EXPERIENCES WITH THE SURGICAL TREATMENT OF HYPERTENSIVE CARDIOVASCULAR DISEASE IN MAN*

R. H. SMITHWICK, M. D.

Massachusetts General Hospital, Boston

Hypertensive disease, a frequent cause of premature disability and death, is an extremely complex problem and deserves the serious consideration of workers in all fields of medicine.

At the turn of the century, with the advent of a method for measuring blood pressure in human beings, hypertensive patients were divided into two main groups, those having some primary kidney disease and those having little or no evidence of kidney disease. The latter group is the larger, and to it the term essential hypertension is commonly applied. With this particular group we have been primarily concerned during the past twelve years.

The instability of the vascular bed in many hypertensive patients as observed by Hines and Brown[1] and others strongly suggested the participation of the autonomic nervous system in this disorder. Clinicians have long recognized that an outstanding characteristic of the blood pressure of many hypertensive patients is its unusual variability. As compared with the average normotensive person they are particularly sensitive to many stimuli, physical and mental. Accordingly, it is difficult to evaluate accurately the blood pressure of most of them. This variability suggested to Hines and Brown the need for a standard method of studying their blood pressure in order to detect these physiologic characteristics.

These workers described the hyperreactivity of the vascular bed to various stimuli, particularly to cold, and found that under resting basal conditions most hypertensive patients reacted to cold stimulus, such as immersion of one hand in ice water for one minute, by an excessive rise of both systolic and diastolic pressures (more than 20–15 mm. of mercury). They found that similar reactions occurred in about 15 per cent of normotensive persons, who because of unusual susceptibility to continued hypertension should be considered in the prehypertensive stage of the disorder. They collected evidence which suggested that this characteristic could be inherited and transmitted according to the mendelian

* Frank E. Bunts Institute Lecture.

law. They believed that in some instances hyperreactivity might be acquired in later life.

The surgical approach to hypertension in man is based on the role of the autonomic nervous system in cardiovascular disease, particularly in peripheral vascular disorders. Abolition of vasoconstrictor nerves to blood vessels of the extremities is followed by improvement in blood flow through the extremities and is of proved value in the clinical management of a variety of properly selected peripheral vascular disorders. Methods have been devised for selecting cases for surgery and for revealing the effect of surgical intervention upon the autonomic nervous system.

In approaching the problem of human hypertensive disease, it seemed advisable to obtain in a standard fashion data concerning blood pressure. This would be helpful in estimating the nature and severity of the hypertensive state of the particular individual, would reveal the underlying physiologic characteristics of the disorder, could be utilized in studying the effect of surgical procedures upon blood pressure, and might be helpful in selecting patients who would derive the greatest benefit from surgical treatment. Accordingly, a postural and cold test for blood pressure, a modification of the Hines-Brown cold test, was developed.

The data are obtained in a particular fashion. After two or three days of hospitalization, most of the time being spent in bed, the patient is taken to a quiet room and placed upon a comfortable bed. After a rest period of fifteen to twenty minutes, readings of pulse rate and blood pressure are taken at one minute intervals by a trained technician. Since the presence of a physician often acts as a pressor stimulus to hypertensive patients, and since, consequently, reflex responses may not be revealed, lower readings can be obtained by a technician, and abnormal reflex responses are more likely to be detected. Preliminary hospitalization and rest are also helpful in establishing the diagnosis of continued hypertension. Not infrequently a patient appears to have reached this stage of hypertension because ambulatory data indicate that the blood pressure is always elevated. It is surprising at times to find that, when studied in this fashion, the horizontal resting blood pressure may be normal, even in the presence of considerable cardiovascular disease as judged by the eyegrounds, the heart, or the kidneys.

The technic of testing is briefly as follows: Readings of pulse and blood pressure are taken every minute for five minutes, the patient first lying down, then sitting, then standing. During a rest period of five minutes in the horizontal position, readings are continued at one minute intervals. One hand is then immersed in ice water for one minute only,

and readings taken at the end of thirty seconds and one minute. After this readings are continued for five minutes. The patient then stands, and the cold test is exactly repeated (figs. 1, 2, 4, 5).

