tients had plasma diodrast clearances which were below the mean

normal value (609 cc. per minute) and which ranged from slightly

subnormal to very low values. Thus the majority of hypertensive

subjects exhibit a renal ischemia in the absolute sense.

Smith moreover observed that a progressive destruction of

renal parenchyma occurs in essential hypertension. This was

established by determinations of diodrast-Tm in the 60 subjects

with essential hypertension. The diodrast-Tm is defined by Smith

as the maximal rate of tubular excretion of diodrast. This
value may be determined by subtracting the quantity of diodrast
filtered through the glomeruli per minute (as determined by the
inulin clearance which Smith has demonstrated is a measure of the
rate of glomerular filtration inasmuch as inulin is neither ex-
creted nor absorbed by the tubules) from the total quantity of
diodrast excreted per minute, when the plasma level of diodrast
has been raised to a sufficiently high level to promote the maxi-
mum rate of excretion of the diodrast by the tubule cells. Dio-
drast-Tm thus measures the number of active excretory tubules; it
is therefore a measure of the total quantity of intact tubular ex-
cretory tissue in the kidney. With the exception of three sub-
jects (two of whom were in the group with normal plasma diodrast
clearances), the diodrast-Tm was below the mean normal value
(51.6 mgm. of iodine per minute) and ranged from slightly subnor-
mal to very low values, thus indicating a decreased quantity of
intact renal parenchyma. The lowest diodrast-Tm values were found
in subjects with advanced retinopathy and significant proteinuria.

In view of the progressive destruction of the renal parenchyma
in essential hypertension, it is not surprising to observe a con-
comitant renal ischemia. In fact, the degree of renal ischemia and
the extent of destruction of renal parenchyma (as measured by the
renal plasma flow and diodrast-Tm, respectively) were approximately
proportional. It is, however, obviously more interesting and
should be of greater bearing to the etiology of essential hyper-

tension to know the plasma flow per unit of residual functionally intact renal tissue. Inasmuch as diodrast-Tm is a measure of intact tubular tissue and since plasma diodrast clearance is a measure of the total effective renal plasma flow, it follows, obviously, that the ratio of diodrast clearance to diodrast-Tm ($C_D/Tm_D$) in any given instance is an expression of plasma flow per unit of intact tubular tissue. If the value of the ratio $C_D/Tm_D$ in hypertensive subjects were equal to that determined in normal individuals, i.e., if the plasma flow per unit of residual intact renal tissue in a hypertensive kidney were numerically equal to the plasma flow per unit of normal renal tissue, then the renal plasma flow in essential hypertension should decrease in direct proportion with the renal parenchyma. As stated abóut this was only approximately the case. Actually as determined by Smith 45 of the 60 subjects had a plasma flow per unit of residual intact renal tissue equal to or below the normal value, i.e., $C_D/Tm_D$ in 45 of the 60 cases of hypertension was equal to or below the normal value. This preponderant distribution below the mean suggests that some factor is operating in hypertensive subjects to produce a relative ischemia in the residual, functional tissue.

The purport of the results obtained in the determination of $C_D/Tm_D$ in hypertensive subjects becomes apparent only in the light of the determinations of inulin clearance and the ratio of inulin clearance to diodrast-Tm ($C_{IN}/Tm_D$) for the 60 cases with hypertension. Inulin clearance (the volume of plasma in cubic centimeters

equivalent to the amount of inulin which appears in the urine each minute) as stated above is equal to the volume of glomerular filtrate formed each minute. The ratio $C_{IN}/Tm_D$ is obviously an expression for the relative value of the rate of glomerular filtration per unit of functional tubular tissue. Inulin clearance in all but five of the subjects was equal to or below the mean normal value (131 cc. per minute). There was, however, a tendency for the inulin clearance to remain within the lower range of normal values (92 to 131 cc.) until diodrast-Tm had been markedly reduced. The reduction in inulin clearance was very probably due to obliteration of glomeruli.

In spite of the absolute reduction in inulin clearance, its relative value per unit of functional tubular tissue ($C_{IN}/Tm_D$) exceeded the mean normal value in 43 of the 60 subjects, and in 21 of these it was greater than the mean normal value (M) plus twice the standard deviation ($\sigma$), i. e., greater than $M+2\sigma$. In those individuals which did not exhibit an elevated $C_{IN}/Tm_D$, the ratio assumed approximately a normal value except for two cases with a value distinctly below normal. Smith (86,88) has suggested that an abnormally high value of $C_{IN}/Tm_D$ may be explained on the basis of the formation of so-called impotent tubules, i. e., tubules which have lost their excretory capacity but which remain connected with intact, functioning glomeruli. Thus impotent tubules could contribute to glomerular filtration but not to the tubular excretion of diodrast ($Tm_D$). Therefore, if the formation of impotent

tubules has proceeded to a considerable extent, it is reasonable to expect an abnormally high $C_{IN}/Tm_D$, the relative value for the rate of filtration per unit of intact and functional tubular tissue. The abnormally high $C_{IN}/Tm_D$ observed in the majority of cases with hypertension may be explained on this basis. Smith, moreover, has suggested that the vascular remnants persisting around defunct tubules may within a certain radius of diffusion irrigate the nearby residual functional tissue and thus produce a relative hyperemia. This supplementary vascularization, however, would not contribute to diodrast-Tm since the functioning tubules are already secreting diodrast at the maximum capacity in this test, and, therefore, the only possible indication of its presence is an abnormally high $C_{IN}/Tm_D$. In addition, a high $C_{IN}/Tm_D$ may be expected to be accompanied by an abnormally high value of $C_D/Tm_D$, since diodrast clearance equals inulin clearance plus diodrast-Tm. Accordingly, the 21 subjects with an abnormally high $C_{IN}/Tm_D$ were considered anomalous and therefore deleted. Then renal plasma flow per unit of functional tubular tissue ($C_D/Tm_D$) in the remaining subjects was with three exceptions below the mean normal value and in many subjects had decreased to very low values. This fact leads to the conclusion that, so far as the effective renal blood flow is concerned, some factor or occlusive tendency is operative in essential hypertension which tends to produce a relavite ischemia of the residual, functional tissue. The ischemic factor may of course be operative in the 21 subjects with an abnormally high

$C_{IN}/Tm_D$. However it is masked by the abnormally high rate of glomerular filtration per unit of excretory mass.

The existence of a functional renal ischemia in essential hypertension has led Smith (86) to conclude, also, that renal ischemia precedes the actual destruction of renal parenchyma. If this were incorrect, one should not expect to observe ischemia in the functionally, intact renal parenchyma. The destruction of renal parenchyma, then, appears to be a result rather than a cause of ischemia.

Smith (86,87), moreover, has demonstrated that the occlusive tendency which is responsible for the relative ishcemia of the residual, intact renal tissue in essential hypertension must in a great measure, at least, be functionally reversible under the experimental conditions which give rise to hyperemia in the normal kidney. Hyperemia was readily produced in the kidneys of normal individuals by injection of small amounts of certain samples of inulin which acted anomalously in that a pyrexial reaction including headache, lumbar pain, nausea, and ultimate fever resulted. The pyrexial reaction was invariably accompanied by renal hyperemia as evidenced by a markedly increased plasma diodrast clearance. Adequate doses of pyrogenic inulin produced increases in renal plasma flow of from 50 to 75 per cent. A similar effect was also noted in hypertensive subjects after administration of the pyrogenic inulin in that hyperemia of variable degree was consistently produced which in some instances was sufficiently great to estab-

lish a blood flow of the order of magnitude observed in the normal
kidney. Thus the occlusive tendency must be functionally rever-
sible.

Smith (86,88) has also accrued data which reveal that the
occlusive tendency giving rise to the renal ischemia is confined
to the efferent glomerular arterioles. These data were obtained
in experiments which measured the filtration rate and the filtra-
tion fraction before and during experimentally produced hyperemia
of the hypertensive kidney. The filtration rate as stated above
is numerically equal to the inulin clearance and the diodrast
clearance is numerically equal to the renal plasma flow. By divid-
ing the filtration rate by the renalplasma flow, the fraction of
the plasma filtered through the glomeruli (filtration fraction) may
be calculated. In almost all the 60 subjects with hypertension the
filtration fraction was greater than the mean normal value of 19
per cent. Smith has reasoned that the relative value of the fil-
tration fraction may be interpreted so as to define the locus of
the obstruction in the ischemic kidneys of hypertensive subjects.
Were the lumen of the arterioles afferent to the glomeruli de-
creased in the hypertensive kidney, the glomerular pressure would
have been reduced and the filtration fraction consequently
lessened. A decreased lumen in the efferent arterioles, however,
would increase the glomerular pressure and consequently increase
the filtration fraction. Thus the increased filtration fraction
is strong evidence for an occlusive tendency in the efferent

arterioles. Moreover, the tendency for the filtration rate to remain within the lower range of normal values until diodrast-Tm had been markedly reduced is likewise consonant with this hypothesis. The increased glomerular pressure due to efferent obstruction tends to compensate for the decreased plasma flow to maintain a nearly normal filtration rate even in the face of rather extensive destruction of renal parenchyma. However, an obstruction in the afferent arterioles would conversely be expected to effect a marked decrease in filtration rate.

