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Malignant hypertension

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by

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Table of Contents

Table of Contents (cont.)

INTRODUCTION

The past two or three decades have brought an increasing universal interest on the part of the general public in the subject of high blood pressure. Perhaps this has come to pass mainly through the widespread publication of statistics on death rate as put forth by the leading Life Insurance Companies in which it is shown that hypertension is one of the leading causes of death. Consequently it is a very common event for a physician to recognize cases of hypertension for the first time during a routine life insurance examination. Not to be outdone by public interest in this subject, the medical profession has kept pace by innumerable investigations into the various phases of essential hypertension. Unfortunately the literature is quite confusing as far as terminology is concerned, and as a result there is not universal agreement in the classification of these hypertensive states. The purpose of this paper is not to consider all phases of essential hypertension, but more specifically to discuss the various aspects of the so called malignant hypertension. There has been many theories propounded concerning the etiology, pathology,

and clinical nature of this disease, but as may always be expected in those instances where the exact cause of a disease process is not known, these theories tend to be quite conflicting and diversified. The chief problem seems to be in arriving at general agreement as to whether it is a phase or complication of the benign essential hypertension. In addition the question of etiology is as yet an open field, and full agreement has not been reached in determining the exact pathological processes, both as to character and initial location. It is therefore the purpose of the writer to review the literature on all phases of this subject, and in so doing present the ideas of the leading authors, pro and con and if possible eventually arrive at some conclusions or reconcilations of these diversities of opinions.

HISTORY

It has been only a relatively recent advancement to recognize malignant hypertension as a definite syndrome, both in this country and abroad. However, it is very interesting to review the literature and find that many of the outstanding men of the nineteenth century described quite accurately conditions which today we would undoubtedly classify as malignant hypertension. This condition is vitally concerned with pathological processes occuring in the kidney, and, no historical review can be complete without a recognition of the early classical work on renal disease which was published by Bright in 1836 (1). From his papers we find reports of a group of patients with contracted kidneys associated with cardiac hypertrophy, and in whom was found no direct evidence of a typical nephritis. Accurate observations on blood pressure were not possible at that time because of the lack of suitable apparatus for such determination. In 1852, Wilks (2) further brought out the point that it was possible to have renal disease without presence of albuminuria. In autopsies of such patients it was found that a red contracted kidney was a consistent finding. Perhaps, however, the first specific reference to

sclerotic changes occurring in the smallest vessels of the kidney is made in the reports of Gull and Sutton (3) in 1872, when they described an "arterio-capillary fibrosis" which occurs in the kidney and over the body generally. These cases, they believed, were typical of the constitutional form of Bright's disease with contracted kidney. Whereas most authors now agree that the capillaries are not involved in this condition, it must be conceded that this work was a definite step toward our present day conceptions of arteriolar sclerosis. It was then in 1872 that Johnson (4) directed his attention toward this condition and described a diffuse disease of the smallest arteries and proposed a theory that renal disease was primary with subsequent diffuse thickening of the walls of the smallest arteries, leading to increased peripheral resistence, elevated blood pressure, and cardiac hypertrophy. Eight years later Mohomed (5) published a series of cases of chronic Bright's disease, in which his autopsy reports describe pathology in the kidney which was very similar to arteriolar sclerosis. He calls this a "red kidney" and suggests classifying such cases under the "arterio-capillary fibrosis" of Gull and Sutton. Then with the advent of the sphigmomanometer in 1893, recognition of essential hypertension was inevitable.

With such recognition comes the opening of a debatable subject with controversial theories as to the classification, ethiology, pathology, clinical course, and treatment of this so called essential hypertension. First attempt at such classification was made in 1914 by Volhard (6) and Fahr (7). These men divided hypertension into two classes, namely the benign and malignant. Their principle interest was in the kidney pathology and perhaps for this reason, chose to call their cases benign and malignant nephrosclereses respectively. Hence the spark was set off which ignited heated interest in the subject of hypertension. In this country we credit Keith and Wagener (8) for the pioneering work in the syndrome of malignant hypertension. Their reports simulate clinical findings as brought out by Volhard and Fahr but they also show that there need not be obvious renal failure, and further attempt to classify the types of malignant hypertension. Since 1924, therefore, when this work was published, the literature shows a rapid influx of new ideas and theories. We find that in general there has developed two main schools of thought concerning this subject. First, there is that theory held by most authors including Fishberg (9), Christian (10), O'Hare (11), Roleston (12), and others;

who believe that malignant hypertension is a phase, or complication of the benign essential hypertension. While on the other hand Fahr (7), and more recently McMahon (13) consider this to be a distinct and separate clinical and pathological entity. In the past decade we find the reports of such outstanding men as Klemperer and Otani (14), Pilcher and Schwab (15), Shapiro (16), Pickering (17), Murphy and Grill (18), Bell and Clawson (19), Goldblatt (20), Kimmelstiel and Wilson (21), and many others, all trying to clear up this rather complicated syndrome. Their work will be considered more in detail elsewhere in this paper.

CLASSIFICATION

Not only is malignant hypertension a complicated syndrome in itself, but also further difficulty is encountered in an attempt to understand the terminology assigned to this condition by various authors. Hypertension in itself is merely a sympton and as it's name implies designates a high blood pressure. In a small percentage of cases we can give a definite cause for such a blood pressure elevation. However, in the majority of cases the exact cause for the hypertension and associated chain of events is not well understood. To such cases has been given the name of essential hypertension. We may also recognize this same condition under the heading of primary or idiopathic hypertension. It must be recognized, however, that all cases of this so called essential hypertension do not present the same clinical picture. Hence further classification is obviously necessary. As a result we have two main groups, namely the benign and malignant hypertension. Briefly, the essential differences between the two are as follows: (8), (14), (137), (18), (21)

1. The age of the individual -- seen much earlier in cases of malignant hypertension.

2. The clinical course -- runs a rapid downhill course with early fatal termination in the malignant, while the benign may persist for years with death due to some other pathological process.

3. Symptoms -- much more severe and disabling in the malignant as compared to the benign. Severe grades of retinitis being a consistent finding in the malignant and not so in the benign.

4. Pathology -- processes by far more severe and advanced in malignant than in the benign, although both are chiefly arteriolar lesions.

Yet even though a differentiation between the benign and malignant forms is comparatively easy, we find that recent trend has been toward further classification of the types of malignant hypertension. Perhaps the reason for this may be the introduction of the term "malignant nephrosclerosis" into the literature by Volhard (6) and Fahr (7). In reality this is malignant hypertension but the original description was of cases with definite renal failure. However, Keith and Wagener (8) have shown that there are clinical cases of malignant hypertension in which there is no obvious renal failure.

As a result of their work, these men have divided malignant hypertension into four types depending upon which organ is most severely affected in this syndrome. They divide their cases into the cardiac, renal, cerebral, or the combined type. Ellis (22) has called attention to the fact that the present terminology is inadequate and confusing. He tends to be in accord with a general classification of malignant hypertension as being a term which can properly be applied to designate clinically a severe and rapidly fatal form of arterial hypertension. He goes further to say that malignant nephrosclerosis may be reserved as a descriptive name applied to the pathologic changes observed in the kidneys of a group of patients dying of rapidly progressive renal insufficiency. However, a general review of the literature will show that for the most part clinicians accept the terms malignant hypertension and nephrosclerosis as being synonymous. Nevertheless, it does seem logical to accept the above types of Keith and Wagener (8) as being particularly descriptive of the clinical manifestations and fatal terminations in cases of malignant hypertension.

Definition

Malignant hypertension is a disease found pri-

marily between the third and fifth decades of life; of undetermined origin, and characterized by symptoms referable to the brain, heart, or kidney, depending upon the organ most severely injured in the pathological changes which occur principally in the arterioles and which vary from hypertrophy to sclerosis to actual necrosis with endarteritis. The course of the disease is short and steadily downhill terminating fatally from a few weeks to four years after onset of severe symptons.

ETIOLOGY

For an adequate control and treatment of any of the diseases known to the medical profession, an accurate and specific understanding of the etiological factors involved is indispensable. Unfortunately we are found wanting in this respect as far as malignant hypertension is concerned. Consequently, we may expect to find widely diversified and conflicting ideas as to the predisposing factors and exciting causes of this disease.