Blood pressure data are again obtained one year after operation and as often thereafter as possible. Postoperative data in the charts are cross-hatched. It was originally intended that the patients be hospitalized and studied exactly as before operation. Unfortunately, this has been impossible because of shortages of beds incident to the war. The data therefore are not strictly comparable. After operation the tests are made by appointment, with the patients ambulatory, and are carried out immediately after entrance to the hospital, with a preliminary rest period of fifteen to twenty minutes in the horizontal position.

Before discussing results, I shall comment briefly upon the extent of the operation we employ. Operative technics designed to denervate portions of the visceral vascular bed were devised by Adson, Craig, Peet, and Crile. Our first experience was with certain of these operations. We were impressed by anatomic variations in the autonomic nervous system, between patient and patient, as well as between two sides of the same individual. Consequently it occurred to us that, if one operation or another failed to modify hypertension, extension of the operation might convert failure into success. This was found to be true. Also, previous experiences with operation upon the autonomic nervous system, particularly for peripheral vascular disorders of the upper extremity, indicated that regeneration of interrupted vasoconstrictor pathways was possible and that hypertension might recur. This did happen in certain cases, and the recurrent hypertension was corrected by further surgery. Both considerations led to development of a more extensive operation, lumbodorsal splanchnicectomy.

The operation is performed in two stages eight to ten days apart. Its extent has been varied in order to determine the minimal effective procedure. It is not so extensive as the near-total sympathectomy of Grimson, the principal difference being that the heart is not denervated in the lumbodorsal procedure. The sympathetic trunks are removed at least from the tenth dorsal through the first lumbar inclusive, at most from the sixth dorsal through the third lumbar inclusive, and usually from the eighth dorsal through the first or second lumbar. In all cases the great splanchnic nerves are removed from the celiac ganglia to the midthoracic region. All divided rami are carefully clipped with silver dural clips to guard further against regeneration. As the operation became more extensive, there was physiologic evidence that the visceral vascular bed had been thoroughly denervated: Postural hypotension occurred in the acutely denervated state. This phenomenon is important,

principally because it indicates that important pathways have not been overlooked. Consequently, when the operation fails to modify the hypertensive state, one can be reasonably certain that inadequate surgery is not the explanation if postural hypotension was present immediately after operation. This makes it possible to evaluate other factors which might better explain the failure. Postural hypotension usually disappears in a few months, rarely being present at the end of a year. The magnitude and duration of the effect is related primarily to the extent of the operation into the lumbar region.

Results of operation are judged by the lowering of the diastolic blood pressure measured in the resting horizontal position one or more years after operation. Preoperative resting diastolic pressures ranged from 100 to 182 mm. mercury.

In a six year period over 600 unselected patients were operated upon, the great majority of operations being performed during the last three years. There were 36 deaths, a total mortality of 7.8 per cent. Operative mortality comprised 2.2 per cent; deaths within one year 2.0 per cent; and deaths one or more years after operation 3.6 per cent. These cases were reviewed to determine the circumstances under which poorer results could be expected. As a result, several rules were formulated to lower the mortality and to help in the selection of patients for operation.[1]

In one small group of men with resting diastolic levels of 140 mm. mercury or more the mortality was extremely high and accounted for nearly two-thirds of the total. Most of them had advanced eyeground changes and one or more of the following complications: cerebral accidents or encephalopathy, actual or impending congestive heart failure, or poor kidney function. Improvement was slight in three patients and pronounced in one. The remaining twenty odd patients in this group died. Operation seems inadvisable in such cases unless (1) there have been no cerebral accidents or attacks of encephalopathy, (2) the cardiac function is good, and (3) the renal function is normal or nearly normal. Under these circumstances one may hope to save an occasional patient without a prohibitive risk.

The majority of a series of 179 unselected patients observed for one to five years were improved. Favorable changes in eyegrounds, electrocardiograms, and cardiac and renal function, as well as improvement in the patient's general well being, were noted. In 42 per cent (group 1) the diastolic blood pressure was lowered 30 mm. mercury or more; in 18 per cent (group 2) 20 to 29 mm.; in 20 per cent (group 3) 10 to 19 mm.; and in 12 per cent (group 4) 0 to 9 mm. The blood pressure was higher in 8 per cent (group 5). In the first two groups (figs. 1, 2, 4, 5) the effect upon the blood pressure was obviously significant and was prob-

ably significant in the third. Certain patients in the fourth and fifth groups are clinically improved. In some, although there was no significant lowering of the diastolic level in the horizontal position, there were other changes such as lowering of peak levels after stimulation, generally associated with narrowing of pulse pressure and with a variable effect upon the magnitude of reflex responses. The latter may be absent, moderately reduced, or remain essentially unchanged.