The existence of an occlusive tendency in the efferent glomerular arterioles in essential hypertension is further confirmed by the observation that during experimentally produced hyperemia the filtration fraction in the hypertensive kidney was never increased but invariably decreased. Theoretically, an elevated filtration fraction should occur were the obstruction localized in the afferent arterioles since the glomerular pressure would be increased during hyperemia thus giving rise to an increased filtration rate and consequently an elevated filtration fraction.

In summary, Smith has established the existence of ischemia in the functionally intact renal parenchyma of subjects with essential hypertension. The functional ischemia is the result of an occlusive tendency present in the efferent glomerular arterioles which is reversible under conditions which give rise to hyperemia in a normal kidney. It is concluded that the obstruction occurs

in the efferent arterioles because :  (a) the filtration fraction
was greater than normal in the majority of cases; (b) the filtra-
tion rate in many instances was only slightly subnormal even when
rather marked destruction of renal parenchyma had occured; (c) the
filtration fraction invariably decreased during experimentally in-
duced renal hyperemia.

Chassis and Redish (91)obtained similar results in the deter-
minations of diodrast clearance, inulin clearance, and diodrast-Tm
in the separate kidneys of 15 subjects with essential hypertension.
Urine was collected from each kidney by means of ureteral catheters
passed only 12 cm. up the ureter, i.e., into the portion of the ure-
ter having the narrowest lumen.  Thus leakage around the catheter
was usually avoided.  Representative patients with hypertension were
selected at random.

In every instance diodrast clearance and diodrast-Tm were less
than one-half of the normal value thus indicating renal ischemia
in the absolute sense and a progressive destruction of renal paren-
chyma, respectively, in both kidneys of hypertensive subjects.  No
significant difference in the diodrast clearances or diodrast-Tm
of the separate kidneys of the same subject was observed.  The
ratio $C_D/Tm_D$ was equal to or below the mean normal value in 21 of
the 30 kidneys.  Thus in the majority of instances individual kid-
neys of these subjects were relatively ischemic.  The ratio
$C_{IN}/Tm_D$ in 25 of the 30 kidneys exceeded the mean normal value.

In the expectation that an abnormal value of $C_{IN}/Tm_D$ would be accompanied by an abnormally high value of $C_D/Tm_D$, the kidneys with an abnormally high $C_{IN}/Tm_D$ (greater than $M+ 2\sigma$) were considered anomalous and therefore disregarded in the study of the $C_D/Tm_D$ ratio. Then in every instance $C_D/Tm_D$ was invariably below normal, i. e., a relative ischemia of the intact, tubular mass of each kidney was invariably present. In no instance was there an indication of a unilateral ischemic kidney.

Further confirmation of Smith's work is found in a report by Friedman, Selzer and Rosenblum (92). These investigators determined the renal blood flow in patients with fluctuating hypertension of one year duration (5 patients), early persistent hypertension of six years duration (6 patients), and long-standing hypertension of ten years duration (15) patients). The effective renal blood flow and the rate of glomerular filtration were determined by means of diodrast and inulin clearances, respectively. From these data the filtration fraction was calculated. The renal blood flow was moderately reduced in 18 of the 21 patients with essential hypertension. Also, among the five patients with variable hypertension a reduction in the renal flow was observed in three of the patients whose diastolic pressures were elevated to 85 mm. Hg or above at the time of the clearance tests. The remaining two patients in this group, despite previous elevations of blood pressure, maintained normal pressures during the determinations and gave normal values for the renal blood flow The inulin

clearances, however, were not materially altered in this series
of hypertensive cases. Therefore increased values for the fil-
tration fraction were obtained. It is thus apparent that irres-
pective of the duration or persistency of the hypertension, the
average renal clearances of the three groups were approximately
equal. Accordingly, Friedman determined whether a correlation ex-
isted between the height of the diastolic blood pressure and the
clearance values. For this purpose 41 patients with hypertension
were classified according to the level of diastolic blood pressure
into four groups, as follows: (a) 13 subjects with diastolic pres-
sures of 80 mm. Hg or less; (b) 16, with diastolic pressures be-
tween 80 and 100 mm. Hg; (c) 8, with diastolic pressures between
100 and 120 mm. Hg; (d) 6, with diastolic pressures between 120 and
140 mm. Hg. As evident from Fig. 7a, a progressive diminution in
renal blood flow and inulin clearance and a progressive increase
in filtration fraction with each interval increase in the level of
diastolic pressure was observed. The increase in filtration frac-
tion was due to the fact that the relative decrease in renal blood
flow was greater than the corresponding decrease in glomerular fil-
tration.

Results analogous to those of Smith were likewise obtained by
Foa, Woods, Peet, and Foa (93) in a study of twenty patients with
hypertension ranging in age from 26 to 54 years. Effective renal
blood flow, filtration rate, and in addition for ten subjects,
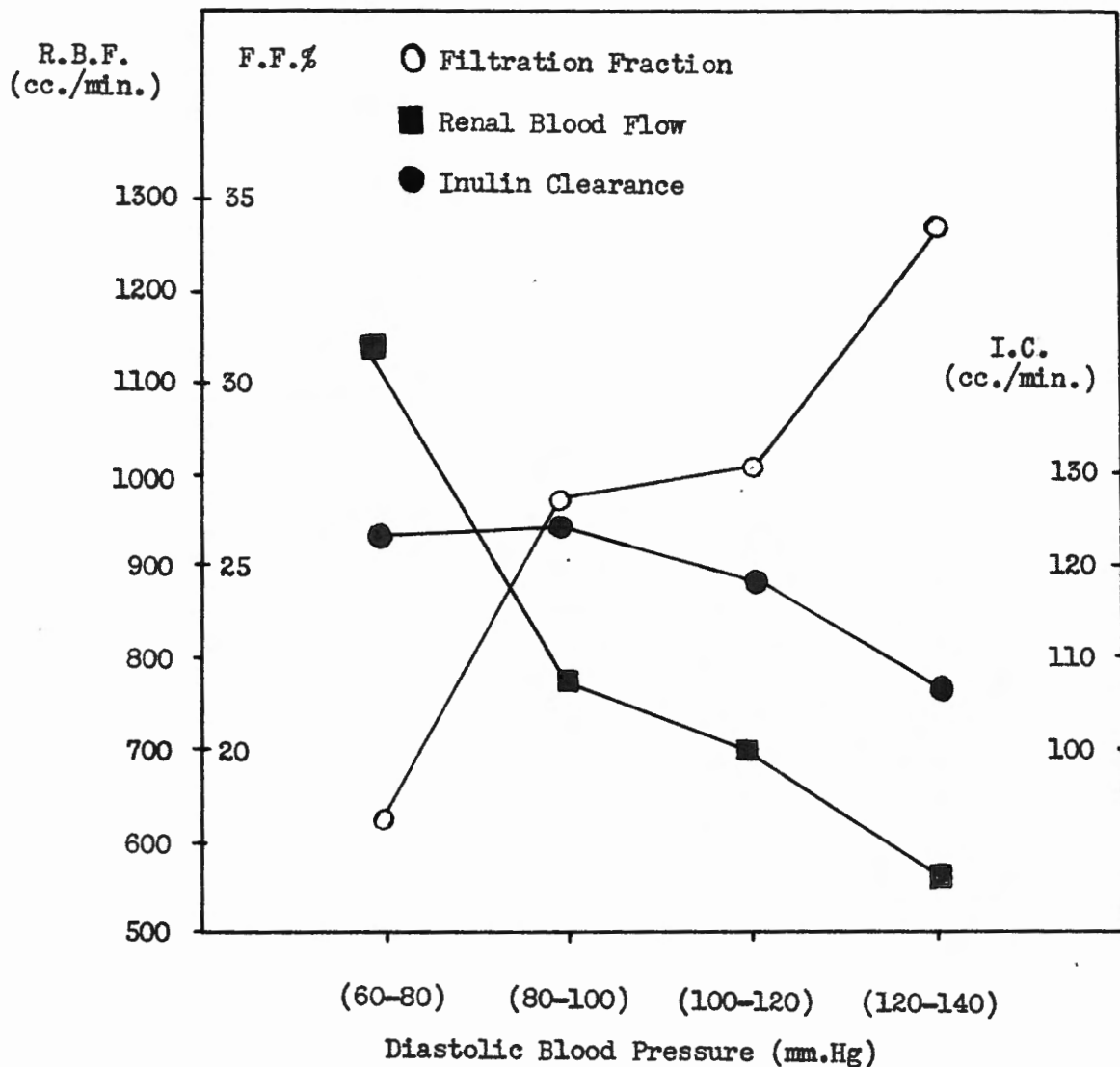tubular excretory mass (diodrast-Tm) were determined. Seven normal

Fig. 7a. Relation of the mean values of the renal blood flow, the inulin clearance, and the filtration fraction to the diastolic pressure of the 43 patients studied.

subjects without hypertension were used as controls. A compari-
son of the results obtained for subjects with and without hyper-
tension revealed that the latter had a greatly reduced renal blood
flow and a decreased filtration rate. The decrease in filtration
rate, however, was proportionately less than the decrease in blood
flow; therefore, the filtration fraction was elevated. The tubular
excretory mass (diodrast-Tm) was not significantly reduced in most
instances. The filtration rate per unit of excretory mass
($C_{IN}/Tm_D$) was increased. However, in spite of the increased
$C_{IN}/Tm_D$, the plasma flow per unit of excretory mass ($C_D/Tm_D$) was re-
duced. Investigators stated that a correlation between the se-
verity of the hypertension as measured by other clinical and morpho-
logic observations and the renal clearance studies was not justified.

