1947

Surgical treatment of hypertension

Carl Donald Koutsky
University of Nebraska Medical Center

THE SURGICAL TREATMENT OF HYPERTENSION

Carl D. Koutsky

Senior Thesis

Presented to the College of Medicine

University of Nebraska, Omaha

1947

Table of Contents

THE SURGICAL TREATMENT OF ESSENTIAL HYPERTENSION

Introduction

Hypertension is related to more deaths in the United States than any other disease. According to Page and Corcoran[51] in their recent edition on hypertension, 90% of all patients suffering from this disease have the essential type. In 1943, there were 1,459,544 deaths in the United States; 44% were due to cerebral hemorrhage, cerebral thrombosis, hemiplegia, chronic nephritis, and heart disease (excluding rheumatic heart disease). At least 40% of these conditions were associated with hypertension. Malignant tumors caused 169,000 deaths in the same year.[36] If 90% of the deaths due to hypertension were of the essential group, then essential hypertension far exceeds malignancy as a cause of death.[36] About 15% of all adults have high blood pressure, and 23% of all deaths in the population over fifty years of age are due to this cause.[14]

Craig[14] defines arterial hypertension as a systolic pressure of 140 mm. of mercury or more and a diastolic pressure of 90 mm. of mercury or more.[48] Page has listed fifty causes of hypertension under five major headings including renal, cerebral, cardiovascular, endocrine, and unknown. Hypertension of unknown etiology, primary

hypertension, or essential hypertension are the same entity; therefore, a diagnosis of this disease is made only by eliminating the other types of hypertension. Through laboratory and physical examination and history taking, such factors as coarctation of the aorta, kidney pathology, and endocrine malfunction, including adrenal tumors, are excluded.[14]

Any disease process of unknown etiology has many treatments prescribed. The latest attempt at treatment of hypertension is surgical. This more radical treatment has been brought about by two factors. The first factor was the prognosis of the disease. Keith, Wagener, and Barker[40] divided hypertension into four degrees of severity, and in 1939, published the prognosis of the groups on a four year mortality basis. The first group had a 30% mortality, the second group 42%, the third group 78%, and the fourth group 98%. The second factor stimulating surgical intervention was the unsatisfactory results obtained from medical treatment. Drugs used fail to produce lasting and definite results, and often have side reactions.[14] It is the object of this paper to evaluate the surgical treatment of essential hypertension as it is practiced today.

PART I: Essential Hypertension

1. Etiology

The modern concept of the etiology of essential hypertension became popular with the publication of Goldblatt's experiments. Through disruption of the circulation in the kidney by various methods, he was able to produce hypertension in dogs. He constricted one main renal artery with a clamp and produced transient hypertension; however, if he constricted both renal arteries, or removed a kidney and constricted one artery, the hypertension became permanent.[27] By constricting the abdominal aorta above the kidney, he produced hypertension; while constriction below the kidney was ineffective.[26] He concluded that renal disturbance was of etiological importance in this disease. This work has been repeated by Pickering and Prinzmetal[60] in the rabbit with the same results. Blalock and Levy in 1939,[4] reported an experiment that included complete occlusion of the celiac axis, and the inferior and superior mesenteric arteries in dogs. This did not cause a sustained rise in blood pressure, nor did occlusion of arteries of the extremities or head. Kohlstaedt and Page[41] compressed a renal artery in a dog without evidence

of diminished blood flow through the kidney, thus reducing pulse pressure, but not producing ischemia; hypertension resulted.[47]

Page in 1939, produced persistent hypertension by enclosing the kidney in a cellophane sac which resulted in a constricting capsule of scar tissue and ischemia of the kidney. The kidney was shown to contain increased amounts of renin.[35] This combined with a renin activator in the blood to produce angiotonin, a pressor reagent.[50] Normal kidney tissue contains an antipressor reagent that inactivates angiotonin, and this substance has been actually used to treat hypertensive patients.[52] Page attempted to show that a circulatory hormone was important in producing hypertension;[47,50,52] however, in 1945, Gregory and co-workers,[29] by using a special bio-assay method, failed to demonstrate any such circulating vasoconstrictor substance. They assayed the material from plasma of patients with normal blood pressure, with essential hypertension, and with high blood pressure produced by injection of angiotonin. The vasoconstrictor substance was demonstrated to be significantly higher in only the patients receiving angiotonin injections. According to their findings essential

hypertension is probably not due to an increased production of angiotonin.[54] Page and Heuer denervated the kidneys in a patient with severe high blood pressure. They did not produce any lowering of the blood pressure and concluded that the nervous mechanism of the kidney had little to do with essential hypertension.

These experiments leave no one important theory or factor predominant. Both the renal neurogenic and renal hormone theories have advocates.[66] Schroeder believes there is a "constitutional component" which predisposes individuals to high blood pressure. This may be due to heredity or environment, but the implication is of a sympathetic reaction on the blood vessels increasing peripheral resistance, or at least causing the vascular system to be more easily subjected to whatever causes high blood pressure. Another factor that could possibly have an effect on hypertension is the adrenal gland. There is evidence that hyperadrenalism may be the most important theory.[59] Perara reported a case of essential hypertension who developed hypo-adrenalism. He had a persistent high blood pressure as long as he received desoxycorticosterone; however, when put on salt therapy alone the blood pressure returned to normal

limits.

Recent advances in the study of kidney function may uncover more evidence concerning the renal theory of hypertension.[70,71,72,73,74] Using diodrast, inulin, and phenol red clearance tests, the function of glomeruli and tubules can be studied separately, as well as the amount of urine flowing through a kidney in a given period of time. Under basal conditions it is found that only 50% of the kidney functions, and that the function is not changed with spinal anaesthesia; demonstrating that under resting conditions the autonomic system does not alter renal blood flow. If a stimulus is applied to the patient, renal blood flow is immediately reduced, also a lowered renal blood flow results when the patient assumes the upright position. The diminished flow results from constriction of afferent renal arterioles. Adrenine produces constriction of the efferent glomerular arteriol, and an increase in body temperature causes an increase in renal blood flow. An examination was made of the kidneys in hypertensive patients.[73] Under basal conditions renal blood flow was below normal, accompanied by early and progressive loss of the tubular function of the kidney caused by con-

striction of the efferent arterioles.

After considering the progress made in the study of etiological factors, the only conclusion that can be drawn is that we do not know what causes hypertension; however, most evidence today points to some kidney pathology in a chain of events resulting in high blood pressure.

2. Pathology and Physiology

As in any disease that produces a strain on the cardiovascular system it is expected to find at post-mortem examination evidence of involvement of the heart and blood vessels. A group at the Mayo clinic (1939) published a report on the pathology of severe hypertension.[39,44,45,63] They found arteriosclerotic involvement of the myocardium, pancreas, liver, gastro-intestinal tract, spleen, and brain. The lesions were widespread and were both arterial and arteriolar. At autopsy, with the exception of the spleen, the kidney is the most frequent and most marked organ involved.[79]

The renal character of hypertension was first noted by Richard Bright in 1836; however, Gull, in 1872, stated that the disease was due to a widespread vascular pathology.[39] The important factor is the physiological process causing the disease, whether it be local in the kidney or generalized.[15] Craig and Brown in their discussion of the rationale of splanchnicectomy mentioned the following events in the production of arteriosclerosis. The first and only finding of early hypertension was a hyperactive reaction to the cold pressor test; this reaction became

more active as the hypertension increased. A group of normal subjects with an immediate family history were given the cold pressor test, and 75% were found to react abnormally. They concluded from the above findings that a constitutional factor caused excess wear and tear on the arterioles resulting in an irreversible pathology if allowed to progress long enough. Their suggested treatment was to stop the wear and tear by means of splanchnicectomy.