In first considering the role of the predisposing factors we must consider the importance of age, sex, race, environment and heredity in producing hypertensions. By extensive studies into the causes of high blood pressures, with special respect to personal and familial histories some fairly definite conclusions may be made. However, all these theories have not yet fallen into universal agreement.

Recently Moritz, and Oldt (23) have made extensive studies of arteriosclerotic diseases in which they reviewed the clinical and autopsy records of two hundred cases in whom the systolic pressure was over one hundred and fifty and the diastolic pressure was over one hundred. From this work it was shown that, if the entire autopsy

population was considered, the percentage of negroes afflicted with this disease was higher than the percentage of whites. However, death from cardiac decompensation, uremia and cerebral manifestations was of the same percentage in blacks, whites, males and females. Of these terminal phases, death due to renal failure appeared at an earlier mean age than in those cases dying from cardiac or cerebral manifestations. From a racial standpoint, Hines (24) believes that there is a marked difference in Nationalities so afflicted, pointing out that in general, hypertension is found more in negroes, and on the other hand much less among the Chinese. Contrary to these ideas, is that of McMahon and Pratt (13) who concluded, after a study of sixty clinical cases of malignant Nephrosclerosis, that there was no constant relationship to past disease, to race, to sex, or to occupation that was of importance.

Of all predisposing factors, heredity seems to be most generally accepted as an etiological factor. Ayman (25) perhaps has studied this phase as much as, if not more than, any other present day authority. After a study of one thousand five hundred and twenty-four members of two hundred and seventy-seven families, he finds there is an unusually high incidence of elevated blood

pressure readings in the children, brothers, sisters and parents of subjects with arteriolar hypertension, as compared with similar relatives with normal pressures. In perfect agreement with such findings is the result of a study of three hundred unselected cases of hypertension, by O'Hare, Walker and Vickers (26). These men conclude that heredity undoubtedly plays one of the most important roles in the production of hypertensive disease. It is also their contention that the offspring in such families should be watch over, and protected against the stresses and strains of life that also play an important role in the production of hypertension. Even more specifically, Zemp (27) stresses the role of inherited characteristics of the general arterial and autonomic systems and their response to intrinsic and extrinsic factors. McMahon and Pratt (13) also agree that the constitutional factor, including the age of the patient and the familial or individual tendencies are important considerations. Smith (28) gives the very interesting account of two negro brothers who died at an early age from malignant hypertensive complications. The following facts, which he gives concerning these cases, seem significant of the importance of heriditary factors:

Brother #1

Age -- 24 at time of death

Onset of Symptoms	1 mo. preceding hospitalization
Previous Illness	Influenza, 10 years previously
Blood Pressure	200/160
Hospital days before death	11 days
Weight loss	24 pounds

Brother #2

Age -- 28 at time of death

Onset of Symptoms	3 mo. preceding hospitalization
Previous Illness	Influenza, 11 years previously
Blood Pressure	200/160
Hospital days before death	10 days
Weight Loss	40 pounds

Some authors have contended that certain chronic infections seem to predispose to hypertension. Shapiro (16) indicates that perhaps syphilis predisposes to nephrosclerosis in general, but not to malignant nephrosclerosis in particular. While on the other hand, Murphy and Grill (18) believe syphilis has no bearing on the disease. Cain (29) found syphilis in two cases out of twenty-seven studied. However, in this series he did find that seventeen gave a history of having had either scarlatina, or repeated attacks of tonsilitis. Fahr (7)

considered rheumatic arthritis as an important factor. Rose (30) stressed the possibility of chronic infections in general as being important predisposing factors. It is also interesting to note that this man also points out the fact that coffee and tea if in excess, may play a role, and that the "pace of modern life" is not important except to hasten sequelae.

Age Incidence

In general the concensus of opinion is that malignant hypertension is found primarily between the third and fifth decades of life. Keith and Wagener (8) in their classical description of the malignant hypertension syndrome, reported eighty-one cases in whom the age variation was from nine to sixty-four years, with the average age being forty-two. However, the majority of their cases were subjects between the ages of thirty-three and fifty-five years. Riseman and Weiss (31) hold that the onset of the steep rise in the age incidence curve of hypertension occurs almost five years earlier for women than for men. Whereas, we may expect therefore, to find clinical manifestions of malignant hypertension in the middle-aged, we must not lose sight of the possibility of finding this syndrome in the very young. Davis and Vanderhoof (32) describe two cases of

malignant hypertension in a male and female, aged nineteen and twenty-three respectively. Mitchel (33) describes cases of nephrosclerosis in childhood; although from his paper we are led to believe that these cases were more closely allied to an actual Nephritis. However, Craig (34) does present a case of malignant hypertension in a child, eight years old in which the diagnosis was confirmed by necropsy findings. That this syndrome may exist in childhood has also been substantiated by Ayman (25), and Keith and Wagener (8).

Exciting Factors

The exact causative agent or agents in the production of malignant hypertension are not yet well understood. As a result many theories have been propounded in an attempt to explain why such a syndrome results. The kidney has always been closely associated with these hypertensive states of unknown etiology. However, as yet there is some disagreement as to which comes first, the renal disease or the hypertension. Briefly, the three main earlier theories were:

1. Renal disease was primary.
2. The renal disease was but a part of the diffuse primary vascular disease.
3. The hypertension in itself was primary with the

renal and vascular changes being secondary to it (23).

Moritz and Oldt (23) have recently reviewed the etiological factors and have come to some conclusions as to the cause and effect relation of arteriolar sclerosis and the hypertension. Excluding such possible causes as nephritis, urinary obstruction, obesity, hyperthyroidism, pituitary tumor, lead poisoning, adrenal tumor, aortic insufficiency, coarctation of the aorta and arteriovenous aneurysm, they believe the hypertension to be the result of primary renal arteriolo sclerosis. This sclerosis might be because of a generalized reflex spasm of the peripheral vessels beginning in the ischemic kidneys; or on the other hand due to the retention or elaboration of pressor substances following the decreased blood flow in the kidney. They also contend that the arteriolar degenerative changes occurring in the kidney and elsewhere in the body are secondary to the arteriolar spasm. Such secondary changes may, or may not, tend to increase the intensity of the hypertension as a result of the organic narrowing of the lumen. However, the subject of the causative factors is not as simple as this, if we are to consider the various opinions of other investigators. We shall, therefore, in an attempt to simplify

this maize of material, consider these other ideas under appropriate, separate headings.

Renal Ischemia

Beginning with the earlier works of Volhard (7) on malignant nephrosclerosis, we find that he describes his clinical entity as being the end result of a prolonged ischemia through contraction of the larger arteries. Following this trend of thought we find Goldblatt, Lynch, Hanzal and Summerville (20) in 1934 carrying out experiments on dogs, in which, by means of a special silver clamp, they constrict the renal arteries. By so constricting both main vessels with only moderate compression in the beginning, they find an elevation of the systolic blood pressure, unaccompanied by signs of materially decreased renal function. These cases they believed, resembled the benign type of nephrosclerosis. However, if from the beginning, they brought about almost complete constriction of the renal arteries, there resulted a great elevation of blood pressure which was accompanied by severe disturbance of renal function and uremia, which in their opinion simulated malignant nephrosclerosis. Then more recently (May, 1937) Goldblatt (35) carried out more experiments in which, because experimental hypertension has never been attempted in monkeys, he used the

giant type of Macque. The results again were a persistant elevation of systolic and diastolic blood pressures. As yet there has not been a report of the tissue findings, which undoubtedly will be valuable. Using a similar technique, other investigators have confirmed his findings in animal experiments.