The four characteristic effects of lumbodorsal splanchnicectomy are (1) lowering of diastolic levels, (2) narrowing of pulse pressure, (3) reduction in ceiling levels after stimulation, and (4) reduction in the magnitude of reflex responses. These changes in various combinations were noted in most cases after operation. The rules so far suggested have lowered the percentage of group 5 results but have made no significant difference in the others. These cases are being reviewed in order to determine the conditions under which one may be most certain that operation will be worth while. A larger series followed for a longer time will soon be available.

Certain general remarks may be made at this time regarding factors which appear to have a bearing upon the outcome. Results indicate that women are better subjects than men. From groupings made according to the width of the pulse pressure in the resting horizontal position, it is apparent that the wider the pulse pressure, the higher the percentage of poor results. Accordingly, we have divided the cases into three types. In type I (fig. 1) the pulse pressure is less than one-half the diastolic pressure. In type II (fig. 2) the pulse pressure is equal to, or up to 19 mm. mercury more than, one-half the diastolic pressure. In type III (figs. 4, 5) the pulse pressure is 20 mm. mercury or more greater than one-half the diastolic pressure. The highest percentage of better results is in type I women, in whom blood pressure was favorably modified to a significant degree in 81.8 per cent. The lowest percentage of better results was noted in the type III men, only 23 per cent of whom did well. The results in type II hypertension were between these extremes, again being better for women than for men.

In order to discuss the outlook for an individual patient with greater accuracy, other obvious factors must be considered. Thus patients must be further classified according to the preoperative resting diastolic level and also according to age. The age range so far is from 6 to 58, the average being a little under 40. It becomes apparent that the more variables that can be held constant, the more likely that one is dealing with similar forms and stages of human hypertensive disease. A large amount of data will be needed for such a detailed analysis. One certainly cannot group teen age hypertensive patients with those in the fifth decade, nor can

one group together cases of hypertensive disease of widely varying severity has judged by resting diastolic levels. There are many other factors to be considered: the state of the brain, eyegrounds, heart, and kidneys and the response to sedation. Likewise the duration of hypertension must be important, but the patient is rarely sure about this. We hope before long to consider some of these other factors, so that circumstances under which better results may be expected can be more accurately predicted.

An interesting aspect of this clinical investigation is the accumulation of data concerning the state of the renal arterioles in living hypertensive patients. The operative exposure permits gross inspection of the kidneys and the taking of biopsy material for microscopic study. Dr. Castleman described the changes and in patients with continued hypertension noted variation in arteriolar damage ranging from none to extremely severe. Biopsies are divided into five grades, 0 through 4. In grades 0, 1, and 2 changes are described as absent, minimal, and mild. Changes in biopsy grades 3 and 4 are regarded as moderate and severe respectively. Biopsy data also help to confirm the diagnosis of pyelonephritis in some patients and to establish it in others in whom it has not been suspected.

Renal blood flow data were obtained from small groups of cases representing the different biopsy grades. It was noted that, as the degree of arteriolar disease increased, renal blood flow decreased, ranging from normal in grade 0 biopsies to severe reduction in grade 4. Filtration fractions charted for the biopsy groups appear progressively to increase as the evidence of vascular disease increases. Filtration fractions were almost always normal in biopsy grades 0, 1, and 2 and elevated in most cases with biopsy grades 3 and 4. Biopsy grades of the two kidneys checked closely, as did split renal clearance determinations.

Approximately one half of the first 100 biopsies showed changes graded 0, 1, and 2. In the other half the changes were more severe, 3 and 4. We hoped that the result of operation might correspond to the degree of renal arteriolar damage as judged by biopsy material. However, the percentage of successes and failures in cases having biopsy grades 0, 1, and 2 was almost identical with that in those having biopsy grades 3 and 4. It is of interest to note that after operation, regardless of the effect upon the blood pressure, there is no significant change in either the quantity or nature of renal blood flow when measured in the resting horizontal position. It is also of interest that hypertension associated with known primary kidney disease, such as pyelonephritis, has been no less reversible than that without pyelonephritis.