As in most sound therapy, the physiological process of the disease is the basis of treatment. There are several important factors characteristic of the function of the vaso-motor system which will be discussed in relation to hypertension and sympathectomy.

Normal blood pressure is maintained by three factors: cardiac output, blood volume and viscosity, and peripheral resistance to blood flow.[14] It is the last factor that is abnormal in hypertension and is one of the objects of surgical treatment. A narrowing of the caliber of the peripheral vessels causes an increased resistance, and by sympathectomy it is attempted to release the constrictor influence. The maintenance of normal blood pressure is not significantly changed by section of the sympathetic

nerves.[12] Hypertension does not seem to be a symptom or response to bodily needs of any sort. Patients that have a decrease of high blood pressure feel better, and their kidneys function better; therefore, the surgical treatment of hypertension should not alter the normal maintenance of blood pressure, but it should relieve patients of symptoms and increase their well being. This is brought about by three possible results of extensive sympathectomy: release of vasospasm, increased blood supply to the kidneys, and decrease in the activity of the adrenal gland in its secretion of adrenine.[14]

White and Smithwick[79] summarized physiological factors important in any attempt to denervate structures of sympathetic innervation.[32,33,34,68] Because chemical substances establish the pathway over which a stimulus travels, any nerve cell that has not been cut in an area of attempted denervation is able to produce secretions causing reaction of the denervated cell.[68] This reaction is enhanced by the fact that neuro-effector mechanisms become hyperreactive when ganglionic fibers degenerate, and are set off by minute doses of chemical mediators. The reaction is twice as great after postganglionic

denervation, as compared to preganglionic denervation.[34] Cannon states a general law of denervation as, "When in a series of efferent neurons a unit is destroyed, an increased irritability to chemical agents develops in the isolated structure or structures, the effect being maximal in the part directly denervated."[10]

The regeneration of excised nervous tissue is also a problem to consider. Normal control of blood pressure returns in six months after complete sympathectomy in dogs.[32] Sympathetic growth appears after bilateral removal of the entire sympathetic chain.[33] Preganglionic regeneration is seen even after removal of postganglionic neurons. Restoration of sympathetic activity to some degree occurs after any sympathectomy.[79,69]

When the innervation is interrupted to striated muscle tissue, paralysis results. Smooth muscle paralysis reacts differently. This is due to sensitization of neuro-effector mechanisms to hormones,[34] intrinsic maintenance of muscle tone,[11] and nervous activity assumed by peripheral sympathetic ganglia.[28] These factors make lasting paralysis impossible; however, the degree of dilatation as measured by Brown and Adson[7] remains. The ratio of the arterial wall to the lumen changes from a

normal of 1:2 to 1:3.5.

Three factors are important to any sympathectomy: The denervation must be as complete as possible; it should inhibit regeneration as much as possible; and preganglionic section should be performed because it leaves a lesser degree of sensitization to chemical activators.[79]

3. Anatomy

There are several anatomical considerations that must be reviewed before the surgical problems and technics can be appreciated. The following was taken from White and Smithwick,[79] and a more detailed discussion is available in their book; only general facts and those of importance to this subject will be mentioned. It has been shown that the autonomic nervous system starts as high as the premotor cortex, and descends to the diencephalin, midbrain, and medulla, which are centers of autonomic activity. How the neurons leave these centers and get to the spinal cord is still not certain. In the thoracic segments the axons synapse with sympathetic motor cells in the intermediolateral column, and fibers are given off to peripheral ganglia. Vasomotor functions are bilaterally represented.

Visceral afferent fibers enter the spinal cord in the posterior roots and transmit visceral sensations to the thalamus. The cells lie in the dorsal root ganglia just as in the somatic system. It is still a question as to how the neurons travel; however, several parts of the cord, including both white and gray matter, such as

the posterior horn, spinothalamic tract, and the tract of Lissauer have been shown to contain visceral afferent functions. Peripherally, axons go through the posterior roots, and the white and gray rami to the various plexuses.

Grossly, the sympathetic nervous system is represented by two paravertebral ganglionated chains consisting of twenty-four ganglia and running parallel to the vertebral column. Each sympathetic ganglion is connected with a spinal nerve by the rami communicantes, except the fifth lumbar ganglion and the cervical ganglia. The chain runs from the base of the skull to the coccyx and fuses in front of the coccyx in the ganglion impar. The cervical ganglia are formed into the superior, middle, and inferior cervical ganglia. The inferior may also be joined with the first thoracic which is known as the stellate ganglion. The remaining ganglia are not as large as the stellate and cervical and compose the rest of the chain.

Ganglia serve as distributing centers to the glands and smooth muscle of the entire body. Of surgical importance are the many variations that may occur in the distribution of the fibers. The spinal ganglia in the

thoracic and upper lumbar region give off a white ramus communicans to the corresponding sympathetic ganglia. The myelinated fibers of the white rami originate in the intermediolateral cell column and are the preganglionic axons which end in the sympathetic ganglion and synapse with many postganglionic neurons. Gray rami communicantes are an outlet for the postganglionic neurons to peripheral structures. There are no white rami in the lower lumbar or sacral segments.

Distribution to peripheral structures varies with the function and location of the parts concerned. Preganglionic axons that enter a sympathetic ganglion may synapse there, run up or down the chain and synapse in other ganglia, or go through to synapse outside the chain in a plexus. Each preganglionic fiber synapses with several postganglionic neurons; this is the reason for the general response to sympathetic stimuli.

Gray rami that go to the spinal nerves are regular in size, but the rami that go to the viscera vary greatly in size. The most important of these rami are the cardiac nerves and the splanchnic nerves. Cardiac nerves originate from the cervical ganglia, and splanchnic

nerves originate from the third to the twelfth thoracic ganglia. The major splanchnic is usually made up from the fifth to the tenth thoracic segments; however, contributions as high as the third thoracic segment have been found. It innervates the stomach, small intestine, blood vessels of the abdomen, liver, pancreas, and part of the large intestine. The minor splanchnic innervates the adrenal gland and receives gray rami from the tenth and eleventh thoracic segments. The least splanchnic originates from the twelfth thoracic segment and ends in the renal plexus, innervating the adrenal gland and the kidney, along with the first lumbar and possibly the second lumbar nerves.[19]

If we attempt to denervate the kidneys and the adrenal glands, and release maximun vasospasm of the splanchnic area, then interruption of sympathetic fibers from the fifth thoracic through the second lumbar segments is necessary. Various anatomical factors will again be mentioned in the sections considering the technics.

PART II: Surgical Treatment

1. History of Surgical Treatment

In certain forms of primary vasospastic disease, sympathetic ganglionectomy causes permanent vasodilatation. This factor led to the attempt of producing permanent vasodilatation in hypertension.[6] Jean,[37] in 1921, and Danielopolu,[21] in 1923, suggested the resection of the splanchnic nerves for the treatment of hypertension. Rountree and Adson performed a bilateral lumbar sympathetic ganglionectomy for hypertension in 1925, removing the second, third, and fourth lumbar ganglia on both sides.[64] The effect was only transient, and it was their opinion that insufficient vascular areas had been denervated. Unilateral resection of the splanchnic nerves was attempted in the treatment of intestinal atomy by Pieri,[61] 1927. These men took the first steps in the treatment of disease through interruption of sympathetic innervation.