Pressor Substances

As has been mentioned previously, Moritz and Oldt (23) recently considered that it was possible that hypertension was due to an elaboration of pressor substances in the ischemic kidney. These men are not alone in their hypothesis since considerable experimental work has been done in an attempt to prove this theory. In 1934, Bohn and Schlapp (36) claimed to have shown experimentally that a pressor substance can be demonstrated in the ultra filtrates from the plasma of patients suffering from malignant hypertension. However in 1935, Aitken and Wilson (37), by following closely the technique of Bohn, were not able to find satisfactory evidence of a pressor activity in the blood of nine patients diagnosed as malignant hypertensive cases. The following year, Prinzmetal and Friedman (38) working with extracts made from ischemic kidneys, found results showing a less pronounced preliminary depressor and a more pronounced

pressor effect than from those extracts prepared from normal kidneys. However, they do not feel that the data so obtained is in itself sufficient to establish a definite etiologic relationship between pressor substance in the kidney and an elevated blood pressure. Such date, they do believe, is in accord with the theory that hypertension may be due to an excess amount of pressor substance which may normally be found in the kidney. Using the blood serum of thirty patients suffering from essential hypertension and fifteen patients with normal pressures, Wakerlin and Bruner (39) performed experiments involving these sera reactions on the mesenteric arterial segments of beeves. They found no significant differences in the vasoconstricting properties of the two sera. Consequently it appears that the field is open to considerable more research and that along with the recent work of Goldblatt (35) on ischemic kidneys, there may eventually be worked out a plausible etiological factor for these hypertensive states.

Glandular Theories

Numerous theories have been advanced in an attempt to associate malignant hypertension with various endocrine imbalances. McMahon, Close, and Hass (40) have found that in certain cases of Basophilic adenoma of the

pituitary and malignant hephrosclerosis, the cardiovascular renal lesion present in each instance corresponded to the picture that was originally described by Fahr (6). Later Close (41) again described a basophilic adenoma of the pituitary in a case of malignant hypertension. McCann (42) in his review of the recent literature on the subject concluded that malignant nephrosclerosis was a distinct clinical entity, but that it was closely associated with basophilia of the pituitary body. McMahon and Pratt (13), in their study of sixty cases of malignant nephrosclerosis, found pituitary basophilism associated with basophilic adenoma of the pituitary that showed clinical and pathological malignant nephrosclerosis. Cushing (43) in discussing the syndrome which bears his name, describes the high blood pressure as being "one of the characteristic symptoms of a peculiar disease."

The thyroid gland, often associated with high blood pressure in certain conditions, has also been suggested as an etiological agent in certain cases of malignant hypertension. Wohl (44) describes the similarity of some cases of hyperthroidism to the syndrome of malignant hypertension. For the most part the association of these two conditions has come mainly from the standpoint of removal of a part of the thyroid as treat-

ment for certain cases of hypertension. Becher (45) in 1932, recommended such a procedure in the treatment of malignant hypertension. Understanding the normal action of the secretions from the adrenals, it is only natural to suspect that in certain instances this gland may play an etiological role. Cecil (46) has described cases of suprarenal tumors in which there was marked hypertension of a persistent nature rather than of the paroxysmal type. McMahon and Pratt (13) in their series found some instances of cortical tumors of the adrenal which showed clinical and pathological evidences of malignant nephrosclerosis. Bain (47), in discussing probable etiological factors, does not specify any single endocrine imbalance but suggests that ultimately the cause of arteriolar constriction will be found to be a deficiency disease with particular reference to some hormone.

Neurogenic Factors

Since there is the possibility of Vasospasm being the initial pathological process we find that many authors hold to the neurogenic factor as the basic etiological factor. Pickering (48) has performed numerous detailed experiments on the upper arm on subjects with persistent hypertension, among whom were cases of definite malignant hypertension. Using adequate normal

controls he compared the rate of blood flow, Viscosity and hyperemia in these patients and the normals under varying conditions. As a result he finds that probably in all cases of persistent hypertension (definitely in chronic nephritis and essential hypertension) the causative factor in bringing about the narrowing of the vessels was not nervous. However many of the prominent surgeons of today feel that there is a definite relationship between the arteriolar constriction and their innervation, and because of such, they hold that various nerve resections are advantageous in treatment (see section on treatment) (49), (50), and (51). Brown (52) believes that there is a hyperactive vasomotor center in the diencephalon which is susceptible to various stimuli and thus produces an abnormal or excessive reaction of the blood pressure. Hence there is an overreactability and the arterioles become overworked with subsequent hypertrophy. Yater, Coe, and Rodis (53) are also in accord with this theory of excessive stimulation of the vasonotor center. Shapiro (16) contends that the etiology of the nephrosclerosis is not on the basis of a glomerular ischemia or on arteriolar occlusion, but rather on a hyperemia that is associated with a retardation of flow. Such retardation is based on a

neurogenic dissociation in the reaction between arterial constriction and peripheral dilatation. He goes further to say that a moderate retardation leads slowly to the organic changes of benign nephrosclerosis, while severe retardation will rapidly induce the pathologic changes of malignant nephrosclerosis and terminate in uremia. He concludes therefore that malignant nephrosclerosis is simply an "atherosclerosis renum accelerata gravis."

Intoxications

Fahr (6) believed that the causative factor in his cases of malignant nephrosclerosis was a "toxin" which directly injured the vessel wall and led to necrosis and inflammatory changes. As a general rule, however, the present day concept quite generally seems to be that this type of hypertension is not on an inflammatory basis. For as it has been so well pointed out by Klemperer and Otani (54) in a study of eighteen cases of malignant hypertension, there is in no case found a polymorphonuclear infiltration as in glomerulo nephritis; intoxication reaction in these cases. Koenigsberger, Bannick and Beaver (55) however, have reported a case in which the onset of symptoms followed an attack of acute tonsilitis, probably of streptococcic origin. Following this there was vasospasm which ultimately led to infec-

tion in setting off the hypertensive changes. Finally we must also consider the fact that McMahon and Pratt (13) in their extensive study of cases found diptheria in two patients and lead poisoning in some of the others. By way of review, therefore, we have found a great variety of suggested etiological factors embracing renal ischemia, pressor substances, endocrinology, neurology, and intoxications, none of which has been definitely proven, but many showing apparent strong points in their favor.

PATHOLOGY

Confusion reigns when clinicians and pathologists attempt to reach an agreement for an accurate classification of malignant hypertension. The important question centers about the query as to whether this malignant hypertension is a distinct clinical-entity, or if it is really not only a more progressive stage of the benign essential hypertension. However, all authorities seem to agree that the pathological picture, seen at the autopsy table in cases of this malignant type, is a distinctly characteristic lesion and undoubtedly of a much more severe nature than any similar lesion seen in the other hypertensive states. As to the possibility of the lesions being due to a separate and distinct etiological agent, or if they are merely terminal or more rapidly fatal pathological processes complicating the benign forms, is as yet a question to gain universal agreement. In this chapter, therefore, let us consider the pathological picture as seen by various authorities on hypertension.

The Site of the Lesion

Nearly all agree that the outstanding pathological changes occur in the arterioles. The kidney is

always involved and in all cases usually shows the most severe changes; but all arterioles may be subjected to these changes. Going back into the literature we find Gull and Sutton (3) describing their "arterio-capillary fibrosis" as occurring quite generally throughout the body, and that the kidneys merely shared in the disease. Of the earlier writers Johnson (4) and Ewald (57) also share this view of the generally wide spread lesions. Later Jores (58), Evans (59), Fishberg (9), and Bell and Clawson (19) describe this wide spread arteriolar disease, but fail to find similar changes in the smallest vessels of skeletal muscle. Brown (52), who advocates operative procedures in the treatment of this disease, believes that biopsy of skeletal muscle will show something of the general arteriolar changes. He holds that such biopsy results are good criteria for the advisability of operation in these cases. Adams (60), in describing his finding in malignant nephrosclerosis, found changes extensively in the kidney, but also in the heart, brain, pancreas, capsule of the adrenal, G. I. Tract, spleen, and skeletal muscle. Even the child who shows malignant hypertension, may give this diffuse arteriolar picture. Craig (34), in a case of malignant hypertension in a child, found typical arteriolar changes

in all organs except the lungs. The order of severity of the lesions he found to be in the kidneys, spleen, suprarenals, bladder, liver, voluntary and heart muscle. After a general review of the literature, therefore, it seems that whereas the arteriolar lesions are quite wide spread, most discussion is centered about the kidney pathology. With such in mind, most of the detailed pathological report in this paper shall be concerned mainly with the renal lesion.