The exposure in a lumbodorsal splanchnicectomy permits palpation and inspection of the adrenal glands. These appeared normal in the great majority of cases. In about 5 per cent tumors were found. These

were mostly cortical adenomas and varied in size from a few millimeters to several centimeters. Apparently the tumors and the hypertension are not closely related; for in most patients the response to excision of the tumor and unilateral splanchnicectomy was the same as in patients without tumors, that is, there was no effect upon the blood pressure.

Two patients with pheochromocytomas were exceptions to this statement. In each the hypertension responded so dramatically to removal of the tumor and unilateral splanchnicectomy that the tumor was undoubtedly the dominant factor. The physiologic characteristics of the hypertension in these two patients were identical. Both had severe continued nonparoxysmal hypertension of the narrow pulse pressure variety. Renal function was excellent, and biopsy material showed little or no evidence of renal arteriolar damage. Both had retinitis with severe retinal arterial changes. One had had a cerebral vascular accident and early congestive heart failure as well. The physiologic reactions of these patients during the preoperative postural and cold test were identical and very unusual when compared with those of most patients with so-called essential hypertension. Before operation both had postural hypotension associated with a definite increase in pulse rate. Both were hyporeactive to cold stimulation. There is little reason to doubt that in these patients the hypertension was mediated by a circulating humoral substance of an adrenalin-like nature. After operation the blood pressure returned to normal, and postural hypotension disappeared. Both continued to do well several years after operation.

SUMMARY

In summarizing these experiences with the surgical treatment of hypertensive cardiovascular disease in man, one is first of all favorably impressed by the objective improvement so far observed. It is evident that an adequate surgical procedure upon the autonomic nervous system is of real therapeutic value in the management of this disorder. From the viewpoint of the individual patient, it is important to determine the circumstances under which better results may be expected. Soon we hope to discuss this matter with particular reference to the accurate selection of cases.

It seems probable that this type of surgical intervention modifies hypertension specifically in a manner not similar, in our experience, to the effect of nonspecific operation. The explanation for the lowering of pressure has not been completely clarified and may be complex. In general, one suspects that smooth muscle tone is decreased, and that peripheral resistance to blood flow is thereby lessened. Whether this effect is solely the result of modifying neurogenic vasoconstriction or in

some way, as yet undetermined, the result of a modification of some humoral mechanism remains for the future to divulge.

The correct explanation for the success and failure of surgical treatment in human hypertensive disease may clarify causative mechanisms and may reveal in which respects human hypertensive disease resembles one form or another of experimental hypertension. Close cooperation between the clinician, the research worker, and the surgeon should hasten the solution of this problem.