In 1929, Peet[55] sectioned the splanchnics for gastric crisis and severe abdominal pain using the supradiaphragmatic approach.[58] Pereira (1929) objected to the necessary resection of bone in the supradiaphragmatic approach

and in the danger of injuring the pleural sac. He suggested section of the splanchnics below the diaphragm avoiding resection of bony structure. In 1930, Adson[2] attempted to relieve gastric crisis in a patient by resecting the dorsal and ventral nerve roots from the sixth thoracic to the second lumbar segments. The patient was not noticeably inconvenienced by the paralysis of the abdominal muscles.

From the above surgical procedures, several methods of disrupting sympathetic impulses to the splanchnic area have been devised. The more popular or important practices that have been used and are still being used in the treatment of hypertension will be discussed. These include celiac ganglionectomy, resection of the anterior nerve roots (rhizotomy), and splanchnicectomies, using the sub-, trans-, and supra-diaphragmatic approach. Subtotal adrenalectomy, although not a sympathectomy in the true sense of the word, must be considered also.

2. Subtotal Adrenalectomy and Celiac Ganglionectomy

DeCourcy, (1934)[23] on the theory that essential hypertension was due to the hyperplasia of the adrenal medulla under constant sympathetic stimulation, removed a portion of the excess tissue and reportedly aided sixteen patients. In 1915, Crile tried unilateral adrenalectomies on a series of eleven cases, and only transient falls in blood pressure resulted. Next, bilateral denervation of the adrenals was tried, and this also failed.[16] These results led Crile to abandon the practice.[67] However, workers as late as 1946, still believe that hyperadrenalism is the cause of essential hypertension and advise subtotal adrenalectomy. Since the adrenal glands are essential to life the operation has no little risk. Faulty judgement at the time of operation could cause either adrenal deficiency or lack of any effect on the hypertension.[20] This method of surgical treatment immediately has two major faults: It does not produce results, and it is a hazardous operation.[55]

Crile, after abandoning adrenalectomy,[16] advocated celiac ganglionectomy in the treatment of hypertension.[18]

The operation consists of bilateral excision of the celiac ganglia and resection of the major and minor splanchnic nerves.[16] The effects of bilateral celiac ganglionectomy are dramatic; blood pressure falls to normal or below during, or immediately after the operation. The symptomatic results are even more striking than the fall in blood pressure. Headache was a complaint in forty-eight cases of a series of sixty-nine,[18] and all were improved in seven to twelve months after operation with 42% completely relieved. Thirty-six cases complained of nervousness, and in a seven to twelve months postoperative follow-up 89% were improved and 22% cured of nervousness. Palpitation was reported in twenty-eight cases, and complete relief was reported by all. Fatigue, dizzyness, irritability, and precordial pain were also decreased in many cases. The duration of the symptoms before operation had no effect on results.[18]

By this less extensive sympathectomy, many negative effects are of advantage. There are no findings of interference with metabolism; no orthostatic hypotension; no change in the rate of activity of the heart; genito-urinary and sexual functions are not hindered;

digestive activity is not bothered; daily changes in the blood pressure do not become abnormal; there are no changes in the skin; nor is there any adrenal insufficiency resulting.[18]

According to White and Smithwick,[79] Crile's technic is an unsound surgical procedure, because it is strictly a postganglionic sympathectomy.[17] Crile bases his celiac ganglionectomy on certain comparative anatomy findings that he interprets as showing the celiac ganglion to be comparable to an "abdominal brain". Whether his approach is correct or not is difficult to say, but comparatively few surgeons have published anything on it which seems to justify a very doubtful attitude.

3. Rhizotomy

Probably the only positive method of removing all sympathetic motor innervation to the splanchnic region is by section of the anterior nerve roots as they leave the spinal canal. By resection of the anterior roots from the sixth thoracic through the second lumbar segments, all vasoconstrictor impulses should be interrupted to the vessels below the diaphragm, which includes 75% of the total vascular field.[8]

The sixth to the twelfth thoracic motor nerves supply intercostal muscles, and the seventh thoracic to the first lumbar motor nerves supply abdominal muscles.[53] The first and second lumbar segments contribute part of the flexor supply of the hip. The ilio-inguinal, iliohypogastric, lateral cutaneous, and genito-femoral nerves receive contributions from the first lumbar segment. The second lumbar fibers contribute to the genito-femoral and lateral cutaneous nerves.[53] All of the anterior nerve roots contribute to the innervation of the cutaneous vessels and sweat glands. The fifth to the tenth thoracic segments, and the ninth thoracic to the tenth, or the tenth to the

twelfth segments make up the major and minor splanchnics respectively. The splanchnics join in the celiac plexus and from there innervate the stomach, intestine, liver, adrenals, pancreas, and kidneys.[53]

Interruption of the anterior root near the cord results in motor paralysis of abdominal musculature, and in sympathetic paralysis of abdominal viscera, except for the colon, rectum, bladder,and genital organs. The inferior mesenteric ganglion, the vagus and the phrenic nerves, and the intrinsic nerve supply remain intact, enabling vital functions to continue. By this procedure sufficient arteries are sympathectomized to alter peripheral resistance, intra-abdominal pressure is minimized, and the suprarenal glands are relieved of their sympathetic influence. All sympathetic fibers of the thoracolumbar system below the fifth thoracic segment are interrupted. Paralysis of the abdominal muscles causes need for wearing an abdominal support.[1]

The surgical procedure consists in general of exposure of the laminae, removal of the sixth to the second lumbar segments, incision of the dura to expose the cord, and division of the anterior roots

midway between their origin and union with the posterior roots.[53] Page and Heuer, in reporting a case, state that the blood pressure fell rapidly and progressively to normal. Postoperative recovery was uneventful except for difficulty in bowel evacuation for one week. There was no abdominal protrusion resulting from the paralysis, and the patient soon learned how to manage motion of her trunk with confidence. Symptoms such as headaches, palpitation, and precordial pain disappeared.

Laboratory examination was done in detail before and after surgery, and the findings showed the power of the kidneys to concentrate urine was somewhat diminished. Changes were insignificant in total lipid, total and free cholesterol, lipid amino-nitrogen, total lipid nitrogen, and lipid phosphorus in plasma. Hemoglobin, plasma protein, basal metabolic rate, cardiac output, and electrocardiogram findings were all normal. The blood pressure fell quickly to normal and remained for seven months.[53]

The operation has untoward effects. Patients have difficulty in assuming the sitting position, and weakness of abdominal muscles is subjectively noticed.

however, objectively is not evident.[1] The obvious nature of the operation also brings to mind the chance of serious complication that is assumed on exposing the spinal cord, when effects almost as complete can be obtained through less dangerous technics. For this reason Craig[13] abandoned the practice in preference to the more simple and less dangerous splanchnicectomies and lumbar ganglionectomies.