The Gross Pathology

In this disease entity, if we disregard other coexisting pathological states, the two organs showing most pronounced gross pathology are the heart and kidney. (13) McMahon and Pratt (13), in a series of cases, found the heart to average six hundred grams with left ventricular hypertrophy. They point out that grossly it is difficult to differentiate the heart of malignant nephrosclerosis from that of chronic glomerulo nephritis, except that in the latter the cardiac hypertrophy seems to be less pronounced. From their cases they find that in general the kidney is of about normal size with congestion of the cortex, medulla, and petechial hemorrhages throughout the kidney and beneath the epithelium of the kidney pelvis. Such changes they do not recognize

in the benign nephrosclerosis. In accord with these findings, Klemperer and Otani (54), in a general survey of autopsies in sixteen cases of malignant hypertension, report the findings of an enlarged heart, and kidney only slightly reduced in size and characterized by pin head or larger hemorrhages. The post-mortem findings in Craig's (34) case of malignant hypertension in a child, showed that one kidney was reduced in size while the other was near normal. Of all the autopsy reports reviewed for this paper the majority of cases have shown that in general the kidney varied from two-thirds normal to normal in size. One is also impressed in these reports by the consistent ease with which the capsule stripped from the kidney (in contrast with the difficulty encountered in cases of chronic glomerulo nephritis) and the frequency of the presence of small white granulations on the surfact of the kidney. (8), (54), and (13).

Microscopic Findings

We now come to a discussion of the most important pathological changes seen in malignant hypertension. As has been mentioned before, microscopic sections of the arterioles are usually the positive differentiating criteria between this disease and the more benign hypertensive states. This section, then, shall be

devoted to a description of such microscopic findings as seen by various authorities on this subject. Whereas most of the descriptive pathology will be referred specifically to the renal arterioles and associated changes, it must be remembered that similar arterioler changes, although perhaps not so severe, may be seen elsewhere in the body.

Although the term malignant hypertension has been used extensively only for the past two or three decades, we find some of the earlier writers describing arterioler findings. In 1872, Gull and Sutton (3), in their cases of "arterio-capillary fibrosis," held that the minute pathology was one of degeneration rather than a hypertrophy. Later in 1877, Ewald (57) found a medial hypertrophy to be the predominent arterioler change. Four years after this work, Mohamed (5) reported cases of chronic Bright's disease without albuminuria in which he found hyaline thickening of the arteries and occasionally of the adventitia. Also he saw a fibro hyaline thickening of the capsule of the malpighian tufts involving the vessels of the glomeruli and in some cases obliterating them. In 1914 Fahr (7) described his arteriolar sclerosis and necrosis in cases of malignant nephrosclerosis. From 1921 to 1928 the following patholog-

ical reports are outstanding. Evans (59) described a medial hypertrophy as well as intimal proliferation and hyalinization. Jores (58) held that there was a wide spread intimal hyalinization of the arterioles. While Bell and Clawson (19) in study of a large series of cases, conclude that definite sclerosis of the afferent glomerular arterioles and in the loops of the corresponding glomeruli is typical.

More recently (since 1929) there has been published numerous detailed pathological descriptions in the findings of microscopic study of tissues in cases of definite malignant hypertension. From these reports a few have been chosen as being very descriptive and typical of the general concensus of opinion. Klemperer and Otani (14) in a study of eighteen cases, describe a necrosis of the arterioles, and a cellular intimal proliferation of the distal portions of the interlobular arteries. In these cases they show that sixty-two per cent of the glomeruli were unaltered, and in no case was there evidence of a polymorphonuclear infiltration. Two years later they published a more detailed report of microsopic sections in these cases of malignant hypertension. (54) They report an extreme narrowing of the interlobular arteries caused by a cellular intimal

proliferation, and the necrosis of the arterioles which was present in every instance. Whereas the arteriolar changes were the most outstanding, they do recognize a less conspicuous alteration of the glomeruli. Here there was a collapse of the capillaries and anemia, and degeneration changes in the capillary wall and epithelial lining. This degeneration varied in degree from fatty infiltration and hyaline degeneration to complete necrosis. These men also pointed out that an acute alteration of the tubular parenchyma, as was evidenced by fatty infiltration, hyaline degeneration and necrosis, was never lacking. Cain (29) from his necropsy studies of twenty-seven cases of malignant hypertension, described diffuse changes involving the glomeruli, tubules, arterioles, arteries, and interstitial tissue. He, too, found the most marked changes to occur in the arterioles. These changes consisted in extreme narrowing of the lumen, apparent increase in the numbers of endothelial cells, sub endothelical fatty and hyaline degeneration, apparent thickening of the tunica media and an increased amount of connective tissue chiefly in the tunica adventitia. The ratio between the wall and the lumen of the renal arterioles was markedly reduced. In sixteen selected cases of malignant hypertension, Murphy and Grill

(18) found six in which there had developed necrotic lesions in the walls of the afferent glomerular arterioles and in the loops of the corresponding glomeruli. In 1936, Kimmelstiel and Wilson (21) declared that endarteritis in its diffuse form is to be regarded as the most characteristic histological sign of malignant hypertension, while arteriolitis (or necrosis) is to be more closely related to terminal renal failure than to hypertension itself. More recently Moritz and Oldt (23), considering arteriolar sclerosis in general, defined three main types of chronic arteriolar disease; namely, intimal hyalinization, medial hypertrophy and degeneration, or intimal proliferation as the case may be. The second type of these three semms to fit in most closely with the generally accepted pathological process seen in malignant hypertension. Choisser (61) in 1937 arranged a classification of the nephritides which may be well to reprint here to indicate the site of the renal lesion in malignant nephrosclerosis, as compared to other kidney malfunctions.

A. Inflammatory

1. Glomerulonephritis

a. Focal

1. Embolic

2. Benign hemorrhagic

b. Diffuse

1. Acute

2. Subacute

3. Chronic

B. Vascular

1. Nephrosclerosis

a. Arterial

b. Arteriolar

c. Arteriolo

1. Sclerosis

2. Necrosis

C. Degenerative

1. Simple Nephrosis

a. Bacterial Toxic

b. Jaundice

c. Eclamptic

d. Chemical

e. Amyloid

D. Lipoid Nephrosis

His hypertensive kidney is that reserved for cases in which the afferent arteriole of the glomerulus is primarily affected. Sclerosis designates the benign and the necrosis is symbolic of the malignant hypertensive state.

Pathogensis

McMahon and Pratt (13), who are outstanding among the minority who consider malignant nephrosclerosis to be a distinct clinical entity, have done considerable and extensive study on tissue pathology in their cases. They believe the pathogenesis not to be a single change, but in reality a variety of transformations. It seems, therefore, to be of advantage to review here their ideas on how these end results occur. They see a hypertrophy of vessels with marked thickening of the media and a dilatation of the lumen of the larger vessels. In the intima and adventitia there seems to be a reduplication of the internal elastic lamina and an increase in connective tissue. In the smaller arteries and arterioles, they find a fluid mucoid material accumulating beneath the endothelium; such accumulation may present an apparent occlusion of the lumen. Then there is a proliferation of endothelial cells which become incorporated in this underlying ground substance. Later there may be

organization within the thickened intima, fibrils appearing within the amorphous ground substance, and an increase in cells beneath the endothelium. These cells become drawn out as spindle like forms and tend to arrange themselves in concentric layers which are separated by collagin fibrils. This picture, they point out, has been called -- 1. "fibrosis of the intima," 2. "endarteritis obliterans," 3. "intimal swelling." Eventually from this process there is a narrowing of the lumen, which a thrombosis may hasten. Now in some cases they believe there is a continuation of the process with "marked distruction of the entire wall with fragmentation of the vessel wall resembling a dissecting aneurysm, a saturation of the wall with red blood cells, plasma and fibrin, necrosis of the muscle fibers, and hemorrhage into the surrounding stroma." These latter changes they believe to be the most spectatular lesion of the disease. It is also their opinion that the tubules may show varying types of degeneration and necrosis, and that the stroma of the kidney increases and shows signs of chronic resorptive inflammation with a tendency toward foci of lymphocytes and mononuclear cells.