Further confirmation of Smith's results has been reported by
Chesley and Chesley (93). Employing the diodrast clearance method,
effective renal blood flow was measured in 11 women with essential
hypertension who gave no history of toxemia of pregnancy. The
diagnosis of essential hypertension was established on the basis
of an elevated blood pressure, the absence of or only minimal pro-
teinuria, edema, and hematuria, and a urea clearance consistently
above 70 per cent of the normal. A rough estimation of the rate
of glomerular filtration was made by assuming that 60 per cent of
the urea in the glomerular filtrate was excreted in the final urine.
In these cases, with three exceptions, the data confirm Smith's
findings. A diminished blood flow was observed in all but three

cases which exhibited a normal blood flow. The filtration frac-
tion was invariably elevated except for the three cases with nor-

mal blood flow.

Smith's observations which have been repeatedly corroborated
lead inevitably to one conclusion, namely, that arteriolar scle-
rosis does not antedate essential hypertension. The occlusive ten-
dency in the efferent arterioles very probably accounts for the
functional renal ischemia in essential hypertension. The perturba-
tion of the normal vascular state responsible for the occlusive
tendency may conceivably be either a structural or functional
change in the efferent glomerular arterioles. The former would be
arteriolar sclerosis effecting a progressive occlusion of the vas-
cular bed and the latter a spasm of the efferent arterioles. It
is, however, unlikely that an arteriolar sclerotic process would
be confined to the efferent arterioles. Actually, Moritz and
Oldt (14) have observed a greater incidence of arteriolosclerosis
in the afferent glomerular arterioles than in the efferent arteri-
oles in hypertensive cases at autopsy. Moreover, a constriction
due to sclerosis would be irreversible under experimental condi-
tions which give rise to hyperemia in a normal kidney. Therefore,
it may be concluded that the occlusive tendency responsible for
the functional renal ischemia is due to efferent arteriolar spasm
and not sclerosis. This conclusion is further substantiated by
the observation of Friedman (92) that the renal blood flow,

glomerular filtration rate, and filtration fraction correlate
with diastolic blood pressure in hypertensive individuals and
not with the duration of hypertension. If arteriolar sclerosis
were responsible for the ischemia in hypertensive kidneys, it would
be reasonable to suppose a relationship between the duration of hy-
pertension and renal blood flow. However, actually, the reduction
in blood flow in cases of fluctuating hypertension was of the same
order of magnitude as observed in cases of long-standing hyperten-
sion. Only a reversible, functional change such as efferent hyper-
tonus is consistent with these observations. Finally the demon-
stration that angiotonin when injected into normal subjects repro-
duces the characteristic functional changes in the vascular state
observed in hypertensive kidneys is confirmatory evidence that the
efferent arteriolar obstruction is a functional constriction (65).

Thus the variant intrarenal hemodynamics in essential hyper-
tension as determined by Smith's clearance procedures are allied
with a functional constriction of the efferent glomeruli and ap-
parently not with a permanent structural alteration such as ar-
teriolar sclerosis. Evidence (72) obtained in the study of the
pathogenesis of experimental hypertension in animals suggests that
essential hypertension is probably initiated by an anomaly in intra-
renal hemodynamics (reduction in pulse pressure and/or renal
ischemia). If this hypothesis is correct, and since the deviated
renal vascular state in essential hypertension may be attributed
to a functional, reversible spasm of the efferent glomerular

arterioles, renal vascular disease could not be primary in the sequelae leading to hypertension. This conclusion is further substantiated by Smith's observation that the functional renal ischemia in hypertension precedes the actual destruction of renal parenchyma. If the sclerosing process is inwroght in the progressive destruction of renal parenchyma in hypertensive kidneys, then renal arteriolar sclerosis is secondary to renal ischemia.

Direct evidence that renal arteriolar sclerosis does not precede essential hypertension is found in the recent observations of Castleman and Smithwick (95). These investigators employing the surgical treatment of hypertension by dorsolumbar sympathectomy have obtained renal biopsies from 100 patients in various states of essential hypertension. The patients ranged in age from 18 to 56 years with an average of 39 years. The systolic and diastolic blood pressures in the majority were over 200 and 100 mm. Hg, respectively. The disease had been present an average of six years, ranging from one month to fifteen years. The severity of the disease was determined on the basis of eyeground changes which were classified into four grades: grade 1 showed various degrees of arteriolar narrowing or constriction without nicking of venous crossings; grade 2, arteriovenous compression and narrowing, caliber changes, tortuosity or wide light reflexes in the arterioles; grade 3, retinal exudates or hemorrhages in addition to the other types of arteriolar changes; and grade 4, edema of the optic disks with measurable elevation, usually with exudate and hemorrhage and any or all of the other changes mentioned. Of the 100 cases, 32 per

cent gere grade 1, 28 per cent grade 2, 26 per cent grade 3, and 14 per cent grade 4. Thus all stages of essential hypertension were well represented and the renal biopsies should reveal the relation of arteriolar nephrosclerosis to the hypertensive state. The biopsies were wedge shaped specimens approximately 6 mm. wide and 5 mm. deep. Immediately after removal the specimens were fixed in Zenker's fixative. In 25 cases biopsies were removed from each kidney. In every case the microscopic appearance of the two sections thus obtained were similar. The pathological changes observed were classified according to the method of Moritz and Oldt (14) as intimal hyalinization, medial hypertrophy and degeneration, or endothelial hyperplasia. Most of the biopsies which showed arteriolar sclerosis exhibited all three types. Only rarely was one type present exclusively. Sufficient differences were noted in the degrees of arteriolar sclerosis to classify the sections according 5 grades of increasing severity; grades 0, 1, 2, 3, 4. Grade 0, comprising 7 patients, was marked by the absence of arteriolar sclerosis. Grade 1, comprising 21 patients, was characterized by very mild arteriolar disease which might not be detected at a cursory examination. Only a relatively few vessels were involved. Grade 2, comprising 25 patients, was characterized by a more advanced arteriolar disease than observed in grade 1 but not sufficiently so that it was apparent at a cursory glance with low magnification. An occasional hyalinized glomerulus was seen. Grade 3, comprising 33 patients, was characterized by arteriolar disease which was

~~characterized by arteriolar disease~~ which was usually severe in
every vessel. Many scars and hyalinized glomeruli were visible.
Grade 4, comprising 14 patients, was characterized by the most
severe vascular disease. Every vessel was involved; many glo-
meruli were scarred and surrounding tubles were atrophic. Except
for the absence of necrotizing arteriolitis, these biopsies sug-
gested so-called malignant nephrosclerosis.

The most significant result is the high percentage of renal
biopsies in which vascular disease was either entirely absent or
only minimal. Seven per cent were grade 0; 21 per cent, grade 1;
25 per cent, grade 2; 33 per cent grade 3; and 14 per cent, grade 4.
Thus 28 per cent (7 plus 21) and possibly 53 per cent (28 plus 25)
exhibited so slight a degree of arteriolar sclerosis as to make it
appear unlikely that the sclerosis by itself could have caused a
sufficient deviation in the renal vascular state to be responsible
for the hypertension. Moreover, the observation that seven cases
in this series, some with severe long-standing hypertension (two
exhibited retinal vessel changes of grade 3 severity), revealed no
renal arteriolar sclerosis is incontrovertible evidence that essen-
tial hypertension antedates renal vascular disease.

In further study, Castleman, Smithwick, and coworkers (96)
determined the rate of renal plasma flow ($C_D$), glomerular filtra-
tion ($C_{IN}$), and the tubular excretory mass (diodrast-Tm) in 20 of
the patients in this series. The renal biopsies of 2 patients in

this group were in grade 0; 4, in grade 1; 3, in grade 2; 8, in grade 3; and 3, in grade 4.