4. Subdiaphragmatic Splanchnicectomy

In 1934, Craig and Brown published a report on the resection of the splanchnic nerves and its effect on hypertension.[15] Their technic consists of a skin incision from the eleventh rib to the crest of the ilium. The dissection is carried through the posterior layer of lumbodorsal fascia, serratus posterior inferior muscle, sacrospinalis muscle, anterior layer of lumbodorsal fascia, quadratus lumborum muscle, and finally to the peritoneum, which is separated from the quadratus lumborum. Dissection goes to the vertebral column and turns upward to the crura of the diaphragm through which come the splanchnic nerves; three or four centimeters are resected. Dissection then goes downward, and the first and second lumbar ganglia can be removed. The postoperative course is expected to be uneventful, and operative mortality is negligible. In 237 patients operated on at Mayo's, after careful selection of cases, there were no operative deaths.[14]

Craig and Brown[15] emphasize the importance of selection of patients in this treatment. They describe

an ideal patient as being less than forty five years old, and having a wide blood pressure level response to anaesthetics and cold pressor tests. These tests demonstrate a lack of organic changes in the vessels. There should be no severe changes in the kidney, heart, or brain, and the basal diastolic pressure level should be less than 120 mm. From their experience, they came to the conclusion that operation was applicable for early hypertension in young subjects. Contraindications for operation include congestive heart failure, angina pectoris, marked renal insufficiency, and advanced arteriosclerosis.[14] The operation produces interruption of the sympathetic control of the kidneys, adrenals, intra-abdominal regions, and large portions of the lower extremities.[14]

Prognosis is definitely better in the vasospastic type of hypertension without much organic change in the arterioles. The duration of the hypertension did not change this significantly, nor did age of the patient. Results were generally good if the diastolic pressure could be lowered to 100 mm. with rest and anaesthesia, and if sclerosis of the retinal vessels was minimal. They were generally poor if the diastolic pressure

remained above 120 mm. with rest and anaesthesia, and if arteriosclerosis was advanced.[14]

In a large series of cases operated on at Mayo's,[14] it was evident that symptomatic relief did not parallel the decrease in blood pressure. Results were recorded as good, fair, and poor, as regards the lowering of blood pressure; however, in considering the poor classification along, 76% were relieved of headaches, 67% of nervousness, and 60% from non-anginal pain in the left thorax. Even though the operation was considered a failure, relief from symptoms appeared in many cases.[14]

Craig[14] does not believe that operation should be carried out if the hypertension is of the slowly progressive type and is regulated by a medical regime. The fact that in some cases results are negligible must be accounted for. Lack of effect may be due to a failure of completely denervating the splanchnic area, because of fibers descending on the aorta and ascending from the lumbar ganglia. Organic hypertrophic changes in the arterioles may be too advanced, or a pressor element may be present that is not effected by sympathectomy.[14]

The operation is safe; it does not cause disability and may produce remarkable results, or at least delay complications that all too frequently cause an early death.[14]

5. Supradiaphragmatic Splanchnicectomy

Peet[55] published several reasons for preferring supradiaphragmatic splanchnicectomy. He chooses it over rhizotomy because of the extensive laminectomy necessary, the paralysis of abdominal muscles that results, and because of the danger of paralysis resulting from injury to the blood supply of the cord, either from injury of the nutrient vessels along the anterior roots, or from extensive extra and intradural hemorrhage. He believes it is advantageous because it enables section of fibers leaving the greater splanchnic to go to the celiac plexus along the aorta; these are inexcessible from the subdiaphragmatic approach.

The technic used by Peet[55] is a one stage operation in which the bilateral excision of the tenth, eleventh, and twelfth thoracic sympathetic ganglia, and the bilateral resection of the greater, lesser, and least splanchnic nerves is attempted. Vertical incisions are made posteriorly, about eight cm. from the midline and centering over the eleventh rib. Three cm. of the eleventh rib are dissected free and removed; the pleura is carefully moved from the bodies of the

vertebrae, and the ganglia located. The eleventh ganglion is usually near the eleventh rib at the middle of the lateral surface of the vertebrae. The twelfth ganglion often lies in the fibers of the diaphragm, and separation of these fibers is necessary. The greater splanchnic is found along the anterolateral surface of the vertebrae and is easily resected. The tenth, eleventh, and twelfth intercostal rami are divided, and the tenth and eleventh ganglia removed with the lesser splanchnic which is resected just above the diaphragm. The twelfth ganglion is also removed with the least splanchnic coming from it, or if the twelfth ganglion is not found, then the rami from the twelfth intercostal nerve are sectioned.[55]

The space left by separation of the pleura is filled with Ringer's solution to displace any remaining air, and the fluid is then forced out by using positive pressure in the lungs with the anaesthetic mechanism.[55] Muscles are closed in layers. Peet is not alarmed at any tear in the pleura, but finishes the operation and then closes the muscles with positive pressure in the lungs; only rarely has it been necessary to aspirate one side of the chest for air trapped

when the lung was expanded. He does not consider a tear in the pleura as being reason to place his method after others in choice of technic.

The mortality in the series of 100 cases was 4%,[55] and in another 350 cases, 3.4%.[57] Postoperative discomfort lasts from a day or two, to three weeks. Usually the discomfort consists of back pain, low abdominal pain or cramps, or a combination of the two. Gastro-intestinal and bladder functions are not affected; however, there is a diminished sweating in the areas innervated by the tenth, eleventh, and twelfth thoracic nerves around the abdomen.[55]

Peet's[55,57] indication for splanchnicectomy is a systolic pressure of 200 mm. or more during the patient's regular activities. He prefers his cases to be below fifty years old with a compensated heart. The non-protein nitrogen should not exceed a high normal, and the urine should be concentrated to a specific gravity of 1.010, with a urea clearance above 30%. He advises operation for symptoms such as headache, dizzyness, nervousness, palpitation, weakness, dyspnea, and failing vision. Operation is imperative if renal impairment, ocular changes, cerebral damage,

and cardiac damage are likely to appear, or are starting to appear.[55]

In a series of cases followed four to twenty-three months,[55] 7% were considered failures and 15% as complete cures. Slight improvement occurred in 16%; 29% had a drop of 25-50 mm. systolic pressure, and 33% had a drop of 50 mm. or more. Before the operation 54% of the patients were unable to work; almost half of these were able to be active after the operation. Eight cases had already suffered cerebro-vascular damage of some sort before the operation; there are no recorded symptoms from this postoperatively. The results of this operation were recorded in 290 cases in 1940.[57] The blood pressure was reduced in 59% of the cases, leaving about 30% of the cases without benefit as far as the blood pressure goes. Peet claims 86.6% of cases improved symptomatically, and renal function, heart size, and eye grounds all improved in over 50% of the cases.[57]

The main objection to the operation is that the first and second lumbar ganglia are not excised;[55] however, some anatomists believe there are no sympathetic fibers going through the lumbar ganglia to the celiac

plexus or other structures of the upper abdomen.[55]

Failure of this operation is explained by Peet[55] as being due to accessary sympathetic fibers going to the aorta at levels above the tenth thoracic ganglion, and to advanced degrees of arteriosclerosis.

6. Thoracolumbar Sympathectomy

Thoracolumbar sympathectomy is the most complete operation of the modern procedures. Two methods have been described of which only one, Smithwick's,[75] is in extensive use. The other method described by Grimson[31] in 1941, reported only eleven cases. It consisted of a three stage operation in which two thoracic and one abdominal procedure were used to remove bilaterally the stellate ganglia and entire sympathetic chain to or including the fifth lumbar ganglia.

Smithwick's[75] method is not as complete as Grimson's[31] but is the only method that can be evaluated. Considering the advantages of the supra- and infradiaphragmatic approaches, the clinical results, and anatomical variations encountered, a new transdiaphragmatic approach was started.[75] The new method attempted to eliminate any anatomical variation that might cause failure of the other technics.[79] Patients that had failed to improve after being subjected to supradiaphragmatic sympathectomy were operated on with the intention of extending the sympathectomy to the subdiaphragmatic area, by removing the sympathetic trunk from the tenth thoracic to the third lumbar

inclusive, and excising the splanchnics bilaterally. In these cases, the patients had a decrease in their blood pressure. The thoracolumbar, transdiaphragmatic approach allows the advantages of both the supra- and infradiaphragmatic approaches. The twelfth thoracic ganglion that may be difficult to reach from either the supra- or infradiaphragmatic technic is, by using this method, definitely removed.[79]

Resection of the sympathetic chain from the ninth thoracic segment to the second lumbar segment is easily accomplished, along with removal of the splanchnic nerves from the semilunar ganglion to the mid-thoracic region. The kidney is readily accessible for biopsy and examination, as is the adrenal gland.[79] The operation does take longer but does not carry a higher mortality than the other procedures.