SIGNS AND SYMPTOMS

In general the symptoms of this disease are similar to other cardio-vascular-renal diseases, but at the same time tend to be definitely characteristic. In every instance such symptoms are particularly outstanding because of their very rapid onset, their extremely severe nature, the lack of response to therapy, and their definite downhill course with ultimate fatal termination in a very short time after onset. Uremic symptoms are often associated with malignant hypertension in its terminal phase, but as pointed out by Keith and Wagener (8) clinically there may be four main classes of this disease dependant upon the predominant manifestations. Consequently they recognize the cardiac, cerebral, renal and combined forms. Even though all of the symptoms are the result of vascular disease, we choose to discuss such symptoms under the category of those organs most severely affected.

1. General Symptoms

In the early work of Gull and Sutton (3) we naturally find no reference to a clinical diagnosis of malignant hypertension. Yet from their pathological descriptions we may be lead to believe that today we

would consider a good many of their cases as such. It is interesting to note that the general symptoms of their patients were those of a general malaise, loss of appetite, dyspepsia, failing digestion, loss of strenth, and some emaciation. Today outstanding clinicians comment on the pallor, anemia, loss of weight, and loss of appetite seen in their patients who are suffering with malignant hypertension. (13) That a weight loss may be very striking is seen in the two case reports of Smith (28) in which, though the duration of the disease was only a matter of a few months, twenty-four and forty pounds were lost respectively. Similarly in nearly all their cases of malignant hypertension, Murphy and Grill (18) find a weight loss to be typical, and also they find associated anemia, particularly in the terminal stage. That there is such an anemia is advocated by others as well (54) but it is denied as being a consistent finding by Keith and Wagener (62).

2. Cardio-vascular Symptoms

Of all the cardio-vascular signs and symptoms the chief one obviously is the high blood pressure which is foremost in diagnostic importance. There is a gradually rising systolic and diastolic blood pressure which is maintained at a high level. (13) Subsequently many

cases frequently may show signs of cardiac insufficiency or may go on into a definite cardiac failure. Such failure makes itself known by the usual symptoms of dyspnea, palpitation, ankle edema and ascites plus the finding of cardiac hypertrophy with left ventricular dilatation. (54) Realizing the strain that is put upon the heart in maintaining such high pressure it is easy to understand why the heart may "give out" in these cases and death ultimately result from such failure. Ordinarily, vascular changes manifesting themselves in the extremities are quite rare. However we do find a case report of a pecular vascular disease of the upper extremities in which there were symmetrical painful lesions with subsequent gangrene of the finger tips. (64) At first this was believed to be a case of Raynaud's disease, but later was diagnosed clinically by additional signs and confirmed at autopsy as being a typical malignant vascular nephritis (malignant hypertension). Practically all case reports reviewed for this paper show that a typical finding was cardiac enlargement with or without the above mentioned heart failure. Other characteristic symptoms due to vascular changes are seen in the eyes, brain, and kidney. However, to simplify the picture, let us consider each of these separately.

3. The Eyes

Visual disturbances are a part of the typical story of the malignant hypertension sufferer. He will at first complain of a blurring of vision which grows progressively worse until he is unable to see clearly at all. (54), (13), (16), and (60) The typical sign is that of a very characteristic retinitis. In fact most of the present day clinicians have come to look upon the retinal signs of utmost diagnostic and prognostic significance. However to Keith (65) goes the credit for such adequate and descriptive work on the retinal changes. His description of this retinal picture is used as a basis for the opinions of most clinicians today. For a detailed report of this retinitis please see the chapter on diagnosis.

4. Cerebral Manifestations

The patient will often present himself to the physician because of frequent spells of headaches, dizziness, and vomiting. The headaches are extremely severe, and particularly late in the disease tend to be almost continuous. (54), (13), and (16) In some instances the cerebral symptoms may be so severe as to give definite neurological signs of loss of motor power, paralysis, or cerebellar ataxia. (66) In those patients who present

such cerebral manifestations a fatal termination by cerebral accident is not uncommon. (8) That these cerebral manifestations are a result of this disease itself and not due to changes in the brain coming with age, seems to be well brought out in Craig's case report of a boy of eight years of age dying from malignant hypertension. In this case the chief prodromal symptoms were severe frontal headaches and convulsions at times. However death was eventually due to renal failure. (34) At times the neurological syndrome may become so severe that differential diagnosis from a brain tumor is very difficult. The picture of headaches, vomiting, choked disc, paralysis, etc. has been given the name of hypertensive encephalopathy by Fishberg (66).

Renal Symptoms

In view of the renal pathology found in these cases, it would seem logical to expect to find some symptoms and signs of renal insufficiency. That such is not always true was well pointed out by Keith and Wagener (62) when they described definite clinical cases of malignant hypertension in whom there was adequate renal function. However, the truly typical terminal symptoms in these cases is that of kidney failure. At first the characteristic picture is on a cardio-vascular basis but

later changes to renal manifestations, as evidenced by the fixation of the specific gravity--1.010 to 1.012. Then there follows a polyuria which later changes to an oliguria. Now the typical signs of renal failure occur --the urine shows albumin, casts and red blood cells, while the blood gives an elevated non protein nitrogen and creatinine content. Finally there is fatal termination in a typical uremia. (13) It is the opinion of McMahon and Pratt (13) that 65% of patients with malignant hypertension die in uremia. In his review of twenty-seven cases, Cain (29) found that all but three showed an impairment of excretion of nitrogenous products before death. In the Babot case 20352 (63) it was shown that a patient was first seen with a complaint of headaches and dizzy spells, and diagnosed as a malignant hypertension case. At the first admission the renal function was adequate, but eighteen months later the kidney became markedly impaired with subsequent early death. At the time of this last admission the additional symptoms were choked discs, severe headaches, palpitation, secondary anemia and vomiting. Blaindell (67) believes that malignant hypertension terminates fatally in renal failure. It is his opinion that the malignant form of hypertension is that which produces an early, rapidly

progressive glomerulo nephritis within two or three years after the onset of the hypertension. Whereas the terminal stage of this disease is often characterized by renal failure, it should be mentioned that few actually believe this to be a true glomerulo nephritis.

By way of a brief review therefore we may lump together all of our findings and say that malignant hypertension is characterized by symptoms referrable to the heart, brain, and kidneys, in the main, and that while all symptoms are present in each patient to some degree, one of these three organs usually dominates the picture. The terminal symptoms may be those of a cerebral accident, cardiac or renal failure or a combination of these as the case may be. However in view of what we have learned concerning the renal pathology in this disease, does it not seem logical to assume that if these peculiar pathological processes were allowed to go to the final stage all cases of malignant hypertension would die in uremia?

DIAGNOSIS

To make a clinical diagnosis of malignant hypertension it is not difficult particularly if the patient is seen early after the onset of the disease and an adequate study made on physical and laboratory examination. In the preceeding chapter we learned that the patient may present himself to his doctor complaining of frequent attacks of headaches, vague visual disturbances, some dizziness, a loss of appetite and perhaps some weight loss. Examination will reveal first of all a very high and persistent blood pressure. Adams (60) considers the height of the diastolic pressure plus the comparatively young age of the patient to be good criteria in differentiating the malignant from the benign hypertension. This far the physican will have a fairly typical story, and then by use of his opathalmoscope he may recognize a retinitis characteristic of this disease. (65) Depending upon the case there may or may not be additional urinary findings. However as we have further seen there may be four main clinical manifestations of this disease, namely, the cardiac, cerebral, renal and combined form. (8) Hence if the physican is called in

to see one of these cases when the particular manifestations is quite pronounced, the picture may at first be somewhat confusing. Ellis (22) has also recognized these four clinical types but holds that certain findings are quite characteristic of all. In his opinion a single most important pathognomonic sign is the retinitis, in addition he points out the comparative young age of the patient, the height and fixity of the blood pressure and the evidence of a wide-spread vascular involvement common to all four forms. However each of these clinical types may simulate certain other syndromes; consequently it is of value to point out here some of the differential points in each instance.

1. Basophilic Adenona of the Pituitary

Certain cases of this nature have shown an elevated blood pressure and other signs simulating malignant hypertension. (41) In fact some authors hold that there is an etiological association between these conditions. (40) However such cases of pathology in the pituitary may be recognized by the additional signs of obesity, hirsutism, osteoporosis and polycythemia (Cushing's syndrome) (43).