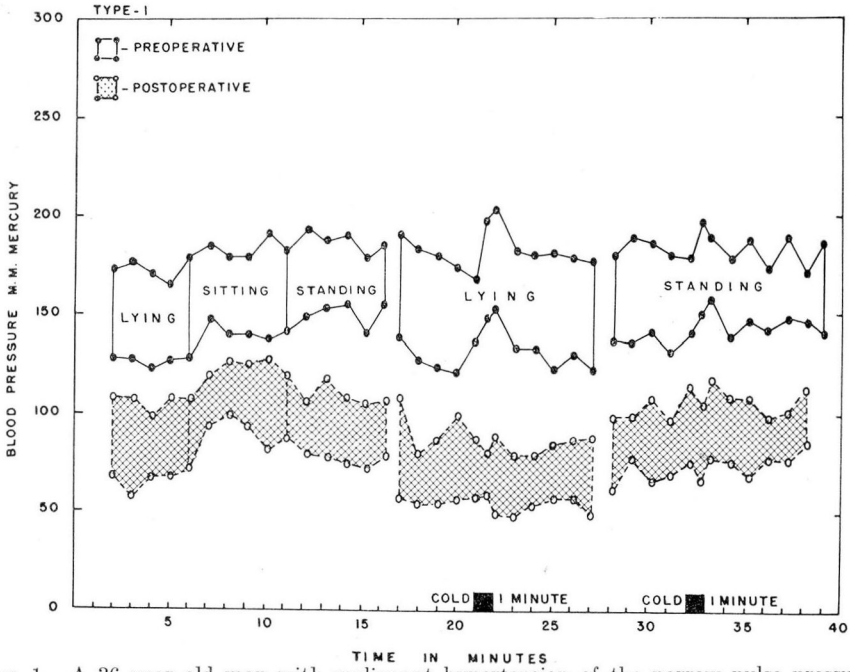

FIG. 1—A 36 year old man with malignant hypertension of the narrow pulse pressure variety (type 1) had grade 4 eyeground changes. Upon roentgen examination the heart was not enlarged or hypertrophied. The aorta was not tortuous. Electrocardiogram showed changes indicative of hypertensive and perhaps of coronary heart disease. Kidney function was normal by ordinary tests. Response to sedation was good, 130–90. Known duration of hypertension was two months.

Blood Pressure Data Before and Twenty-six Months After Operation

	Average		Ceiling Cold	
	Lying	Standing	Lying	Standing
Preoperative	175	189	204(36)	198(18)
(Resting)	128	152	154(18)	160(18)
Postoperative	106	109	90(2)	120(4)
(Ambulatory)	68	77	60(0)	80(2)

Twenty-six months after operation, patient was in excellent general condition and was symptomatically improved. Eyegrounds showed very pronounced improvement to normal, electrocardiogram showed definite improvement, and kidney function remained normal. Renal biopsies showed grade 4 arteriolar disease, changes comparable with those often seen in autopsy material. Physiologically, severe continued hypertension with hyperreactivity was significantly modified. He now may be classified as normotensive without hyperreactivity. All possible blood pressure changes after operation occurred in this case: (1) lowering of diastolic level, (2) narrowing of pulse pressure, (3) reduction in ceiling levels after stimulation by change of position and cold, (4) decrease in magnitude of reflex responses after stimulation. It is of interest that such definite improvement can take place in the most advanced renal arteriolar disease. (To help interpret this and subsequent charts, the average diastolic reflex response in our control series of normal individuals is plus 14 mm. mercury for changing from horizontal to upright position, plus 15 mm. mercury for cold stimulation in the horizontal position, and plus 12 mm. mercury for cold stimulation in the upright position.)