It is a two stage, combined infra- and supra-diaphragmatic technic, completing each side in one stage a week or two apart. The skin incision is made about five cm. from and parallel to the vertebral column, starting over the eleventh rib and going to below the twelfth, then swinging laterally to the postaxillary line. The sacrospinalis muscle is found and retracted

to permit resection of the twelfth rib from the transverse process to the lateral border of the sacrospinalis sheath. The renal fascia is incised lateral to the diaphragm, and the diaphragm divided medially to the crus exposing the kidney and all its structures, adrenal glands, and sympathetic chain. In the more severe cases, the sympathetic trunk is resected from the ninth thoracic to the second lumbar inclusive; however, in relatively benign cases the second lumbar is left. By gentle separation of the pleura from the ribs, it is possible to resect the great splanchnic nerve for about 15 cm. above the diaphragm. The wound is closed in layers, removing any residual air with a soft rubber catheter.[79]

Complications postoperatively are not serious. Variable degrees of hyperesthesia may be found in the lower abdomen and flank and is unavoidable. Sometimes, cramps may result after the second stage, but they can be controlled with atropine. Patients are allowed up in two weeks after the second stage; however, because of orthostatic hypotension their legs must be bandaged from the foot to the knee, and they must wear an abdominal binder. The binders may gradually be

eliminated and in three months are usually not needed. The orthostatic hypotension may last as long as two years but is usually gone by then. If it remains, the patient must learn to move about when he is standing to facilitate circulation and avoid fainting. A disadvantage of the method is the long period of convalescence required which naturally causes some delay in resuming work.[79]

Results compare favorably with results of other technics. In a series of twenty-six cases reported in 1940,[79] 65% had significant improvement in hypertension.[76] In 1944, over 71% had a lessening of the systolic blood pressure between 10 and 30 mm. or more. Eight cases with known renal disease were operated on in 1940,[79] and only 12.5%, one case, had any lowering of blood pressure.[76] In 1944, eleven cases with chronic pyelonephritis were treated, and 90.1% of the cases had a lowering of the systolic blood pressure over 20 mm. This report is the only one that implies any success with cases of known renal pathology. Whether this operation will prove of value in the treatment of hypertension secondary to obvious renal pathology cannot be determined as yet.

In predicting results and selecting patients for surgery, only those with a good prognosis should be operated. If operation is adequate, results are good in the earlier types of hypertension, unless renal function is impaired or the blood pressure is excessively high, indicating a more malignant type of hypertension.[79] In the more advanced cases, results are expected to be good if there is no renal impairment. Cerebrovascular accidents, impaired renal function, and cardiac decompensation indicate unfavorable expectations.

The thoracolumbar technic is probably the most complete method of sympathectomizing a large area, because it avoids any chance of omitting certain fibers of which there may be some anatomical question.

7. Selection of Cases

In evaluating any method of treatment, it is important to know the type of cases that are being treated in relation to the results obtained. This is especially difficult in the surgical treatment of hypertension, because not only are there several classifications of the disease, but also there are as many systems of selecting the patient as there are different surgeons.

Probably the first classification affording any degree of exactness is that of Wagener and Keith.[78] They grouped essential hypertension into four groups, based mainly on the retinal findings. Group one includes the benign case that still retains good health and has only minor sclerotic changes of the retinal arterioles. Group two cases are usually in good general health also, but a few symptoms are present, and the blood pressure is consistently higher than in group one. Retinal sclerosis is more distinct, but retinitis is not seen. Group three characteristically has a mild vasospastic retinitis, without edema of the optic disc. Marked hypertension is evident, and

malfunction of the brain, heart, and kidneys may exist. In group four are put all cases that fit under the "malignant hypertension" heading. In the retina we find spastic and organic changes, with a diffuse retinitis and edema of the optic discs. Visual disturbances are sometimes present. Nervousness, dyspnea, nocturia, and asthenia are characteristic symptoms; however, the most important finding is the persistently elevated blood pressure.[78] In considering this classification in relation to the results obtained, it is assumed that better results would be expected from operation on patients in the first two groups. Patients in the third and fourth groups would not be as likely to respond favorably; therefore, selection of patients for treatment has become an integral part of the technic of each procedure.

Several factors influence the choosing of cases. Theoretically, the question is whether or not the patient has a type of hypertension that will respond to sympathectomy.[15] Craig and Brown believe the problem is to determine if the increased peripheral resistance is due to vasomotor activity, or to organic changes in

the wall of the arterioles. As in any surgical procedure, it is important to consider the age of the patient, cardiac efficiency, and probably most important in this case, the kidney efficiency. To determine the degree of hypertension due to vasospasm, the range in blood pressure is obtained using the cold pressor test to find the highest pressure, and anaesthesia to find the basal pressure. Another method of determining if the sclerotic phase is the more important is by actually looking at the arterioles, either in the ocular fundi, or by taking muscle biopsies.[15]

Of the above procedures, two are still in dispute. Methods for producing a basal condition of the blood pressure do not give reliable results.[65] Allen, Lundy, and Adson,[3] 1936, used sodium pentothal intravenously to determine the effect of operation. White and Smithwick[79] use sodium amytal in their procedure, giving three grains every three hours for a total of nine grains. Russek, Southworth, and Zohman,[65] 1946, believing that sodium amytol, sodium nitrite, and sodium pentothal were not dependable, advocated continuous caudal anaesthesia, and accurately predicted the outcome of eleven of twelve patients subjected to sympathectomy.

A procedure that has its value questioned is muscle biopsy. Foa, Foa, and Peet[25] believe that muscle biopsy is of distinct value; however, deTakats'[24] experience shows that unless careful measurements are made of the arteriolar wall and lumen by the same worker, nothing is determined except that there is luminal constriction. The method of fixation and site of biopsy also influence findings.

In 1934, Craig and Brown[15] stated that an ideal subject for sympathectomy would be forty-five years old or younger; his blood pressure would react to cold pressor tests and anaesthesia, and he would have a basal diastolic pressure of 120 mm. or less. The smaller arterioles would have only minor organic changes, and degenerative changes would not be demonstrable in the heart, brain, or kidneys. Peet,[55] 1937, recommended sympathectomies for all patients with a systolic pressure of 200 mm. or more, if they were not older than fifty years of age. He stated more exact requirements than Craig,[15] and chose to operate only if the non-protein nitrogen was not over high normal, and urine was concentrated to 1.0105. Urea clearance was required to be above 30%, and the patient

had to have a compensated heart.

In 1946, deTakats, Graupner, Fowler, and Jensik[24] published their method for selecting patients that they operating on for essential hypertension. Their routine examination is organized to eliminate poor surgical risks, patients that would not benefit by operation, and to discover such causes of hypertension that might be corrected by other therapy. It is a three day routine. The first day, basal metabolic rates, electrocardiograms, sedimentation rates, complete blood counts, non-protein nitrogens, blood ureas and cholesterols, and urine examinations are done under the guidance of a medical consultant. The fundus is examined by an eye consultant. Complete histories are taken by the surgeon, resident, and intern to bring out any hereditary traits, renal pathology, and possibility of lead or arsenic poisoning. A psychiatrist is called in if necessary. Pituitary, thyroid, adrenal, and ovarian disfunction are looked for, and if the patient is overweight, a reduction diet is started. Renal function is studied on the second day using concentration and dilution tests, phenolsulfonphthalion and urea clearance tests,

and intravenous pyelograms. A chest X-ray is taken also. On the third day, vasomotor activity is determined by cold pressor tests and sodium amytol, using three grains every three hours for a total of nine grains.[24]

In general, the patient that should respond to surgical treatment for hypertension and have good results has good kidney and cardiac function. He also has a minimum of organic changes in the arterioles, and a demonstrable vasospasm.