2. Thyroid Disease

Occassionally there has been difficulty in

differentiating malignant hypertension from the various Thyrotoxicoses. (44) However as a general rule the exopthalmos, fine tremor, palpable thyroid, elevated basal metabolic rate and response to iodine are usually definitely diagnostic of the thyroid pathology. In addition the patient suffering from malignant hypertension will give a quite different story of the mode of onset. Nevertheless we must not lose sight of the possibility of the coexistence of these two diseases.

3. Cardiac Failure

If the patient is seen in a state of cardiac failure, as often he may be particularly late in the disease, some difficulty may be encountered in an attempt to explain the cause of such failure. A thorough review into the previous history should give the typical story of malignant hypertensive disease and in addition a study of coexisting signs and symptoms is usually conclusive. (8), (13), (54), and (16). However we must always consider the possibility of luetic, rheumatic or other chronic infections processes.

4. Brain Tumor

In certain cases of malignant hypertension the cerebral manifestations become so severe that they closely simulate symptoms seen in brain tumor. Pepper (68)

brings out this point very clearly in his discussion of cases of malignant hypertension simulating brain tumor. He shows that this disease may be accompanied by a great increase of intracranial pressure in the absence of gross hemorrhage and without obvious renal failure. The spinal fluid pressure may reach 500 mm. of water, and there may be a papilledema of at least six diopters swelling. In his opinion however an expert opthomologist can differentiate the source of these swellings by a study of the retinal picture. Also he brings out the point that high blood pressure is rarely if ever caused by a slowly developing mass in the brain. In addition the presence of other characteristic symptoms and findings usually make it possible to differentiate malignant hypertension from brain tumor.

5. Chronic Glomerulo Nephritis

The typical latent urinary findings or uremic symptoms often make it very difficult to differentiate certain of these cases from a chronic glomerulo nephritis. McMahon and Pratt (13) admit that in certain cases the terminal stage closely simulates a glomerulo nephritis, except that in malignant hypertension edema is usually absent. It is the opinion of the writer that if the patient were considered for a diagnosis only in this

terminal stage, a differentiation between these two conditions is practially impossible unless one is very adept with the use of the opthalmoscope. However if it is possible to get an accurate history of the patients condition previous to this stage, considering the onset of signs and symptoms and the progressive course of the disease, there should be sufficient clues to make the diagnosis.

6. Other Conditions

From a standpoint of differential diagnosis, there are certain other syndromes in which hypertension is the predominate sign that must be considered. Such conditions are urinary obstruction, obesity, lead poisoning, adrenal tumor, aortic insufficiency, coarctation of the aorta and arterio-venous aneurysm. (23) However adequate history, physical examination and laboratory findings easily rule out each of these conditions.

Because so many authors have referred to the value of retinal study as being signficant from a diagnostic and prognostic standpoint in malignant hypertension, it seems important to present a description of these findings here. In the literature the most accurate and detailed reports of these findings are given by Keith (65) In his opinion it is the type of retinitis and not

its severity that is characteristic. The edema of the disc is a striking feature in all cases and is often out of proportion to the other retinal changes. He believes that the retinitis of whatever grade runs a characteristic course of four stages. Under the circumstances it is felt that for adequate description of Keith's beautifully descriptive work, it is only fitting and proper to quote him directly.

Stage 1--"there is hyperemia and mild edema of the disc and peripapillary portion of the retina with a few superficial hemorrhagic areas and cotton wool exudates".

Stage 2--"the edema of the disc and retina becomes more marked and spreads into the maccular region and periphery; the hyperemia continues; the areas of hemorrhage and cotton wool exudate become more numerous and are found farther away from the disc and in the deeper layers of the retina as well. A few punctate exudates are seen."

Stage 3--"the edema begins to recede from the peripheral portion of the retina and small spots of proliferated pigment are seen in its stead. Punctate exudates begin to out number the cotton wool exudates and in the maccular region arrange themselves into imperfect star figures. The hemorrhagic areas are relatively fewer and in the main more peripherally situated. The hyperemia

of the discs is less apparent and may gradually fade. As the retinitis progresses through these stages the degree of the associated sclerosis of the retinal arterioles becomes more marked, due partially to perivascular thickening caused by the edema of the surrounding retina."

Stage 4--"the disc has become definitely pale and only blurring and increased connective remains as evidence of the previous edema. Only a few residual small punctate exudates may remain, usually in the maccular region. There is definite perivascular thickening along the walls of many of the vessels, veins as well as arteries. Areas of proliferated pigment are numerous, especially in the macula and periphery. Patchy clerosis of the choroidal arteries is noticeable, and occassional small hemorrhagic areas may be present."

From the diagnostic and prognostic standpoint it is his idea that retinal changes are more significant and occur earlier than noticeable renal changes.

PROGNOSIS

The outlook for patients who have developed the malignant hypertension syndrome is very poor. In a series of fourteen cases so diagnosed and followed, death occurred in from one to forty-four months. (8) If one makes a survey of definite cases of malignant hypertension reported in the literature, he is impressed by the very rapid downhill course of the disease with almost one hundred per cent fatal termination. It has been said that once this disease has become established, there are no remissions. (18) However this is not always true if we are to consider those reports of cases in which operative procedures have been employed. (52), (50), and (49) In such cases it was shown that those who did survive the operations showed quite definite improvement for a time. Such remissions however, have been reported after only a few months observations; what happened after that time is not quite clear. For the most part the prevalent feeling as to the outlook for patients suffering from malignant hypertension is quite well summed up by Davis and Wanderhoof (32) when they say that the prognosis is almost entirely hopeless.

TREATMENT

The possible etiological factors giving rise to the syndrome of malignant hypertension have been considered elsewhere in this paper. After a general review of the various opinions as to the cause of the disease, we found ourselves unable to state specifically what brought on this condition. It is a well grounded fact that if the medical profession is to adequately treat and cure a disease process, treatment must be directed at the cause. Realizing then the vagueness of the etiology, we are not surprised to find the treatment quite inadequate and tending to be mainly symptomatic or palliative rather than curative. Treatment outlined for these patients has been attempted both from the medical and surgical standpoint.

The Medical Treatment

The medical regime for a patient with malignant hypertension will be quite similar to that for essential hypertension in general. At the onset there must be moderation in everything. Adequate rest with sufficient sleep must be had in full measure at all cost, giving sedatives when necessary; of these chloral is one of the

best. When these cases are seen early the diet need not be changed markedly and there is no particular indication for fluid restriction. Exercise is to be moderate but as a rule, absolute advoidance is not advisable. However as it has been pointed out symptoms rapidly grow more severe and treatment must be directed toward those outstanding special symptoms. Headaches are usually quite severe. The morning headache and dizziness and other head symptoms often respond to one or more of the following procedures:

1. Hot coffee on awakening
2. A saline purge
3. Aminophyllin or phylicin with or without phenobarbital.
4. Intrait de gui
5. Venesection
6. Sweat baths (dangerous)

When the patient develops a cardiac failure digitais is indicated, and apoplexy will require the generally accepted routine treatment. When renal function becomes inadequate, treatment consists of much the same management as is given for glomerulo nephritis. In an attempt to find a drug which is of benefit in these conditions, or some procedure which will bring relief, many therapeutic measures have been tried. Among such are all the nitrites, bisub-

nitrate, the iodines, benzyl benzoate, theobromine and allied drugs, atropin and various belladonna derivatives, garlic, ackinton, calcium salts, misletoe extracts, potassium sulphocyanate, organ extracts such as liver, pancreas ovarian and thyroid, high frequency currents, venesection, lumbar puncture, low protein diets and Allen's low salt regime. (11), (69) In the opinion of O'Hare (11) all of these have been found wanting. In other words therefore the best treatment for these cases is a routine symptomatic management with particular attention to special symptoms as they arise.