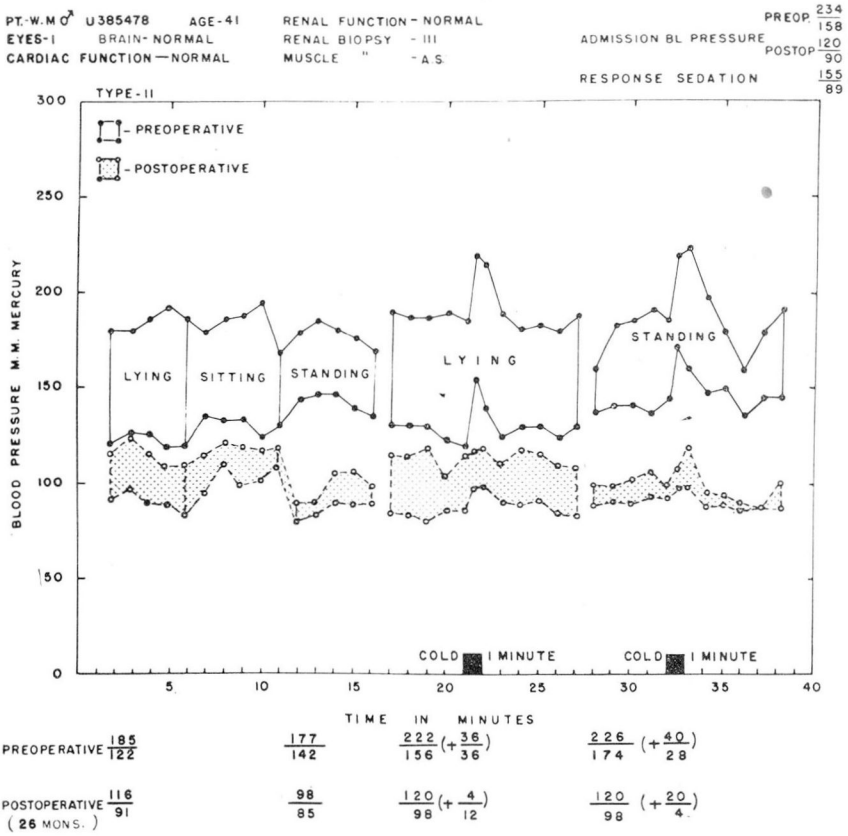

FIG. 2—A 41 year old man with severe essential hypertension of the intermediate pulse pressure variety (type II) had grade 2 eyeground changes, slight cardiac hypertrophy without enlargement. The aorta was not tortuous. Electrocardiogram showed changes illustrated in figure 3. Kidney function was normal by ordinary tests. Response to sedation was good, 155–89. Known duration of hypertension was nine years.

Blood Pressure Data Before and Twenty-six Months After Operation

	Average		Ceiling Cold	
	Lying	Standing	Lying	Standing
Preoperative	185	177	222(36)	226(40)
(Resting)	122	142	156(36)	174(28)
Postoperative	116	98	120(4)	120(20)
(Ambulatory)	91	85	98(12)	98(4)

Twenty-six months after operation the patient was greatly improved symptomatically. Eyegrounds were improved and normal. Electrocardiogram showed a completely normal tracing. Kidney function remained normal. Renal biopsies showed grade 3 arteriolar disease, changes of moderate severity. Physiologically, the hypertension was significantly modified, but the change was less dramatic than in case 1. Hypertension became less severe, and all four previously described changes that may occur after operation took place. (See footnote fig. 1.) However, the diastolic level in the horizontal position remained elevated above the normal range for ambulatory patients.

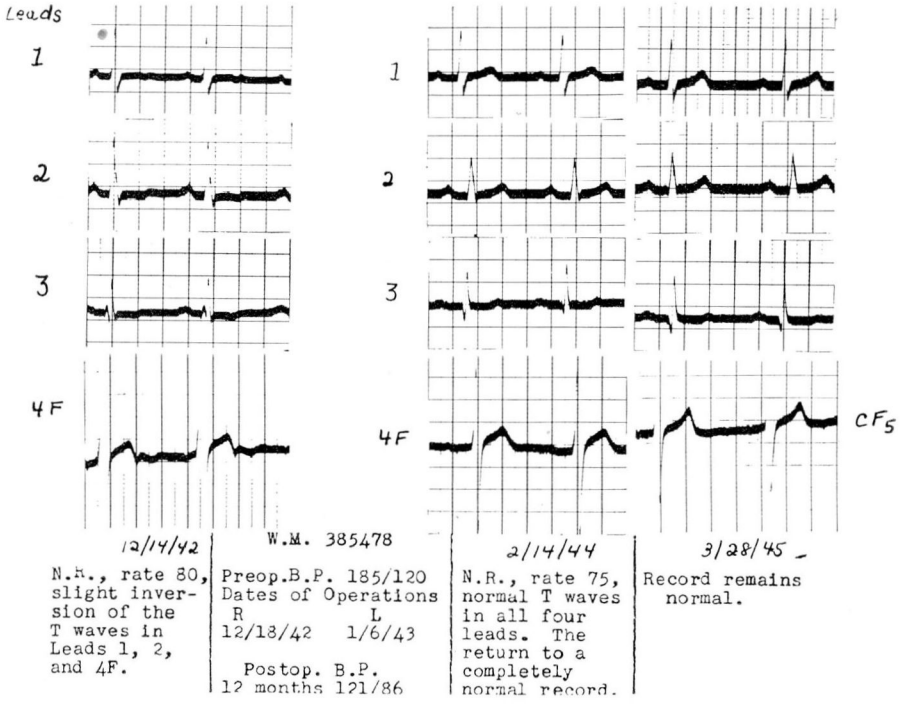

FIG. 3—(Same case illustrated in figure 2.) Prior to operation (December 14, 1942) the electrocardiogram showed normal rhythm, rate 80, slight inversion of T waves in leads 1, 2, and 4 F. One month after operation (February 14, 1944) the rhythm was normal, rate 75, and T waves were normal in all leads, a return to a completely normal record. Twenty-six months after operation (March 28, 1945) the record was normal.