8. Postoperative Effects

Many findings may appear after a patient has had a sympathectomy that are hard to explain. Whether they are due to effects on the kidneys, adrenals, or both; or whether they are entirely due to a relaxed vascular bed is not known.[14] Extensive sympathectomy may produce better results than a partial sympathectomy, but this is not always the case;[14] however, local denervation of the adrenal gland[19] and of the kidney[54] fail to reduce hypertension. A relaxed vascular bed seems to be the only major objective that has not been directly disproved.

Among minor changes following sympathectic denervation, the most important is orthostatic hypotension that is found especially after more extensive procedures.[79] Following the thoracolumbar procedure, the patient is required to wear binding from the instep to the knee, and a firm abdominal support. These are removed gradually, and in three months the hypotension is usually inconsequential.[43] MacLean and Allen elevate the head of the bed following surgery, and the postural hypotension is eliminated. This is probably due to extracellular fluid in the lower extremities

preventing pooling of blood. Veins are also under control of the sympathetic system, and venous engorgement results.[79] Other minor changes include a decrease of sweating over the area affected and changes in skin temperature.[1] Stewart, Evans, Haskell, and Brown, 1946,[77] published a report on changes in skin temperature following thoracolumbar sympathectomy. There was a fall in rectal temperature, which is high in hypertensive patients, when the blood pressure returned to normal. Skin temperature of the upper body increased and that of the lower body decreased. Accompanying temperature changes was a fall in the basal metabolic rate.

Unfortunately, two disconcerting results follow the more extensive ganglionectomies. There is a paralysis of ejaculatory powers, and the male is sterile; however, potentia and libido remain. The menstrual cycle and childbearing facilities are not affected in the female, and there is no variation in the frequency or urgency of urination or defecation.[13]

The actual effect on the life span of hypertensive patients is not yet reportable; however, Peet and Isberg[56] published encouraging results. In a series of

437 cases, 95% of the hypertensives in groups corresponding to groups one and two of Keith, Wagener, and Barker[40] have survived five to eleven years. Without surgical treatment, the prognosis for living four years was 70% in group one and 58% in group two.[40] In the more severe groups there were no survivals at five years; however, 19% of 112 patients with moderate hypertension lived between five and eleven years after surgery.[56] According to Peet and Isberg, surgical treatment for patients with moderately severe hypertension has a one in five chance of prolonging life more than five years. With regular medical treatment, chances of living over five years are one in 146.[56]

Gauging the degree of effectiveness obtained from the surgical procedure is accomplished by evaluating the effects on the cardiovascular system, renal system, eyegrounds, and symptoms related to hypertension. With a lowering of blood pressure, the overload on the heart is reduced; cerebral symptoms are often relieved;[1] and cerebrovascular accidents are diminished.[55] The diminished blood pressure resulting from operation has often been questioned, and it was thought non-specific operations would produce the same results. In answer

to this Rojas, Smithwick, and White[62] published their findings in 100 hypertensive cases undergoing non-specific operations, and 100 hypertensive cases undergoing bilateral lumbodorsal sympathectomies. Twenty months after operation none of the first group had a reduced blood pressure, but 62% of the second group had a decrease in their blood pressure.

Lowering the blood pressure is the main objective of treatment. This has been best accomplished by the thoracolumbar technic.[77,25] In a report by Smithwick,[76] 86.5% of patients in the benign group and 71% of the moderately severe group had good results. Lord and Hinton[42] were able to lower the blood pressure even farther after thoracolumbar sympathectomy by prescribing exercise. In a series of thirty cases with a fall in the diastolic blood pressure of 15 mm., they increased the average fall to 32 mm.

Canabal, Warneford-Thomson, and White,[9] 1945, published a report on the electrocardiogram in hypertensive patients. The electrocardiogram becomes worse as time passes and parallels the clinical course of the disease. The hypertensives showing any improvement in their electrocardiogram are rare, and even

these are questioned. Recently thoracolumbar sympathectomy was shown to result in an improvement in electrocardiograms. Both the limb leads and the precordial leads showed definite changes.[80] Patients showing any evidence of cardiac strain, which is the first sign of actual heart disease, frequently improve.[5] There is one side effect on the heart after surgery, tachycardia; however, this is overcome when the patient learns his capacity for exertion.[13]

The effect on the renal system has been one of controversy.[55] Peet believes the basis of all his results is due to release of vasoconstriction of the renal arteries.[54] According to Page and Heuer, renal denervations fails to produce results.[46] Oppenheimer found that acute urinary retention, with spasm of the bladder, enlarged prostate, and retention of urine in both renal pelves produced hypertension that was relieved with urological surgery. He based his findings on a reflex action in the renal arterioles.

The efficiency of the kidney may not be directly due to the level of systemic blood pressure.[49] In a case reported by Dean and Abels,[22] removal of one sclerosed kidney reduced the hypertension, and the remaining

kidney, by modern testing, not only was undamaged, but also seemed to have improved in its functional capacity. On the other hand, some investigators report a diminished kidney function; however, these are only slight.[54] Study of the effect of lowering blood pressure with high spinal anaesthesia on kidney function in hypertensive patients showed a decrease in inulin and diodrast clearances; this also occurred in normal patients.[30] Smithwick reports[76] that the great majority of his cases had improved concentration, dye excretion, and disappearance of albuminuria. Rare incidences of unfavorable changes in these functions occurred.

Why some patients experience symptomatic relief without any decrease in their hypertension has not been explained. This fact is of so great importance however, that Peet and Crile[55] [16] advocate surgery on the basis of symptomatic relief alone. Headache, dizziness, weakness, tension, dyspnea, failing vision, and other symptoms are often entirely relieved if not diminished.[55] The percent of patients relieved of symptoms is greatest in the group having the greatest fall in hypertension. Headaches were relieved in over 94% of

the patients having good results with their blood pressure, but only about 76% had any relief in the poor result group.[14] Nervousness was relieved in 80% of the cases in the good result group, and thoracic pain in 90% of the cases.[14] Cerebral symptoms were relieved in 61% of cases in one of Peet's series,[55] and of the 54% incapacitated prior to operation, 35% have returned to normal activity.

If the ocular fundi present a picture that exemplifies the rest of the arterioles of the body, the reason for the profound improvement in many cases may be realized. Diminished activity of the retinitis is seen, and Smithwick[76] reports improved eyegrounds in 48.2% of his patients.

The operation has a mortality of 2-3% in all technics;[79] it sometimes gives remarkable results, and it at least may delay complications that cause an early death.[14] Predicting favorable results is the greatest handicap of this treatment.[14] Craig and Allen predict good results if the diastolic pressure is below 110 mm. with rest, and poor results if it is over 120 mm. Peet operates on the extreme hypertensive case.[55] Craig advises against operation on any patient with either

irreparable damage to the cardiovascular system, or with a slowly progressive type of hypertension that is amenable to medical treatment. Surgeons do not seem to know the criteria for predicting results, and because the operation is a major procedure with some side effects, its importance has been questioned.[38] According to Kerr,[38] vigorous medical treatment produces the same results, and he believes the operation will soon be discarded as have other popular phases of treatment.

9. Comment

The over-all effect that sympathectomies have had in the treatment of hypertension is difficult to state. All procedures report improvement after the operation; however, whether the progress made will be permanent can only be told by time. There are two factors that hinder the proper evaluation of the disease.