Surgical Treatment

In the last few years there has been a tendency toward operative procedures in the treatment of this disease. In 1934, Brown (52) reported two cases in whom there was definite improvement. In the first of these he resected the left major and minor splanchic nerves and removed the first lumbar sympathetic ganglion. In the second instance the operation consisted of a laminectomy with subsequent removal of anterior spinal nerve roots from the six thoracic to the second lumbar vertebrae. He advises operation on younger subjects, probably less than forty-five, who have minimal sclerosis of the retinal aterioles and of the arterioles of muscles, who have no demonstrable impairment

of renal or cardiac function and whose expectancy of life is limited. Page (51) similarly by bilateral section of the anterior nerve roots from the sixth dorsal to the second lumbar spinal nerve, treated five cases of malignant hypertension. In these five cases, three suffering from highly malignant hypertension were unaided, while two with less severe symptoms appeared to be improved. Adson (50) is also of the opinion that splanchnic resection, removal of the lumbar ganglia and suprarenal resection are a benefit to these patients. Koenigsberger (49) reports a case of malignant hypertension in which the pressure was 180/100 and eight monts later was 130/100. After reading these various reports one cannot deny the fact that some apparently are improved, however there does seem to be a reasonable amount of doubt as to how long such improvement will last.

Some men have advocated Thyroidectemy in the treatment of malignant hypertension. (44), (70) However O'Hare (11) holds that such procedures as thyroidectemy, unilateral adrenalectomy, denervation of the adrenal and kidney, extensive removal of spinal nerve roots and ganglionectemy, and X-ray of the pituitary are mainly experimental and results are not yet sufficiently adequate to give universal acclaim. In the report of the Cabot case 20352

(63) it was shown that treatment of a case of malignant hypertension by irradiation of the adrenals gave very little effect. Yater, Coe and Rodis (53) in reasoning that the hypertension resulted from an excessive stimulation of the vasomotor center which is thought to be located in the floor of the fourth ventricle, hope that x-radiation over this area would result in a raising of the threshold of excitability without injury to other medullary elements. However their results were not particularly good although they did feel that further irradiation using larger doses would give improvement.

We have found therefore treatment for this condition varying from a conservative medicinal management to a radical surgical procedure. The former shows itself merely palliative, the latter has shown good results in some instances but as yet is considered to be in it's experimental stages.

CONCLUSION

1. Malignant hypertension is a distinct clinical entity that manifests itself chiefly in the middle aged adult, but may be seen in very young or elderly people. Clinically the disease is particularly characterized by its sudden onset and symptoms referable to the heart, brain and kidney which during the course of the disease grow progressively more severe until death intervenes due to a failure of one or more of these vital organs most seriously affected. This disease process is not a phase or a complication of the so called benign essential hypertension; but certain people in whom there is a predisposing hereditary factor, may show what we might call benign malignant hypertension which ultimately may undergo typical malignant degeneration.

2. The etiology is as yet unknown, an inherited constitutional factor plays a most important role in the selection of these people who are to become afflicted by this disease. This constitutional factor is probably on the basis of a vascular susceptibility, particularly of the smallest vessels, to the specific exciting factor whatever it might be. At the present time the most plausable

explanation of this exciting factor seems to be a renal ischemia with an associated increased amount of pressor substance in the kidney. Environmental factors or the "pace of modern life" are not etiological agents in producing this particular type of hypertension, but serve mainly to hasten the sequelae once the disease process has set in.

3. The pathological processes are confined chiefly to the arterioles, consisting of a sclerosis, necrosis and an endarteritis. Anatomically the arteriolar lesions may be found widespread in the body but the renal involvement is most pronounced and probably most important in bringing about the increased blood pressure. Of the other splanchnic vascular system, that of the spleen, pancreas, and kidney come next in importance.

4. The symptoms particularly characteristic of the disease are frequent severe headaches, dizziness, vomiting, visual disturbances, loss of weight and appetite, pallor, and anemia in the terminal stages. Late manifestations are shown by renal or cardiac failure or in the form of a cerebral accident.

5. The diagnostic signs or findings most characteristic of this syndrome are: 1. the blood pressure which is usually high and remains fixed, and shows particu-

larly high diastolic pressure; 2. the retinitis which is a very typical and consistent finding. These retinal changes occur earlier and in many cases are more significant than renal failure signs which are not found early in all cases.

6. Prognosis is invariably very poor particularly for those in whom the disease appears at an earlier age. Death occurs in nearly all cases in one to thirty-six months.

7. Medicinal treatment is of no value except to alleviate the various symptoms as they arise prior to death. In some cases surgery may give remission for a few months, but as yet surgical procedures as a cure for patients suffering from malignant hypertension, is still in an experimental stage. Surgery is, however, of no benefit at all to those patients in an advanced stage of the disease. To give adequate treatment will be dependent upon the determination of the exact cause for the pathological changes giving rise to the elevated blood pressure.

BIBLIOGRAPHY

1. Bright, Richard: Selections from the "Reports of Medical Cases" (1827) (In Long, E. R. : Selected Readings in Pathology. 1929 pp. 165 - 195).
2. Wilks, Samuel: Cases of Bright's Disease with Remarks: Guy's Hospital Reports, 8 : 232, 1852
3. Gull, William, and Sutton, Quoted by Gull, William: Arterio-Capillary Fibrosis, Brit. M. J. 2 : 673, 1872
4. Johnson, George: Lectures on the Pathology, Diagnosis, and Treatment of Bright's Disease. Lecture III, Chronic Bright's Disease. Brit. M. J. 1873, I : 161 - 165.
5. Mahomed, F. A.: Chronic Bright's Disease with Remarks: Guy's Hospital Reports, 8 : 232, 1852
6. Volhard, Franz: The Kidney in Health and Disease, Burglund, Hilding, Medes, Grace, Huber, G. Carl, Longcope, Warfield T., Richards, Alfred, N. Lea, and Febiger, Philadelphia, 1935. (Cited By 23).
7. Falr, T.: Handbuch der Speziellen Pathologischen Anatomie und Histologie, Henke, F., and Lubarsch, O. J. Springer, Berlin, 1934, 6. (Cited by 23).
8. Keith, N. M. ; Wagener, H. P. , and Kernohan, V. W. : The syndrome of Malignant Hypertension, Arch. of

Int. Med. 41 : 141 1928

9. Fishberg, Arthur M. : Anatomic Findings in Essential Hypertension. Arch. Int. Med., 1925, 35, 650-668.

10. Christian, H. A. and O'Hare, J. : Nephritis (in Cecil, R. L. : Text Book of Medicine. Third Edition. W. B. Saunders Co. Philadelphia, 1933, pp. 969-987.)

11. O'Hare, J. P. : Management of Bright's Disease and Hypertension. New Eng. M. J., 212 : 1197-1202, June 27, 1935.

12. Strouse, S. and Saphiro : Hypertension, Nephrosclerosis and Nephritis. M. Clin, North America 16 : 359 - 382, September, 1932.

13. McMahon, H. E. and Pratt, J. H. : Malignant Nephrosclerosis. Amer. J. Med. Sc. 189 : 221 - 236, 1935.

14. Klemperer, Paul and Otani, S. : Studies on "Malignant Sclerosis" of the Kidneys. (Fahr) Arch. Path., 8 : 559 (Sept.) 1929.

15. Pilcher, J. F. and Schwab, E. H. : Arterioles in Malignant Hypertension : Case. South M. J. 28 : 688-693, Aug., 1935.

16. Shapiro, P. F. : Malignant Nephrosclerosis, Arch. Int. Med., 48 : 199, Aug., 1931.

17. Pickering, G. W. : The Peripheral Resistance in Persistent Arterial Hypertension. Clinic Sc. 2 : 209 - 235, May, 1936.

18. Murphy, F. and Grill, F. : So Called Malignant Hypertension: A clinical and morplologic study, Arch. Int. Med. 46 : 75 (July) 1930.

19. Bell, E. T., and Clawson, B. J.: Primary Hypertension Arch. Path. 5 : 939 (June) 1928.

20. Goldblatt, H., Lynch, J., Hanzal, R. F. and Summerville, W. W. : The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia. J. Exp. Med. 59 : 347, 1934.

21. Kimmelsiel, P. and Wilson, C. : Benigh and Malignant Hypertension and Nephrosclerosis; clinical and pathological study. Am. J. Path. 12 : 45 - 82, Jan., 1936.

22. Ellis, L. B. : Clinical Course of Malignant Hypertension. M. Clin. North America 15 : 1025 - 1039, Jan., 1932.

23. Moritz, A. R. and Oldt, M. R. : Arteriolar Sclerosis in Hypertensive and Non Hypertensive Individuals. Reprinted from Amer. J. Path. Vol. 8, 5, Sept., 1937.