The averages of renal plasma flow, glomerular filtration rate, tubular excretory mass, and filtration fraction for each grade of renal vascular disease are plotted against the five grades of renal arteriolar sclerosis in Figures 8, 9, 10, and 11, respectively. It is evident from these graphs that a reasonably constant correlation exists between microscopic evidence of renal vascular disease and renal function as measured by Smith's clearance procedures. Thus renal plasma flow (Fig.8), glomerular filtration rate (Fig. 9), and functional renal parenchyma (Fig. 10) decrease and filtration fraction (Fig. 11) increases with increasing severity of renal arteriolar sclerosis in essential hypertension. In Fig. 10, line 'M' represents the locus of points such that the ratio of ordinate to abscissa ($C_D/Tm_D$) for each point is constant. If renal parenchyma decreased in direct proportion to renal plasma flow in hypertension, the ratio $C_D/Tm_D$ would remain normal and all points would fall on line 'M'. Actually all points, except for grade 0, were below line 'M', thus indicating a relative ischemia in the residual, functioning tubular tissue.

Castleman and Smithwick's data confirm Smith's report in that some of the hypertensive individuals presented the characteristic anomalies in renal function demonstrated by Smith to occur in hypertension. This is particularly apparent in the individuals with
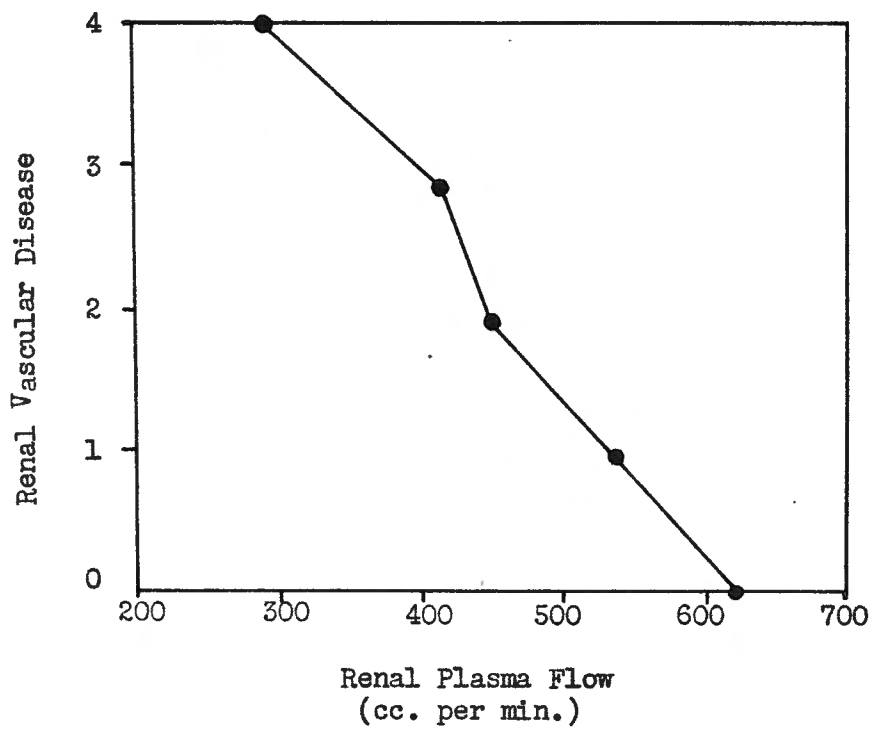
Fig. 8. Average renal plasma flow for each of the five grades of renal vascular disease.
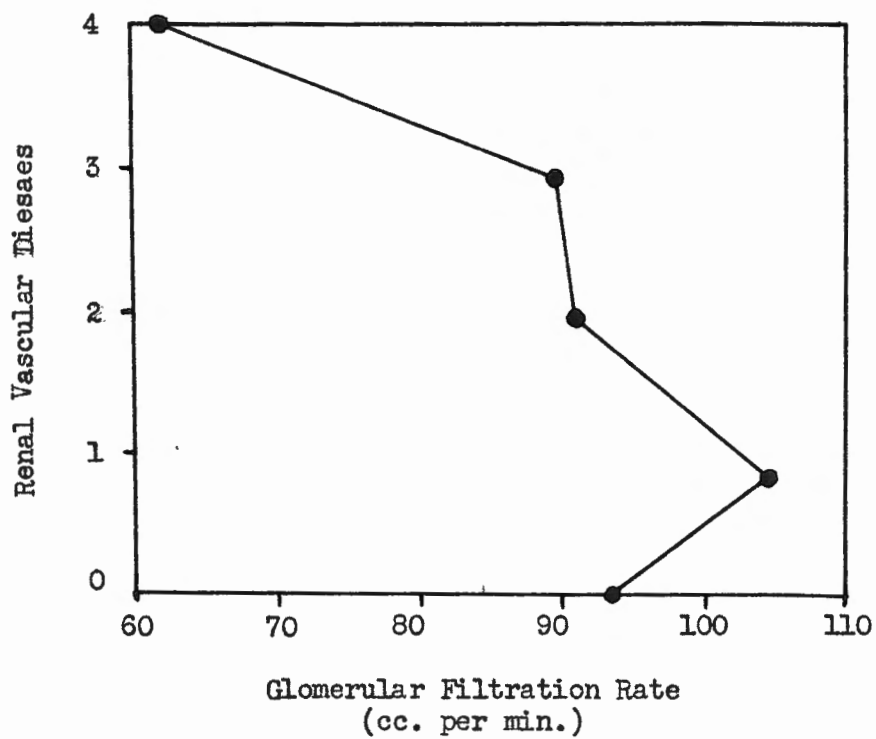
Fig. 9. Average glomerular filtration rate for
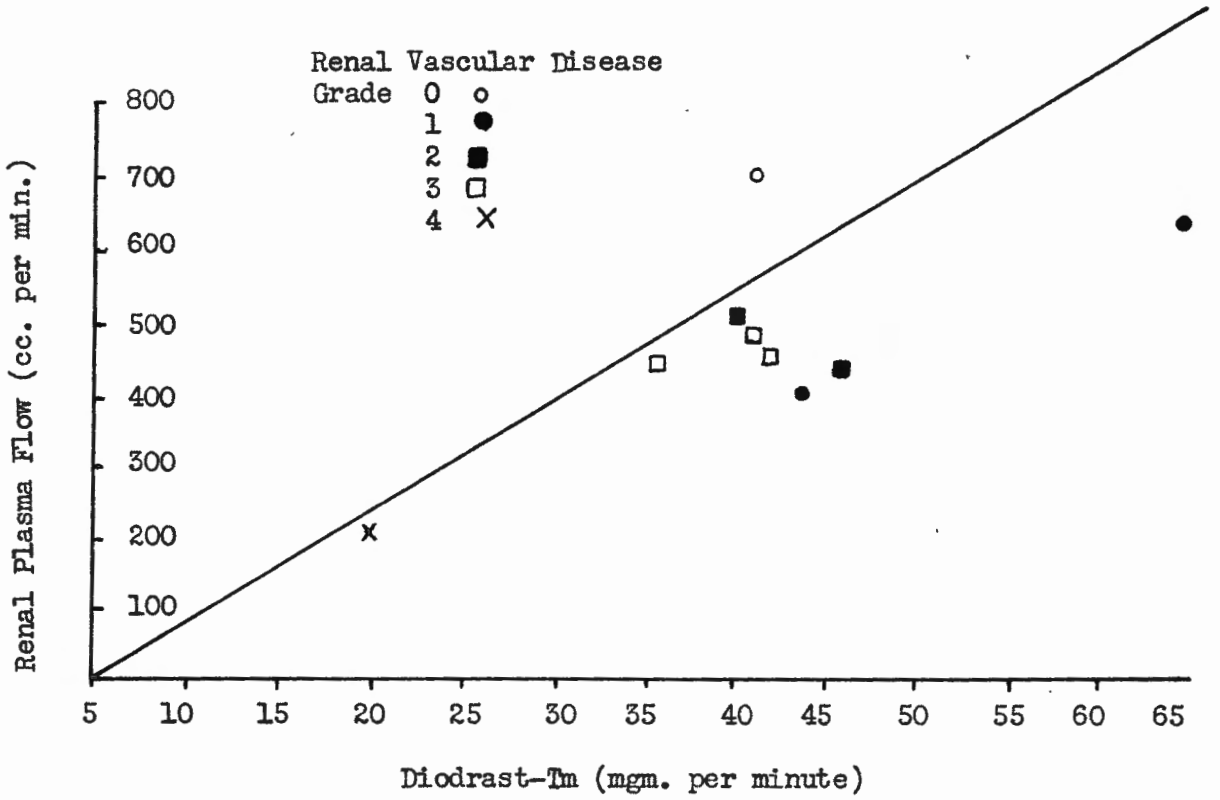each of the five grades of renal vascular disease.