1. Sympathectomy is an attempt to cure a disease of unknown etiology, and the analysis of its effect cannot be determined scientifically.
2. A standard procedure is needed to eliminate errors in technic that produce faulty results. In this way it would be possible to have grounds on which to determine why failures result in the type of case that usually is improved. Smithwick's thoracolumbar sympathectomy is the only operation that is based on reasonable physiological and anatomical findings.

At the present time, the operation seems to be a proper procedure if used in correctly selected patients.

It is safe and does not produce any serious side effects. The future of the operation depends on the results produced as compared to medical treatment. Today, surgery produces as good results as the best medical treatment and is a quicker, surer method.

Summary and Conclusions

1. Essential hypertension is one of the leading causes of death in the United States; 15% of all adults have high blood pressure.
2. After an analysis of important etiological theories, the cause is still unknown.
3. Three factors are important in sympathectomies:
   a. Denervation of the desired area should be as complete as possible.
   b. Regeneration should be inhibited.
   c. Preganglionic section is preferred.
4. The fifth thoracic through the second lumbar sympathetic ganglia are considered in sympathectomies.
5. Celiac ganglionectomy, subtotal adrenalectomy, and rhizotomy are unsatisfactory procedures because of unsound physiological and technical principles.
6. Sub- and supradiaphragmatic procedures must be questioned because of anatomical variations and disputes.
7. Thoracolumbar sympathectomy is the only widely

used procedure that fulfills anatomical, physiological, and technical requirements.

8. The proper selection of patients for sympathectomies is important but is not accurate. This is one of the foremost problems in the field.
9. In general, sympathectomies are safe operations that have only a few inconsequential effects.
10. It is impossible to correctly evaluate the effect of each procedure because the results reported are not based on standard criteria; however, all technics record favorable findings-at least relief of symptoms.
11. At the present time, surgical treatment compares favorably with medical treatment of hypertension.

Bibliography

1. Adson, A. W., and Brown, G. E.: Malignant hypertension. Report of a case treated by bilateral section of the anterior spinal nerve roots from the sixth thoracic to the second lumbar, inclusive, J.A.M.A. 102:1118, 1934.

2. Adson, A. W., Craig, W. McK., and Brown, G. E.: Surgery in its relation to hypertension, Gynec. & Obst. 62:314, 1936.

3. Allen, E. V., Lundy, J. S., and Adson, A. W.: Preoperative prediction of effects on blood pressure of neurosurgical treatment of hypertension, Proc. Staff Meet., Mayo Clin. 11:401, 1936.

4. Blalock, A., and Levy, S. E.: Gradual complete occlusion of the celiac axis, the superior and inferior mesenteric arteries with survival of animals: Effects of ischemia on blood pressure, Surgery 5:175, 1939.

5. Bridges, W. C., Johnson, A. L., Smithwick, R. H., and White, P. D.: Electrocardiography in hypertension, J.A.M.A. 131:1476, 1946.

6. Brown, G. E.: Sympathectomy for early malignant hypertension, M. Clin. North America 18:577, 1934.

7. Brown, G. E., and Adson, A. W.: Physiologic effects of thoracic and of lumbar sympathetic ganglionectomy, or section of the trunk, Arch. Neurol. & Psychiat. 22:322, 1929.

8. Brown, G. E., Craig, W. McK., and Adson, A. W.: The treatment of severe essential hypertension. Effects of surgical procedures applied to the sympathetic nervous system, Minnesota Med. 18:134, 1935.

9. Ganabal, E. J., Warneford-Thomson, H. F., and White, P. D.: The electrocardiogram in hypertension; III. Electrocardiograms of hypertensive patients followed for a long time without splanchnic resection in comparison with those in patients who had splanchnic resection, Am. Heart J. 30:189, 1945.

10. Cannon, W. B.: A law of denervation, Am. J. M. Sc. 198:737, 1939.

11. Cannon, W. B.: Factors affecting vascular tone, Am. Heart J. 14:383, 1937.

12. Cannon, W. B.: Personal communication to Craig and Brown.

13. Craig, W. McK.: Hypertension and its surgical treatment, South. Surgeon 7:141, 1938.

14. Craig, W. McK., and Allen, E. V.: Hypertension and its surgical treatment, Mississippi Doctor 16:11, 1939.

15. Craig, W. McK., and Brown, G. E.: Unilateral and bilateral resection of the major and minor splanchnic nerves. Its effects in cases of essential hypertension, Arch. Int. Med. 54:577, 1934.

16. Crile, G. W.: Genesis and surgical treatment of essential hypertension, Pennsylvania M. J. 40:1017, 1937.

17. Crile, G. W.: Is early hypertension a curable disease?, Proc. Interst. Postgrad. M. A. North America Oct. 30-Nov. 3:365, 1939.

18. Crile, G. W.: Operative treatment of essential hypertension, South. Surgeon 7:220, 1938.

19. Crile, G. W.: Recurrent hyperthyroidism, neurocirculatory asthenia and peptic ulcer; treatment by operations on supra-renal-sympathetic system, J. A. M. A. 97:1616, 1931.

20. Crile, G. W.: The surgical treatment of essential hypertension, Cleveland Clin. Quart. 3:201, 1936.

21. Danielopolu quoted by Pereira.

22. Dean, A. L., and Abels, J. C.: Study by the newer renal function tests of an unusual case of

hypertension following irradiation of one kidney and the relief of the patient by nephrectomy, Tr. Am. A. Genito-Urin. Surgeons 37:239, 1944.

23. DeCourcy, J. L.: Subtotal bilateral adrenalectomy for hyperadrenalism (essential hypertension), Ann. Surg. 100:310, 1934.

24. deTakats, G., Graupner, G. W., Fowler, E. F., and Jensik, R. J.: Surgical approach to hypertension, Arch. Surg. 53:111, 1946.

25. Foa, P. P., Foa, N. L., and Peet, M. M.: Arteriolar lesions in hypertension: A study of 350 consecutive cases treated surgically. An estimation of the prognostic value of muscle biopsy, J. Clin. Investigation 22:727, 1946.

26. Goldblatt, H., Kahn J., and Ramon, H.: Studies on experimental hypertension. IX. The effect on blood pressure of constriction of the abdominal aorta above and below the site of origin of both main renal arteries, J. Exper. Med. 69:649, 1939.

27. Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W.W.: Studies on experimental hypertension, J. Exper. Med. 59:347, 1934.

28. Govaerts, J.: Apparition d'un tonus cardio-accelerateur dans le ganglion stellair deconnecte centralement, C. R. Soc. Biol, 119:1181, 1935.

29. Gregory, R., Ewing, P. L., Levin, W. C., and Ross, G. T.: Studies on hypertension; IV. Bioassay of vasoconstrictor substances in ultrafiltrates of citrated blood plasma from patients with normal blood pressures, patients with essential hypertension, and patients made hypertensive by intravenous injections of angiotonin (hypertensin), Arch. Int. Med. 76:11, 1945.

30. Gregory, R., Levin, W. C., Ross, G. T., and Bennett, A.: Studies on hypertension; VI. Effect of lowering the blood pressures of hypertensive patients by high spinal anaesthesia on the renal function as measured by inulin and diodrast clearances, Arch. Int. Med. 77:385, 1946.

31. Grimson, K. S.: Total thoracic and partial to total lumbar sympathectomy in the treatment of hypertension, Ann. Surg. 114:753, 1941.

32. Grimson, K. S., Wilson, H., and Phemister, D. B.: The early and remote effects of total and partial paravertebral sympathectomy on blood pressure: an experimental study, Ann. Surg. 106:801, 1937.

33. Haimovici, H., and Hodes, R.: Preganglionic nerve regeneration in completely sympathectomized cats, Am. J. Physiol, 128:463, 1940.