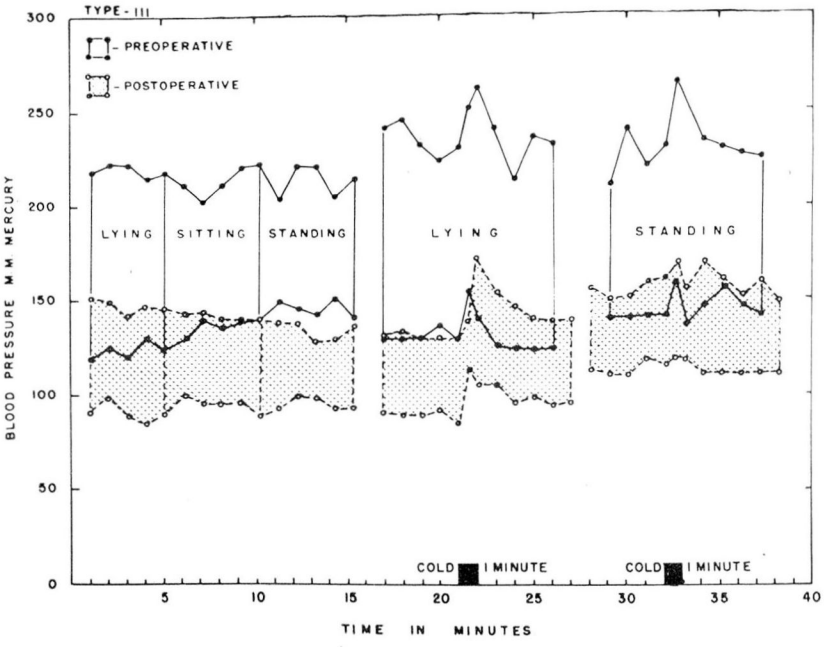

FIG. 4—A 48 year old woman with severe essential hypertension of the wide pulse pressure variety (type III) had grade 1 eyeground changes, a minor cerebral vascular accident, slight cardiac hypertrophy without enlargement, and good cardiac function. The aorta was tortuous. Electrocardiographic changes were indicative of hypertensive heart disease. Kidney function was normal by ordinary tests. Response to sedation was excellent, 120–70. Known duration of hypertension was two years.

Blood Pressure Data Before and Fourteen Months After Operation

	Average		Ceiling Cold	
	Lying	Standing	Lying	Standing
Preoperative	217	212	262(32)	264(34)
(Resting)	122	148	154(24)	158(18)
Postoperative	147	133	170(40)	168(6)
(Ambulatory)	90	95	114(30)	118(2)

Fourteen months after operation, patient felt much better. Eyegrounds showed no abnormality and were graded normal. Electrocardiogram was slightly improved. Kidney function remained normal. Renal biopsy material showed grade 3 arteriolar disease. There were no further cerebral accidents. Blood pressure was significantly modified; diastolic level was lower, and pulse pressure narrower; ceiling levels after stimulation were much lower. Reflex response to change of posture and to stimulation by cold when standing was reduced to within the normal range, but abnormal response to stimulation by cold in the horizontal position persisted. Diastolic level was not quite within the normal range for ambulatory patients.