Fig. 10.  Relation of renal plasma flow to diodrast-Tm for each of the five grades of renal vascular disease.
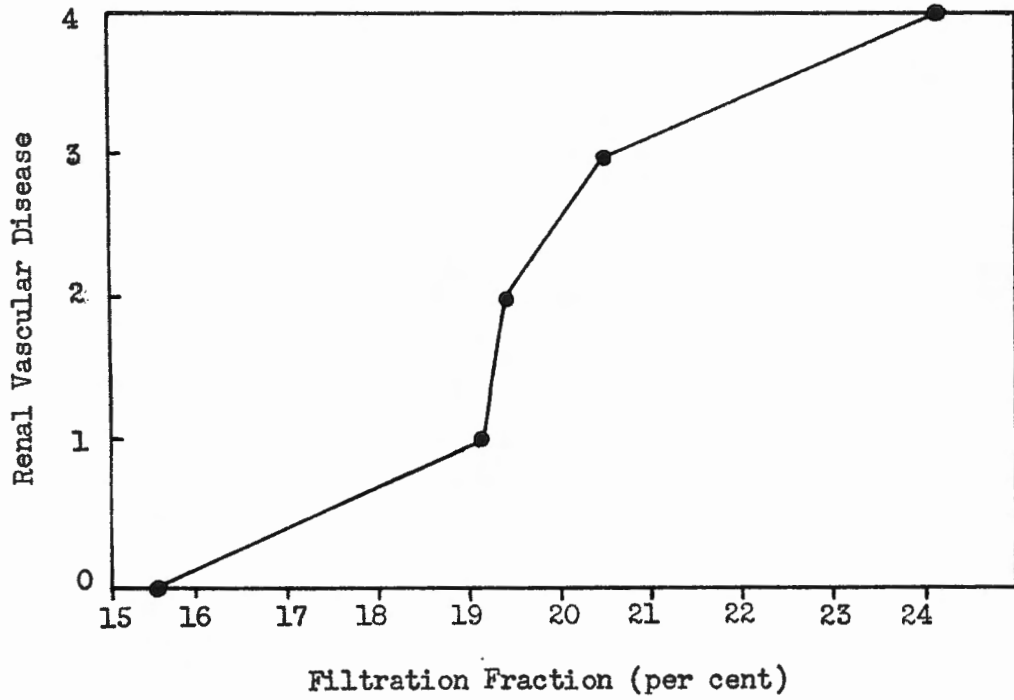
Fig. 11. Average filtration fraction for each of the
five grades of renal vascular disease.

renal vascular disease of grade 4. However, these investigators
observed, furthermore, that not all hypertensive individuals ex-
hibit these renal abnormalities. In the cases with grade 0 and 1
arteriolar sclerosis, the renal clearance observations were either
normal or only very slightly reduced. The filtration fraction was
normal in 7 of 8 cases in biopsy groups 0, 1, and 2; and normal in
5 of 11 cases in biopsy groups 3 and 4. Inasmuch as an elevated
filtration fraction has been construed to indicate efferent glomeru-
lar arteriolar constriction, it follows that efferent hypertonus
and the consequent ischemia are likewise not primary phenomena in
the genesis of hypertension.

Smith's renal clearance procedures have also yielded negative
results when applied to hypertensive patients by other investiga-
tors. Findley and associates (97) determined diodrast and inulin
clearances and diodrast-Tm in 12 subjects with presumably uncomp-
licated essential hypertension. The patients were all less than
50 years of age. They exhibited normal urea clearance and urinary
sediments and had minimal renal parenchyma damage, as indicated by
the absence of cardiac involvement and the appearance of the eye-
grounds. Seven of the 12 had normal values for diodrast-Tm and,
therefore, normal tubular function. None of the 12 showed an ele-
vated filtration fraction, and only 6 exhibited a decreased plasma
clearance and consequently a relative functional ischemia. The de-
crease in renal plasma flow, however, was not in disproportion to

the corresponding fall in inulin clearance in any case. Friedman
(92) similarly observed three patients with normal renal blood
flow in a series of 21 cases with hypertension, and Chesley and
Chesley (94) have reported three instances in a series of 11 hy-
pertensive women. Smith also observed three cases, even after de-
leting subjects with an abnormally high $C_{IN}/Tm_D$. Apparently a
demonstrable renal ischemia is not a constant finding in essential
hypertension.

Of interest in this connection are the epxeriments of Cox and
Dock (98) who determined the capacity of the vascular bed in kid-
neys of hypertensive and non-hypertensive individuals at autopsy.
Special precautions were taken to permit rigor of the blood vessels
to pass off or to counteract it by perfusion at high pressure so
that maximal rate of blood flow could be obtained. In order to
avoid decline in flow consequent on edema formation, kerosene was
employed as the perfusion medium in place of an aqueous solution.
The control group consisted of individuals who died with diseases
in which the kidneys were not directly involved and who had normal
heart weights. In the hypertensive group, the kidneys were from
individuals with marked cardiac hypertrophy and who each had pre-
vious records of a systolic blood pressure over 170 mm. Hg and a
diastolic pressure over 90 mm. Hg. The results are graphed in
Fig. 12. The kerosene perfusion rate revealed a striking decrease
in the capacity of the renal vascular bed between early maturity
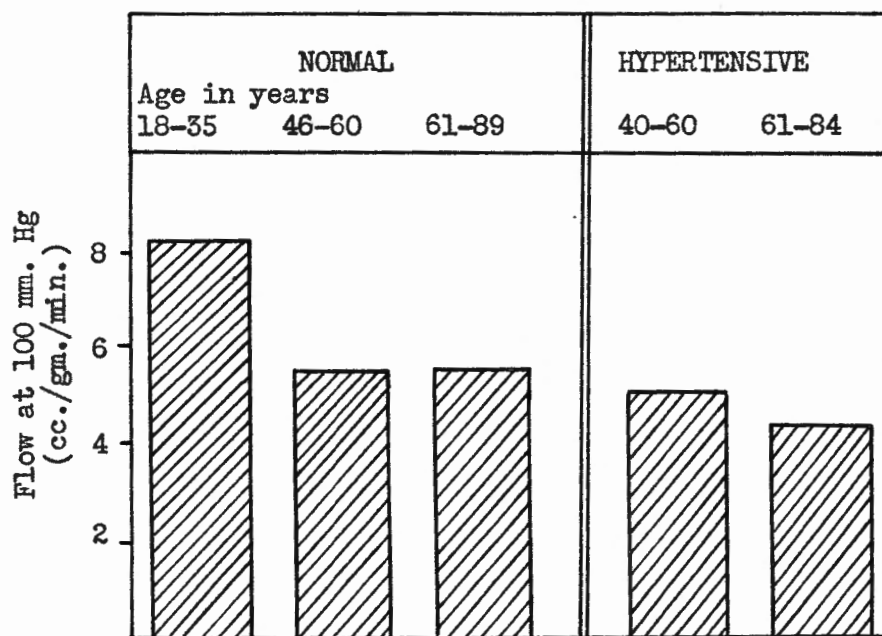(age 18 to 35) and senescence (age 45 to 60) of approximately

| | NORMAL | | | HYPERTENSIVE | |
|---|---|---|---|---|---|
| Age in years | | | | | |
| 18-35 | 46-60 | 61-89 | | 40-60 | 61-84 |

Fig. 12. Average value for kerosene flow in kidneys post-mortem.

25 per cent. The capacity of the renal vascular bed in hyperten-
sion was usually within the normal range for the corresponding
age group, but a few revealed considerable decreases in perfusion
rates.

The demonstration of normal renal blood flow in some instances
of essential hypertension and the observation that the perfusion
rate of kerosene in hypertensive kidneys is frequently normal indi-
cate that irregular hemodynamics do not necessarily obtain in hy-
pertensive kidneys. Thus renal ischemia and efferent glomerular
arteriolar constriction are apparently relegated to the sequelae
in essential hypertension and are not primary manifestations. More-
over, as observed by Castleman and Smithwick the normal renal vas-
cular state in some instances of hypertension is characterized by
the absence of renal arteriolar sclerosis. Nor are the demonstrable
perturbations in the renal vascular state, which subsequently ap-
pear in the course of essential hypertension, the result of renal
vascular disease. It is, therefore, obvious that renal vascular
disease is likewise merely another sequela in essential hyperten-
sion.

The hypothesis that renal arteriolar sclerosis is not the
cause of essential hypertension receives considerable support in
the numerous experimental and clinical observations which prove
conclusively that a protracted elevation in blood pressure produces
hypertension. As early as 1919, Moschcowitz (98) recorded the fol-

lowing.    "Whatever experimental evidence we possess seems to show
that arteriosclerosis is, sometimes at least, the result and not
the cause of a continuous state of hypertension.  The frequency of
arteriosclerotic lesions in animals after repeated injections of
such blood pressure raising substances as adrenaline, nicotine,
barium chloride, etc., are well known.  More convincing, because
a direct toxic effect is eliminated, are the experiments of Harvey
and Klotz who maintained a continuous hypertension in young ani-
mals by placing them in an inverted position for three minutes over
a period of 120 days at the end of which time marked sclerotic
changes in the blood vessels were manifest."  Goldblatt (19) ob-
served that when hypertension is produced in dogs by constriction
on one main renal artery, arteriolar sclerosis with hyalinization
of the arterioles develops after a time in the opposite kidney and
elsewhere but not in the kidney protected from the effects of high
blood pressure by the renal clamp.  Similarly, when one kidney of
a rat was subjected to partial constriction of the main renal ar-
tery, hydronephrosis, trauma, or cellophane compression, arterio-
lar sclerosis occurred in the opposite kidney with great regu-
larity (99, 100).  Acute arteriolar lesions structurally identical
with those of malignant hypertension in man have been demonstrated
in rabbits with arterial hypertension produced by constriction of
the renal artery.  Significantly, no arteriolar changes were ob-
served in the kidney the renal artery to which had been constricted
(101).    Evidently, arteriolar sclerosis may be produced experi-

mentally by an elevation of blood pressure. Arterioles protected from the effects of the high blood pressure do not become sclerotic.