34. Hampel, C. W.: The effect of denervation on the sensitivity to adrenine of the smooth muscle in the nictitating membrane of the cat, Am. J. Physiol. 111:611, 1935.

35. Harrison, T. R., Blalock, A., and Mason, M. F.: Effects on blood pressure of injection of kidney extracts of dogs with renal hypertension, Proc. Soc. Exper. Biol. & Med. 35:38, 1936.

36. Hinton, J. W., and Lord, J. W.: Thoracolumbar sympathectomy in the treatment of advanced essential hypertension, New York State J. Med. 46:1223, 1946.

37. Jean, G.: Les nerfs splanchniques au point de vue chirurgical, Arch. de Med. et Pharm. Nav. 11:292, 1921. Cited by: Craig and Brown.

38. Kerr, W. J.: Cardiovascular disease, J.A.M.A. 132:972, 1946.

39. Keith, N. M.: Pathological studies of the arterial system in severe hypertension; Introduction, Proc. Staff Meet., Mayo Clin. 14:210, 1939.

40. Keith, N. M., Wagener, H. P., and Barker, N. W.: Some different types of essential hypertension; their course and prognosis, Am. J. M. Sc. 197:332, 1939.

41. 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.

42. Lord, J. W., and Hinton, J. W.: Effect of exercise on blood pressure of patients with advanced hypertension, J.A.M.A. 129:1156, 1945.

43. MacLean, A. R., and Allen, E. V.: Orthostatic hypotension and orthostatic tachycardia, treatment with the "head-up" bed, J.A.M.A. 115:2162, 1940.

44. Morlock, C. G.: Arterioles of the pancreas, liver, gastro-intestinal tract, and spleen in hypertension, Proc. Staff Meet., Mayo Clin. 14:210, 1939.

45. Odel, H. M.: Arteriolar changes in the myocardium in diffuse arteriolar disease with hypertension group IV, Proc. Staff Meet., Mayo Clin. 14:210, 1939.

46. Oppenheimer, R.: Urine retention and arterial hypertension, Urol. & Cutan. Rev. 49:602, 1945.

47. Page, I. H.: A method for producing persistent hypertension by cellophane, Science 89:273, 1939.

48. Page, I. H.: Classification of hypertension, J. Indiana M. A. 32:562, 1939.

49. Page, I. H.: The effect on renal efficiency of lowering arterial blood pressure in cases of essential hypertension and nephritis, J. Clin. Investigation 13:909, 1939.

50. Page, I. H.: The vasoconstrictor action of plasma from hypertensive patients and dogs, J. Exper. Med. 72:301, 1940.
Page, I. H., and Helmer, O. M.: A crystalline pressor substance (angiotonin) resulting from the reaction between renin and renin-activator, ibid. 72:29, 1940.

51. Page, I. H., and Corcoran, A. C.: Arteria hypertension: its diagnosis and treatment, Chicago, Year Book Publishers, 1945, pp. 20 and 236. Cited by Hinton, J. W.

52. Page, I. H., Helmer, O. M., Kohlstaedt, H. K., Kempf, G. F., Corcoran, A. C., and Taylor, R. D.: A progress report of investigations concerned with the experimental treatment of hypertension with kidney extracts, Ann. Int. Med. 18:29, 1943.

53. Page, I. H., and Heuer, G. J.: A surgical treatment of hypertension, J. Clin. Investigation 14:22, 1935.

54. Page, I. H., and Heuer, G. J.: The effect of renal denervation on the level of arterial blood pressure and renal function in essential hypertension, J. Clin. Investigation 14:27, 1935.

55. Peet, M. M.: The surgical treatment of hypertension, Proc. California Acad. Med. (35-36) 58-90, 1937.

56. Peet, M. M., and Isberg, E. M.: The surgical treatment of hypertension, J.A.M.A. 130:467, 1946.

57. Peet, M. M., Woods, W. W., and Braden, S.: The surgical treatment of hypertension. Results in 350 consecutive cases treated by bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy, J.A.M.A. 115:1875, 1940.

58. Pereira, A.: Nervi splaenchnici, Porto, Portugal, Tipographia Porto Medico, Ltd., 1929. Cited by: Craig and Brown.

59. Perera, G. A.: The relationship of the adrenal cortex to hypertension, J.A.M.A. 124:537, 1945.

60. Pickering, G. W., and Prinzmetal, M.: Experimental hypertension of renal origin in the rabbit, Clin. Sc. 3:357, 1938.

61. Pieri, G.: La resezione dei nervi splanenici, Ann. ital de chir 6:678, 1927. Cited by: Craig and Brown.

62. Rojas, F., Smithwick, R. H., and White, P. D.: Non-specific major operations and lumbodorsal sympathectomy; a comparison between their effects on the blood pressure, J.A.M.A. 126:15, 1944.

63. Rosenberg, E. F.: The brain in malignant hypertension, Proc. Staff Meet., Mayo Clin. 14:210, 1939.

64. Rowntree, L. G., and Adson, A. W.: Bilateral lumbar sympathetic neurectomy in the treatment of malignant hypertention, J.A.M.A. 85:959, 1925.

65. Russek, H. I., Southworth, J. L., and Zohman, B. L.: Selection of hypertensive patients for sympathectomy, J.A.M.A. 130:927, 1946.

66. Schroeder, H. A.: Essential hypertension; a concept of its mechanism, Am. J. M. Sc. 204:734, 1942.

67. Shaw, R. C.: Essential hypertension; an examination of its mechanism in relation to surgical treatment, Am. J. Surg. 71:181, 1946.

68. Simeone, F. A., Cannon, W. B., and Rosenblueth, A.: The sensitization of the superior cervical ganglion to nerve impulses by partial denervation, Am. J. Physiol. 122:943, 1938.

69. Simmons, H. R., and Sheehan, D.: The causes of relapse following sympathectomy on the arm, Brit. J. Surg. 27:234, 1939.

70. Smith, H. W.: Studies in the physiology of the kidney, University of Kansas, Lawrence, University Extension Division, 1939, 106 pp.

71. Smith, H. W., Chasis, H., and Ranges, H. A.: Suitability of inulin for intravenous administration to man, Proc. Soc.Exper. Biol. & Med. 37:726, 1938.

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

73. Smith, H. W., Goldring, W., Chasis, H., and Ranges, H. A.: Observations on the effective renal blood flow and functional excretory mass, with special reference to essential hypertension, Am. J. Physiol. 123:189, 1938.

74. Smith, H. W. Rovenstine, E. A., Goldring, W., Chasis, H., and Ranges, H. A.: The effects of spinal anaesthesia on the circulation in normal, unoperated man with reference to the autonomy of the arterials, and especially those of the renal circulation, J. Clin. Investigation 18:319, 1939.

75. Smithwick, R. H.: A technique for splanchnic resection for hypertension, preliminary report, Surgery 7:1, 1940.

76. Smithwick, R. H.: Surgical treatment of hypertension, Arch. Surg. 49:180, 1944.

77. Stewart, H. J., Evans, W. F., Haskell, H. S., and Brown, H.: The effect of splanchnic resection on the peripheral blood flow and rectal and skin temperatures in hypertension, Am. Heart J. 31:728, 1946.

78. Wagener, H. P., and Keith, N.: Diffuse arteriolar disease with hypertension and the associated retinal lesions, Medicine 18:317, 1939.

79. White, J. C., and Smithwick, R. H.: The autonomic nervous system, New York, Macmillan, 1941, pp. 22-61, 62-109, 307-346, 410-420.

80. White, P. D., Smithwick, R. H., Mathews, M. W., and Evans, E.: The electrocardiogram in hypertension; II. The effect of radical lumbodorsal sympathectomy, Am. Heart J. 30:165, 1945.