24. Hines, E. A. Jr. : Recent Concepts Concerning Essential Hypertension. J. South Carolina M. A. 29 : 186 - 191, Aug., 1933.

25. Ayman, D. : Heredity in Arteriolar (Essential) Hypertension; clinical study of Blood Pressure of 1524 Members of 277 Families. Arch. Int. Med. 53 : 792 - 802, May, 1934.

26. O'Hare, J. P.; Walker, W. G. and Vickers, M. C. : Heredity and Hypertension, J. Am. A. 83 : 27 (July) 1924.

27. Zemp, F. E. : Hypertension-Cardiac Hypertrophy-Nephrosclerosis. South Med. & Surg. 98 : 202 - 207, April, 1936.

28. Smith, C. T. : Malignant Hypertension. South Med. & Surg. 99 : 115 - 116, March, 1937.

29. Cain, E. F. : Malignant Hypertension: The Histologic Changes in the Kidneys. Arch. Int. Med. 53 : 832 June, 1934.

30. Rose, Edward : Malignant Hypertensive Vascular Disease Simulating Hyperthy Roidism. Med. Clin. North America, Vol. 16, No. 1, 1932.

31. Riseman, F. E. F. and Weiss, S. : Age and Sex incidence of Arterial Hypertension. Am. Heart J. 5 : 172 - 190.

32. Davis, D. and Vanderhoof, D. : Malignant Hypertension in Young People. Virginia M. Monthly 57 : 31 - 33, April, 1930.

33. Mitchell, A. G. : Nephrosclerosis (Chronic Interstitial Nephritis) in Childhood. Am. J. Dis. Childhood 40 : 101 Aug., 1930

34. Craig, J. : Malignant Hypertension in Childhood. Arch. Dis. Childhood 6 : 157 - 164 June, 1931.

35. Goldblatt, H. : Production of Persistent Hypertension in Monkeys (Macaque) by Renal Ischemia. J. Exp. Med. 65 : 671 - 675 May, 1937.

36. Bohn, H. and Schlapp, W. : Untersuchunger Zum Mechanismus Des Blassen Hochdrucks; weitere Erfahrunger Uber Den Nachweis Pressorischer Stoffe Im Blute Beim Blassen Hochdruck, Ztschr F. Klin. Med. 127 : 233 - 242, 1934. (Cited by 37).

37. Aitken, R. S. and Wilson, C. : Attempt to Demonstrate Pressor Substance in Blood in Malignant Hypertension, Quart. J. Med. 4 : 179 - 190, April, 1935.

38. Prinzmetal, M. and Friedman, B. : Pressor Effects of Kidney Extracts from Patients and Dogs with Hypertension. Proc. Sec. Exper. Biol. and Med. 35 : 122 - 124, Oct., 1936.

39. Wakerlin, G. E. and Bruner, H. D. : Question of presence of Pressor Substance in Blood in Essential Hypertension. Arch. Int. Med. 52 : 57 - 65, July, 1933.

40. McMahon, H. E. ; Close, H. G. and Hass, G. : Cardio-vascular-renal changes Associated with Basophil Adenoma of the Anterior Lobes of the Pituitary (Cushing's Syndrome) Am. J. Path. 10 : 177, 1934.

41. Close, H. G. : Basophil Adenoma of the Pituitary Gland with Renal Changes. Brit. M. J. 1 : 356, 1935.

42. McCann, W. S. : Bright's Disease, Review of the Recent Literature. Arch. Int. Med. 57 : 630 - 642. March, 1936.

43. Cushing, H. : Basophilic Activation of Neurophopophysis and its bearing on certain Diseases characterised by Hypertension. Proc. Soc. Exper. Biol. and Med. 30 : 142. June, 1933.

44. Wohl, M. G. : Hyperthyroidism masked as (a) Malignant Hypertension (b) Auricular Flutter as Illustrated by two cases. M. Clin. North American 17 : 751 - 758. Nov., 1933.

45. Becher, Jos. : Zeit F. Klin. Med., 119 : 412. 1932 (cited by 44).

46. Cecil, H. L. : Hypertension, Obesity, Virilism, and Pseudo Hermaphrobitism as caused by Suprarenal Tumors. J. A. M. A. 100 : 463 - 466, Feb. 18, 1933.

47. Bain, C. W. C. : Etiologic Factors in Hyperpiesia. Brit. M. J. 1 : 57 - 58, Jan. 9, 1932.

48. Pickering, G. W. : The peripheral resistance in persistent Arterial Hypertension. Clinic Sc. 2 : 209 - 235, May, 1936.

49. Koenigsberger : Malignant Hypertension - Splanchnic Nerve Resection. Minnesota Med. 18 : 242, April, 1935.

50. Adson, A. W. : Surgical Treatment (Splanchnic Resection, Removal of Lumbar Ganglia and Suprarenal Resection) of Essential Hypertension. West. J. Surg. 44 : 619 - 623, Nov., 1936.

51. Page, I. H. and Heuer, G. J. : Treatment of Essential and Malignant Hypertension by section of Anterior Nerve Roots. Arch. Int. Med. 59 : 245 - 298. Feb., 1937.

52. Brown, G. E. : Sympathectemy for early Malignant Hypertension. M. Clin, North America 18 : 577 - 583. Sept., 1934.

53. Yater, W. M. ; Coe, F. O. and Rodis, I. : Treatment of Essential Hypertension by X-Radiation of Medulla Oblongata. South M. J. 25 : 730 - 733. July, 1932.

54. Klemperer, Paul, and Otani, Sadoa : Malignant Nephrosclerosis (Fahr) Arch. Path. 11 : 60 (Jan.) 1931.

55. Koenigsburger, C.; Bannick, E. G., and Beaver, D. C. : Acute Vasospastic Hypertensive Disease with transfer into Malignant Hypertension. Minnesota Med.

16 : 186 - 192. March, 1933.

56. King, John T. : The Causes of Hypertension. Inter. Clinics 2 : 103 - 124. June, 1933.

57. Ewald, C. A. : Uber Die Veranderunger Kleiner Gefasse Bei Morbus Brightii und Die Darauf Bezuglichen Theorien. Virchows Arch. F. Path. Anat. 1877, 71, 453 - 499. (Cited by 23).

58. Jores, Leonard : Arterien. Handbuch Der Speziellen Pathologischen Anatomie Und Histologie, Henke, F. and Lubarsch, O. F. Springer, Berlin, 1924, 2, 608 - 786. (Cited by 23).

59. Evans, Geoferey: A Contribution To the study of Arterio Sclerosis, with special reference to its relation to Chronic Renal Disease. Quart. J. Med. 1921 : 14, 215 - 282.

60. Adams, Leland J. : Malignant Nephrosclerosis (Malignant Hypertension) with report of two cases. Canad. M. A. J. 35 : 357 - 361. 1936

61. Choisser, Robert : A Pathological Classification of the Nephritides. Med. Ann. of Dist. of Columbia : 138 - 142 May, 1937.

62. Keith, N. M and Wagener, H. P. : Cases of marked Hypertension, adequate renal function and Neuro-Retinitis. Arch. Int. Med. 34 : 374. 1924.

63. Cabot Case 20352 : Malignant Vascular Nephritis. New England J. Med. 211 : 418 - 423 Aug. 30, 1934

64. Cabot Case 19352 : Malignant Vascular Nephritis. New England J. Med. 209 : 459 - 461. Aug. 31, 1933.

65. Keith, N. M. : Classification of Hypertension and Clinical Differentiation of Malignant Type. Am. Heart J. 2 : 597 - 608. Aug., 1927.

66. Fishberg, Arthur M. : Hypertension and Nephritis. Lea and Febiger. Philadelphia. 1931.

67. Blaisdell, E. R. : Malignant Hypertension. Maine M. J. 21 : 222 - 223. Dec., 1930.

68. Pepper, H. P. : Malignant Hypertension Simulating Brain Tumor. Penn. M. J. 35 : 75 - 78. Nov., 1931.

69. Mosenthal, H. O. : Treatment of Essential Hypertension. Inter. Clin. 2 : 145 - 162. June, 1933.

70. Becher, Jos. : Zeit F. Klin. Med., 119 : 412. 1932 (Cited by 44).