The greater frequency and distribution of arteriolosclerosis in hypertensive individuals than in non-hypertensive individuals, as observed by Moritz and Oldt (14), suggests that arteriolosclerosis in humans is also produced by an elevated blood pressure. In fact Moritz and Oldt refer to "arteriolar changes secondary to chronic hypertension" which may "frequently effect such widespread organic reduction in lumen that the severity of the hypertension is increased, thus establishing a vicious circle." Moreover, the marked hypertrophy in the wall of the arterioles in vascular disease suggests hypertrophy in the face of excessive strain (103). This interpretation would mean that the change in the arteriole is secondary to hypertension.

Thus indirect evidence in humans and the experimental production of arteriolar sclerosis by an elevation of blood pressure in animals affords convincing evidence that arteriolar sclerosis may result from hypertension.

In summary, it may be concluded that renal arteriolar sclerosis is probably not concerned in the genesis of essential hypertension but rather is a sequela in view of the following points of evidence. Renal biopsies in 28 per cent of a series of patients with established hypertension reveal no or only insignificant vascular disease. Moreover, abnormalities in renal function in

essential hypertension, as demonstrated by recently developed
clearance procedures, cannot be attributed to renal arteriolar
sclerosis. Lastly, hypertension can produce renal arteriolo-
sclerosis. It is unlikely that arteriolar nephrosclerosis should
be both cause and effect of essential hypertension.

## Discussion

The determination of the relation which renal arteriolar scle-
rosis bears to essential hypertension is obviously of more than aca-
demic interest, especially with the advent of the surgical treat-
ment of the disease. If permanent structural changes in the renal
arterioles are primary, less can be expected of operations (95)
designed to relieve vascular spasm than if the spasm were primary
and the organic changes secondary.

The morphologic changes in the kidneys of patients who died
from essential hypertension have been well established. The struc-
tural pattern at death is informative but offers little information
regarding the intervening processes responsible for the terminal
picture. Recent efforts have been made to complete the gap and as
a result of these it is now possible to define more clearly the
status of renal arteriolar sclerosis in the etiology of essential
hypertension.

It is the contention of this thesis, on the basis of the evi-
dence reviewed, that renal arteriolar sclerosis is not the cause
of essential hypertension but merely a consequence of the disease
itself. The absence of significant arteriolar nephrosclerosis in
28 per cent of a series of clearly defined cases of essential hyper-
tension is irrefragable evidence which eliminates renal vascular
disease as an etiological factor in essential hypertension. The
objection, however, has been advanced that a great many sections

of the kidney must be examined before renal disease can be ex-
cluded. Thus Sachs (104) has recorded: "Scott (15,83) stated in
a recent paper that there are about 1,250,000 afferent arterioles
in each kidney. The pathologist who examines one or two routine
sections will see at most ten preglomerular arterioles, which is
one in 125,000. If he examined 100 sections, he will observe only
one in 12,500 preglomerular arterioles; hence it is difficult to
state with assurance that no arteriolar lesions exist." This objec-
tion is obviated by the results obtained from the 25 cases of essen-
tial hypertension in which Castleman and Smithwick (95) removed
biopsies from both kidneys. The morphologic appearance of the two
biopsies in each case were similar. Such a result could not be
fortuitous and therefore establishes the validity of the microscopic
observations. Furthermore, the instances of essential hypertension
with no renal vascular disease may not be regarded as cases in which
the hypertension is due to sclerosis of the main renal arteries in-
asmuch as this circumstance is observed only rarely at autopsy.

In contrast to the generally supposed integrity of renal func-
tion in the majority of cases of essential hypertension, Smith's
(85,86) renal clearance procedures have revealed very pronounced
derangements in renal function in the greater percentage of hyper-
tensive individuals. The abnormalities in renal function observed
have been construed to indicate a progressive destruction of renal
parenchyma, a relative ischemia of the residual, intact and func-
tioning parenchyma apparently due to efferent glomerular arteriolar

spasm, and that the relative ischemia precedes the destruction of renal parenchyma. It is evident from these interpretations that the phenomenon of renal arteriolar sclerosis does not lend itself to an explanation of the anomalies in renal function of hypertensive individuals. A pathological process supposedly responsible for the genesis of a disease should logically explain the manifestations characteristic of the disease. Failure of renal arteriolar sclerosis to conform to this principle is additional evidence opposing the primary role ascribed to it in the production of essential hypertension.

Moreover, a pathological state would not likely be both cause and consequence of a disease. Yet, if renal arteriolar sclerosis is accepted as the cause of essential hypertension, it must also be regarded as an effect of hypertension since convincing evidence has accrued which indicates that arteriolar sclerosis, in the kidneys and elsewhere, follows a protracted elevation in blood pressure.

The mainstay of the hypothesis that arteriolar nephrosclerosis is the cause of hypertension has been the high degree of correlation between arteriolar sclerosis and hypertension in one situation only, namely, the kidneys. The suggestion has been made that it is improbable that the renal arterioles should be more susceptible to the effects of high blood pressure than arterioles in the other organs and tissues of the body and therefore the only rational explanation for the high incidence of renal arteriolar disease in essential hypertension is to regard it as the initiating factor.

However, as Bell and Clawson (9) have emphasized, in whatever explanation one adopts for arteriolosclerosis, it is just as difficult to explain why the kidneys are affected so much more frequently and intensely in hypertension. Hypersusceptibility of the renal arterioles must be assumed in any case. Furthermore, necropsy reveals the end results of a morbid process with little information concerning the intervening sequence of events. Only the clinical course and experimental data derived from the patient in life indicate the mechanism of a disease. Information of this nature with respect to essential hypertension points unquestionably to renal arteriolosclerosis as a sequela in essential hypertension and not as the cause.

It is not the purpose of this thesis to arrive at a conception of the pathogenesis of essential hypertension but merely to prescribe the relation of renal arteriolar sclerosis to hypertension. However, because of the numerous observations which have been reviewed pertinent to the etiology, a few comments are in order. Evidence obtained in the study of experimental hypertension suggests that a deranged intrarenal hemodynamic state is responsible for the liberation of renin which in turn initiates the humoral mechanism eliciting the rise in blood pressure. A reduction in pulse pressure, rather than renal ischemia, appears to be the provocative circumstance. Renal ischemia is also probably not a primary factor in the genesis of essential hypertension in view of the normal

diodrast clearance exhibited in some cases and the normal perfu-
sion rate of kerosene in the majority of hypertensive kidneys at
autopsy. Reduction in pulse pressure may therefore be the ini-
tiating factor in essential hypertension. However, the manner in
which it becomes established is unknown. Moritz and Oldt (14) ob-
served that afferent arteriolar sclerosis may be widespread at a
time when there is little evidence of arteriolosclerosis elsewhere
in the body. Therefore Page (22) has suggested that the consequent
reduction in lumen of the afferent glomerular arterioles may be
responsible for the decrease in pulse pressure. Accordingly, renal
arteriolar sclerosis would be primarily responsible for essential
hypertension. In view of the evidence reviewed above this sugges-
tion appears untenable and other explanations must be sought for
the reduction in pulse pressure.

## Summary

An attempt has been made to expound the relation between re-
nal arteriolar sclerosis and essential hypertension.  In order to
provide a suitable backgorund for the evidence reviewed, the his-
torical development of the concept of essential hypertension, the
clinical picture of essential hypertension, the pathological his-
tology of arteriolar sclerosis, and experimental observations on
the pathogenesis of essential hypertension are presented.

Renal arteriolar sclerosis has been regarded as primary in the
genesis of essential hypertension principally because it is almost
a constant finding in the disease at autopsy; whereas,in non-hyper-
tensive individuals, it is observed only rarely.  This result ap-
parently becomes significant in view of the observation that the
relative frequency of arteriolosclerosis in other organs and tissues
in hypertensive and non-hypertensive cases is very nearly the same.

The principle evidence relegating renal arteriolar sclerosis
to a sequela in essential hpertension may be summarized as follows.
Renal biopeies in 28 per cent of a series of patients with estab-
lished hypertension revealed no or only insignificant vascular
disease.  Moreover, abnormalities in renal function in essential
hypertension, as demonstrated by recently developed clearance pro-
cedures, cannot be attributed to renal arteriolar sclerosis.
Lastly, hypertension can produce renal arteriolosclerosis.