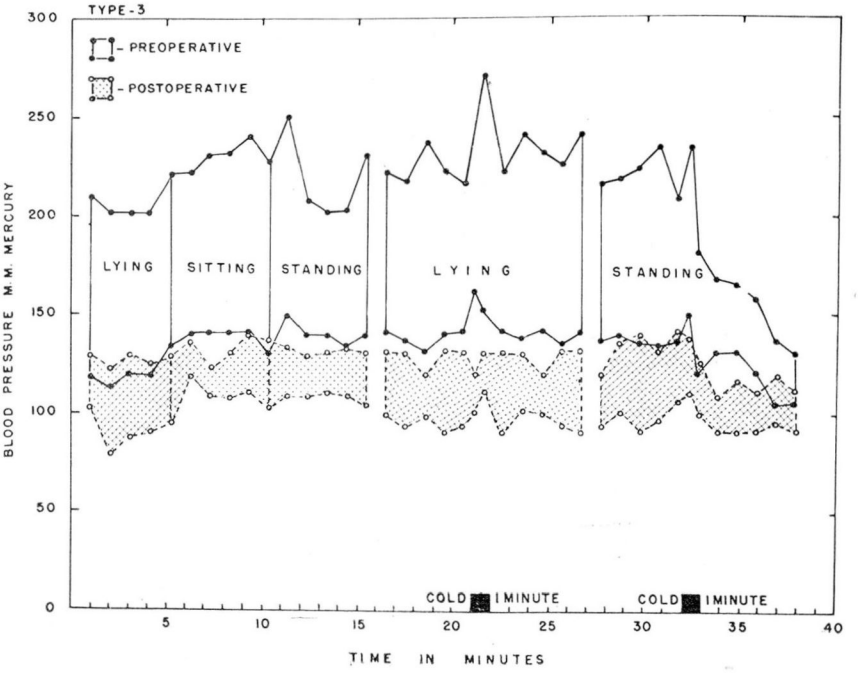

FIG. 5—A 27 year old woman had severe hypertension of the wide pulse pressure variety (type III) associated with bilateral chronic pyelonephritis. Kidneys were extensively scarred and contracted in an irregular fashion. Eyegrounds showed grade 2 changes. Upon roentgen examination the heart was not hypertrophied or enlarged, but the aorta was tortuous. Electrocardiogram showed changes indicative of hypertensive heart disease. Kidney function was normal by ordinary tests. Response to sedation was fair, 155–95. Known duration of hypertension was eleven months.

Blood Pressure Data Before and Thirteen Months After Operation

	Average		Ceiling Cold	
	Lying	Standing	Lying	Standing
Preoperative	204	215	270(56)	234(28)
(Resting)	120	139	160(30)	148(12)
Postoperative	127	131	130(0)	136(—16)
(Ambulatory)	92	107	110(16)	108(+2)

Thirteen months after operation the patient felt much better. Eyegrounds were improved but had not quite returned to normal, grade 1. Electrocardiogram had returned to normal. Kidney function remained normal. Renal biopsy material showed changes typical of pyelonephritis in scarred areas, chronic vascular nephritis grade 3 in nonscarred area of right kidney, and grade 4 in a similar area of the left kidney. Physiologic effect of operation was similar to that noted in the other cases. Hypertension was significantly improved but had

not reached normal. Known kidney disease, pyelonephritis, did not detract from the effect of operation. Results in our series of hypertensive patients with pyelonephritis, unilateral or bilateral, treated surgically have so far been the same as in those with so-called essential or malignant hypertension without pyelonephritis.

REFERENCES

1. Hines, E. A., Jr., and Brown, G. E.: A standard stimulus for measuring vasomotor reactions: Its application in the study of hypertension. Proc. Staff Meet., Mayo Clin. 7:332-335 (1932).
2. Smithwick, R. H.: Surgical treatment of hypertension; some circumstances under which lumbodorsal splanchnicectomy appears to be inadvisable in hypertensive patients. New York State J. Med. (Dec.) 1944.

EDEMA I

MECHANISMS OF EDEMA FORMATION

A. C. CORCORAN, M.D.

Edema is an excessive accumulation of fluid in extracellular spaces. It may be manifest, i.e., felt and seen; occult, located in the viscera; or latent, only demonstrable by chemical means. It may be local, as in inflammation or urticaria, or general and part of a systemic disturbance, as in congestive cardiac failure or nephritis.

Edema fluid may accumulate to the point where it interferes mechanically with tissue function or nutrition, so that what is at first an annoying sign of disease may later cause disability and death. Modes of relief of edema have therefore interested clinicians since the beginning of historic time. Since successful treatment depends primarily on identification and correction of the faulty mechanism, it is based largely on an understanding of physiology.

The purpose of the reports of which this is one is to review (I) mechanisms of edema formation, (II) clinical manifestations and consequences of edema, and (III) means of treatment.

BODY FLUIDS

The water of a unicellular organism lies within the cell; that of a multicellular organism is partitioned into intracellular and extracellular compartments. During life the membranous cell wall which separates intracellular and extracellular fluids is extraordinarily selective, so that these two fluids, although in constant shift and osmotic equilibrium, are chemically very different. Intracellular water is rich in salts of potassium; extracellular fluid has little potassium and much sodium, approximately 6 Gm. sodium chloride and 2 Gm. sodium bicarbonate per liter. The death of cells, as from burns, destroys membrane selectivity, so that sodium enters into cells and potassium leaves them.