An analysis of the evidence pro and con leads one to conclude beyond any reasonable doubt that renal arteriolar sclerosis does not antedate essential hypertension.

## Bibliography

1.  Bright, R.: Cases and observations illustrative of renal disease accompanied with the secretion of albuminous urine, Guy's Hosp. Rep. 1:338, 1836

2.  Johnson, G.:  On certain points in the anatomy and pathology of Bright's disease of the kidney; and secondly, on the influence of the minute blood vessels upon the circulation, M. Chir. Tr. London 51:57, 1868

3.  Gull, W.W., and Sutton, H.G.:  On the pathology of the morbid state commonly called "chronic Bright's disease with contracted kidney," M. Chir. Tr. 55:273, 1872

4.  Mahomed, F.A.:  The etiology of Bright's disease and the pre-albuminuric stage, Brit. Med. J. 1:585, 1874

5.  Von Basch, S.:  Ueber die messung des blutdrucks am menschen, Ztschr. f. klin. Med. 2:79, 1881

6.  Huchard, H.:  Trait'e clinique des maladies du coeur et de l'aorte.  Second edition, Paris, O. Doin, 1893, p. 892.  (quoted from Fishberg, A.M.: Hypertension and nephritis.  Fourth edition. Phila., Lea & Febiger, 1939.)

7.  Allbutt, T.C.:  Abstracts, Trans. Hunterian Soc., p. 38, 1895-96; Diseases of arteries including angina pectoris, London, vol. 1, 1915. (quoted from Fishberg, A.M.: Hypertension and nephritis.  Fourth edition.  Phila., Lea & Febiger, 1939.)

8.  Janeway, T.C.:  A clinical study of hypertensive cardiovascular disease, Arch. Int. Med. 12:755, 1913

9.  Bell, E.T., and Clawson, B.J.:  Primary (essential) hypertension, Arch. Path. 5:939, 1928.

10.  Volhard, F.:  The kidney in health and disease.  Phila., Lea and Febiger, 1935.  (quoted from Moritz, A.R., and Oldt, M.R.: Arteriolar sclerosis in hypertensive and nonhypertensive individuals, Am. J. Path. 13:679, 1937.)

11.  Fishberg, A.M.:  Hypertension and nephritis.  Fourth edition. Phila., Lea & Febiger, 1939.

12. Goldblatt, H.: Experimental hypertension induced by renal ischemia, The Harvey lectures. Baltimore, Williams & Wilkins, 1938.

13. Frank, E.: Deutsch. Arch. f. Klin. Med. 103:497, 1911. (quoted from Fishberg, A.M.: Hypertension and nephritis. Fourth edition. Phila., Lea & Febiger, 1939).

14. Moritz, A.R. and Oldt, M.R.: Arteriolar sclerosis in hypertensive and nonhypertensive individuals, Am. J. Path. 13:679, 1937.

15. Scott, R. W.: Hypertension a century after Bright, J. A. M. A. 111:2461, 1938

16. Thomson, W.W.D.: The renal aspects of essential vascular hypertension, Brit. Med. J. 2:910, 1933.

17. Christian, H. A.: Circulatory tonics versus circulatory depressants in cardiovascular renal disease with hypertension, J. A. M. A. 86:931, 1926.

18. Granger, A. S.: The present concept of essential hypertension, J. A. M. A. 93:819, 1929.

19. Lewis, H. A., and Goldblatt, H.: Studies on experimental hypertension, Bull. New York Acad. Med. 18:459, 1942.

20. Fishberg, A. M.: Anatomic findings in essential hypertension, Arch. Int. Med. 35:650, 1925.

21. Yater, W.M.: Fundamentals of internal medicine. New York, D. Appleton-Century, 1942.

22. Page, I.H.: Arterial hypertension, J. Urol. 46:807, 1941.

23. Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W.: Studies in experimental hypertension; the production of persistent elevation of systolic blood pressure by means of renal ischemia, J. Exper. Med. 59:347, 1934.

24. Kapp, F., Friedland, C. K., and Landis, E.M.: Skin temperature of hypertensive rabbits and pressor effects of heated kidney extracts, Am. J. Physiol. 131:710, 1940-41.

25. Prinzmetal, M., and Wilson, C.: Nature of peripheral resistance in arterial hypertension with special reference to vasomotor system, J. Clin. Investigation 15:63, 1936.

26.  Goldblatt, H.:  Studies on experimental hypertension; the production of persistent hypertension in monkeys (macaque) by renal ischemia, J. Exper. Med. 65:671, 1937.

27.  Wilson, C., and Byrom, F.B.:  Renal changes in malignant hypertension, Lancet 1:136, 1939.

28.  Pickering, G. W., and Prinzmetal, M.:  Experimental hypertension of renal origin in the rabbit, Clin. Sc. 3:357, 1937-38.

29.  Goldblatt, H. Kahn, J., and Lewis, H. A.:  Experimental hypertension in goats and sheep, to be published.  (quoted from Lewis, H. A. and Goldblatt, H.:  Studies on experimental hypertension, Bull. N. Y. Acad. Med. 18:459, 1942.

30.  Goldblatt, H.:  Studies on experimental hypertension; pathogenesis of experimental hypertension, due to renal ischemia, Ann. Int. Med. 11:69, 1937-38.

31.  Gibson, J. G., 2d, and Robinson, R. W.:  Blood volume, cardiac size and renal function in dogs with hypertension produced by Goldblatt technique, Proc. Soc. Exper. Bio. & Med. 39:497, 1938.

32.  Page, I. H.:  The production of persistent arterial hypertension by cellophane perinephritis, J. A. M. A.  113:2036, 1939.

33.  Blalock, A., and Levy, S. E.:  Studies on the etiology of renal hypertension, Ann. Surg. 106:826, 1937.

34.  Glenn, F., Child, C. G., and Heuer, G. J.:  Hypertension experimentally produced by constricting artery of a single transplanted kidney; additional observations, Ann. Surg. 107:618, 1938.

35.  Allen, F. M.:  Auscultatory estimation of the blood pressure of dogs, J. Metab. Res. 4:431, 1923.

36.  Longscopy, W. T., and McClintock, A. T.:  The effect of permanent constriction of the splanchnic arteries and the association of cardiac hypertrophy with arteriosclerosis, Arch. Int. Med. 6:439, 1910.

37.  Goldblatt, H., and Kahn, J. R.:  Experimental hypertension. Constriction of the aorta at various levels, J. A. M. A. 110:686, 1938.

38.  Page, I. H.:  Relationship of extrinsic renal nerves to origin of experimental hypertension, Am. J. Physiol, 112:166, 1935.

39.  Goldblatt, H., Gross, J., and Hanzal, R. F.:  Studies on experimental hypertension; effect of resection of splanchnic nerves on experimental renal hypertension, J. Exper. Med. 65:233, 1937.

40.  Goldblatt, H., and Wartman, W. B.:  Studies on experimental hypertension; effect of section of anterior spinal nerve roots on experimental hypertension due to renal ischemia, J. Exper. Med. 66:527, 1937.

41. Verney, E. B., and Vogt, M.:  An experimental investigation into hypertension of renal origin with some observations on convulsive "uremia," Quart. J. Exper. Physiol. 28:253, 1938.

42.  Freeman, N. E., and Page, I. H.:  Hypertension produced by constriction of the renal artery in sympathectomized dogs, Am. Heart J. 14:405, 1937.

43.  Goldblatt, H.:  Studies on experimental hypertension; pathogenesis of experimental hypertension due to renal ischemia, Ann. Int. Med. 11:69, 1937-38.

44.  Solandt, D. Y., Hassim, R., and Cowan, C. R.:  Hypertensive effect of blood from hypertensive dogs, Lancet 1:873, 1940.

45.  Page, I. H.:  Demonstration of the liberation of renin into the blood stream from kidneys of animals made hypertensive by cellophane perinephritis, Am. J. Physiol. 130:22, 1940.

46.  Braun-Menendez, E., Fasciolo, J. C., Leloir, L. F., and Munoz, J. M.:  The substance causing renal hypertension, J. Physiol.  98:283, 1940.

47.  Tigerstedt, R. and Bergman, P. G.:  Niere und Drieslauf, Skandinav. Arch. f. Physiol, 8:223, 1898. (quoted from Lewis, H. A., and Goldblatt, H.:  Studies on experimental hypertension, Bull, N. Y. Acad. Med. 18:459, 1942.

48.  Helmer, O. M., and Page, I. H.:  Purification and some properties of renin, J. Biol. Chem. 127:757, 1939.

49.  McEwen, E. G., Harrison, S. P., and Ivy, A. C.:  Tachyphylaxis to renin, Proc. Soc. Exper. Biol. & Med. 42:254, 1939.

50.  Page, I. H., Kohlstaedt, K. G., and Helmer, O. M.:  The activation of renin by blood, Am. Heart J. 19:92, 1940.

51.  Page, I. H., and Helmer, O. M.:  A crystalline pressor substance (antiotonin) resulting from the reaction between renin and renin-activator, J. Exper. Med. 71:29, 1940.

52. Abell, R. R., and Page, I. H.: Vascular reactions to renin and angiotonin, Biol. Bull 79:357, 1940.

53. Plentl, A. A., and Page, I. H.: Enzymatic nature of angiotonin formation from renin and renin activator, J. Biol. Chem. 147:135, 1943.

54. Page, I. H., and Helmer, O. M.: Antiotonin-activator, renin- and angiotonin-inhibitor and the mechanism of angiotonin tachyphylaxis in normal, hypertensive, and nephrectomized animals, J. Exper. Med. 71:495, 1940.

55. Page, I. H.: Nature of arterial hypertension, J. Missouri Med. Ass. 39:237, 1942.

56. Harrison, T. R., Grollman, A., and Williams, J. R., Jr.: The antipressor action of renal extracts and their capacity to reduce blood pressure of hypertensive rats, Am. J. Physiol. 128:716, 1940.

57. Page, I. H., Helmer, O. M., Kohlstaedt, K. G., Fouts, P. J., Kempf, G. F., and Corcoran, A. C.: Substance in kidneys and muscle eliciting prolonged reduction of blood pressure in human and experimental hypertension, Proc. Soc. Exper. Bio. & Med. 43:722, 1940.

58. Levy, S. E., Light, R. A., and Blalock, A.: The blood flow and oxygen consumption of the kidney in experimental renal hypertension, Am. J. Physiol. 122:38, 1938.

59. Mason, M. F., Blalock, H., and Hansen, T. R.: Direct determination of renal blood flow and renal oxygen consumption of unanesthetized dog, Am. J. Physiol. 118:667, 1937.

60. Van Slyke, D. D., Rhoads, C. P., Hiller, A. M., and Alving, A. S.: Relationships between urea excretion, renal blood flow, renal oxygen consumption and diuresis; the mechanism of urea excretion, Am. J. Physiol. 109:324, 1934.

61. Corcocran, A. C., and Page, I. H.: Observations on the relationship of experimental hypertension to renal clearance and renal ischemia, Am. J. Physiol. 123:143, 1938.

62. Corcoran, A. C. and Page, I. H.: The effects of renin, pitressin, and pitressin and atropine on renal blood flow and clearance, Am. J. Physiol. 126:354, 1939.

63. Page, I. H., and Corcoran, A.C.: Renal venipuncture: A method of explanation of the kidney for venipuncture in dogs, Surgery 7:389, 1940.

64. Corcoran, A. C., and Page, I. H.: Renal blood flow in experimental hypertension due to constriction of the renal artery, Am. J. Physiol. 133:

65. Corcoran, A. C., and Page, I. H.: Renal aspects of experimental and clinical hypertension, J. Lab. Clin. Med. 26:1713, 1941

66. Mason, M. F., Robinson, C. J., and Blalock, A.: Studies on the renal arterial blood pressure and the metabolism of kidney tissue in experimental hypertension, J. Exper. Med. 72:289, 1940.

67. Levy, S. E., Robinson, C. J., and Blalock, A.: The effect of altering the renal blood pressure and blood flow on the glomerular filtration of a transplanted kidney in unanesthetized dogs, Am. J. Physiol. 123:383, 1938.

68. Corcoran, A. C., and Page, I. H.: The effects of antiotonin on renal blood flow and glomerular filtration, Am. J. Physiol. 130:335, 1940.

69. Friedman, B., Abramson, D. I., and Marx. W.: Pressor substance in the cortex of the kidney, Am. J. Physiol. 124:285, 1938.

70. Kohlstaedt, K. G., and Page, I. H.: The liberation of renin by perfusion of kidneys following reduction of pulse pressure, J. Exper. Med. 72:201, 1940.

71. McMaster, P. D., and Parsons, R. F.: The effect of the pulse upon the formation and flow of lymph, J. Exper. Med. 68:353, 1938.

72. Page, I. H.: The nature of clinical and experimental arterial hypertension, J. Mt. Sianai Hosp. 8:3, 1941.

73. Leiter, L.: "Unusual hypertensive renal disease." 1. Occlusion of renal arteries (Goldblatt hypertension). 2. Anomalies of urinary tract. J. A. M. A. 111:507, 1938.

74. Freeman, G., and Hartley, G., Jr.: Hypertension in a patient with solitary ischemic kidney, J. A. M.A. 111:115, 1938.

75. Riskind, L. A., and Greene, H. H.: Renal torsion with ischemia causing hypertension, J. A. M. A. 119:1016, 1942.

76. McCann, W. S., and Romansky, M. J.: Orthostatic hypertension, J. A. M. A. 115:573, 1940.

77. Rytand, D. A.: Renal factor in arterial hypertension with coarctation of aorta, J. Clin. Invest. 17:391, 1938.

78. Steele, J. M., and Cohn, A. E.: The nature of hypertension in coarctation of the aorta, J. Clin. Invest. 17:514, 1938.

79. Friedman, M., Selzer, A., and Rosenblum, H.: The renal blood flow in coarctation of the aorta, J. Clin. Invest. 20:107, 1941.

80. Fishberg, A. M.: Hypertension due to renal embolism, J. A. M. A. 119:551, 1942.

81. Prinzmetal, M., Hiatt, N., and Tragerman, L. J.: Hypertension in a patient with bilateral renalinfarction, J. A. M. A. 118:44, 1942.

82. Blatt, E., and Page, I. H.: Hypertension and constriction of the renal arteries in man, Ann. Int. Med. 12:1690, 1939.

83. Scott, R.W.: Arterial hypertension, J. A. M. A. 120:1, 1942.

84. Farrell, J. I., and Young, R. H.: Hypertension caused by unilateral renal compression, J. A. M. A. 118:711, 1942.

85. Smith, H. W.: Physiology of the renal circulation, The Harvey lectures, Baltimore. Williams & Wilkins. Vol. 35, 1939-40.

86. Smith, H. A.: Physiology of the kidney, The Porter lectures, Univ. of Kansas, 1939.

87. Smith, H. W., Goldring, W., and Chasis, H.: The measurement of the tubular excretory mass, effective blood flow, and filtration rate in normal human kidney, J. Clin. Invest. 17:263, 1938.

88. Goldring, W., Chasis, H., Ranges, H. A., and Smith, H. W.: Effective renal blood flow in subjects with essential hypertension, J. Clin. Invest. 20:637, 1941.

89. Leadbetter, W. F., and Burkland, C. E.: Hypertension in unilateral renal disease, J. Urol, 39:611, 1938.

90. Boyd, C. H., and Lewis, L. G.: Nephrectomy for arterial hypertension, Preliminary report, J. Urol. 39:627, 1938.

91. Chassis, H., and Redish, J.: Effective renal blood flow in the separate kidneys of subjects with essential hypertension, J. Clin. Invest. 20:655, 1940.

92. Friedman, M., Selzer, A., and Rosenblum, H.: The renal blood flow in hypertension, J. A. M. A. 117:92, 1941.

93. Foa, P. P., Woods, W. W., Peet, M. M., and Foa, N. L.:
Effective renal blood flow, glomerular filtration rate and
tubular excretory mass in arterial hypertension, Arch. Int.
Med. 69:882, 1942.

94. Chesley, L. C., and Chesley, E. R.: Renal blood flow in
women with hypertension and renal impairment, J. Clin. Invest.
19:475, 1940.

95. Castleman, B., and Smithwick, R.H.: The relation of vascular
disease to the hypertensive state, J. A. M. A. 121:1256, 1943.

96. Talbott, J. H., Castleman, B., Smithwick, R. H., Melville,
R. S., and Pecora, L. J.: Renal biopsy studies correlated with
renal clearance observations in hypertensive patients treated by
radical sympathectomy, J. Clin. Invest. 22:387, 1943.

97. Findley, T., Edwards, J. C., Clinton, E., and White, H. L.:
Clearance of diodrast, phenolsulfenephthalein, and inulin in hy-
pertension and in nephritis, Arch. Int. Med. &0:935, 1942.

98. Cox, A.J., Jr., and Dock, W.: The capacity of the renal vas-
cular bed in hypertension, J. Exper. Med. 74:167, 1941.

99. Moschcowitz, E.: Hypertension, its significance, relation to
arteriosclerosis and nephritis, and etiology, Am. J. Med. Sci.
158:668, 1919.

100. Wilson, C., and Byron, F. B.: The vicious circle in chronic
Bright's disease, Quart. J. Med. 10:65, 1941.

101. Schroeder, H. A., and Neuman, C.: Arterial hypertension in
rats, effects on kidneys, J. Exp. Med. 75:527, 1942.

102. Wilson, C., and Pickering, G. W.: Acute arterial lesions in
rabbits with experimental renal hypertension, Clin. Sci. 3:343:1938.

103. Keith, N.M., Wagner, H.P., and Kernohan, J. W.: Syndrome of
malignant hypertension, Arch. Int. Med. 4:141, 1928.

104. Sachs, A.: Renal hypertension, J. Omaha Mid-West Clin. Soc.
4:9, 1943