"Hypertensive Emergency": A Useful Diagnostic Category

In their commendable study, published in this issue of the Journal,[1] Bennett and Shea present convincing evidence of the need for the term "hypertensive emergency", not currently coded in the International Classification of Disease[2] as a legitimate clinical diagnosis. The authors report that lack of such a category has led to the misdiagnosis of complicated hypertension by physicians whose intention is to comply with the current code. Thus, patients with severely elevated blood pressure associated with neurovascular phenomena in the absence of the requisite funduscopic changes are often inappropriately coded as "malignant". Based on the classical work of Keith, Wagener and Barker,[3] the finding of papilledema has traditionally been regarded as necessary for the diagnosis of the "malignant phase," yet even the experts do not invariably accept this criterion.[4] Indeed, the World Health Organization recommended some 10 years ago that the finding of bilateral retinal hemorrhages and exudates, even in the absence of papilledema, was sufficient for the diagnosis of malignant hypertension,[5] a point which remains controversial.[6] A recent study by McGregor, *et al,* demonstrated that the 10-year survival in hypertensive patients with bilateral hemorrhages and exudates but without papilledema was 46 per cent, compared to 48 per cent when papilledema was also present.[7] The term "hypertensive emergency" has been invoked for a number of years[8] and has come into common usage in hospital practice. It has the advantage of obviating the requirement that the pathological status, which distinguishes "benign" and "malignant" forms of hypertension by the presence or absence of arteriolitis, be deduced from the clinical findings. However, the observation of bilateral retinal hemorrhages and exudates does correlate rather well with the presence of arteriolitis,[9] and is unquestionably of prognostic importance, even in the modern drug era.

Some of the problems with the current nosology of hypertensive disorders may be cited. The terms "benign" and "malignant" derive from the pathology of cancer and seem to this reviewer to be poor ones in the context of hypertension. Thus, "benign" designates hypertension in the absence of arteriolitis, but can hardly be considered "benign" in the light of the wealth of epidemiological data on the subject. The clinical categories of "primary" and "secondary" hypertension, based on whether or not an etiological factor can be identified, seem reasonable. If no cause is found, then the peculiar term "essential" frequently replaces the term "primary". These clinical categories of primary and secondary hypertension give no indication of the severity stage of the disorder, i.e., whether or not arteriolitis is present. For this purpose, clinicians utilize the pathologist's term of "malignant" when they believe arteriolitis is present, based on the funduscopic changes.

The clinician has gone one step further by dividing what the pathologist terms "malignant" into "accelerated" and "malignant"stages.[10] "Accelerated" indicates retinitis without papilledema, and "malignant" indicates retinitis with papilledema. While the clinician can identify retinitis and advanced papilledema quite well, there is often a difference of opinion on the presence or absence of mild papilledema.[7] Exclusive of the changes in the optic nerve head, it is doubtful that the pathologist could make the distinction between accelerated and malignant hypertension. If, in fact, the distinction lacks prognostic importance, then it would seem to be of little practical value. Hayreh, *et al,* reported in detail their findings in the optic fundi of rhesus monkeys with accelerated hypertension, produced by renal artery clamping.[11–13] They identified three characteristic lesions: hypertensive retinopathy, hypertensive chorioidopathy, and hypertensive optic neuropathy. The retinopathy, which appeared first, included focal intraretinal periarteriolar transudates, cotton-wool spots, retinal hemorrhage, and retinal edema. The periarteriolar transudates were attributed to focal dilatation of precapillary arterioles secondary to a breakthrough of autoregulation, i.e., a rise in blood pressure that overcomes the vasoconstrictive forces and leading to overstretching and leakage.[14] The choroidopathology included retinal pigment infarcts and peripheral retinal detachment. The optic neuropathy was identified by optic disc edema, which on resolution sometimes resulted in optic atrophy. It was attributed to ischemia of the nerve head, not correlated with an elevation in the cerebrospinal fluid pressure and probably secondary to an intense vasoconstriction of the choroidal vascular bed. It was concluded that the latter led to ischemic hydropic swelling of the axons, appearing as papilledema. The clinical importance of the distinction between Grade III and IV funduscopic changes may rest with the possible increased vulnerability with Grade IV changes to permanent visual impairment on rapid blood pressure reduction.[13]

Modern investigative techniques have also served to clarify another issue with respect to the arteriolar lesion in accelerated/malignant hypertension, the original terminology being "fibrinoid neurosis".[15] On electron microscopy, the "onionskin" proliferation, seen on light microscopy was shown to relate to a "loose laminar arrangement of basement membranes, reticular fibers, elastic fibers, and intimal smooth muscle cells."[16] The smooth muscle cells are necrotic, but there is little or no deposition of fibrin.[17]

The sequence of events by which hypertension changes from non-malignant to malignant is unclear, although there is general agreement that a very high level of pressure (diastolic $\geq$120 mmHg) is requisite for the acute changes in the arterioles ("necrotizing arteriolitis") that characterize the change. Activation of the renin-angiotensin-aldosterone system is a common but not invariable concomitant.[18] It has been postulated that, when absent, this system may have been activated at an earlier stage but was subsequently suppressed by the sodium-retaining consequences of the renal arteriolitis. Proponents of the renin hypothesis assert that a high renin level in conjunction with a high intravascular pressure is responsible for the widespread arteriolar damage.[19] Others point out that malignant hypertension can occur in Conn's syndrome, in which renin is suppressed.[20] Irrespective of this controversy, there is consensus that autoregulation of the microvasculature fails,[21] leading to intimal damage associated with plasma leakage, petechial hemorrhage, thrombotic occlusions, tissue ischemia, and infarction. In the brain, this sequence accounts for the development of hypertensive encephalopathy. In the study

by Chester, *et al*,[22] this syndrome was not associated with cerebral edema, although cerebrospinal fluid pressure was elevated in eight of the 10 instances in which it was measured.[5]

While it was not the purpose of the study by Bennett and Shea[1] to address etiological issues, it would have been of interest if some of the other identifiable epidemiological factors for malignant hypertension had been included in the survey. In the Glasgow study, hypertensive patients who smoked had five times the chance of developing the malignant phase.[23] The use of oral contraceptives by women appears to be an additional risk factor for malignant hypertension.[24] It is implicit that in the context of a hypertensive emergency the burden remains with the clinician to identify the cause. Some examples may be given where the proper approach to the patient in such a crisis varies widely according to the etiology: cerebral hemorrhage, pheochromocytoma, clonidine withdrawal, and the inadvertent use of an MAO (monoamine oxidase) inhibitor in combination with an indirectly acting sympathomimetic agent.

The pattern of clinical findings in the group of 100 patients with "hypertensive emergency" reported by Bennett and Shea was, in most respects, quite comparable to that found in previously published studies on patients with malignant hypertension.[25,26] Of particular interest was the finding that 38 per cent of all their patients admitted to the hospital for "hypertension" during a six-month period in 1986 had Grade III/IV funduscopic changes. This is an indication of the severity of illness required for hospitalization in current practice. It has been estimated that prior to the widespread application of modern antihypertensive therapy at least 1 per cent of hypertensive patients could be expected to develop the malignant phase.[27,28] If the 38 per cent of hypertensive patients admitted for accelerated/malignant hypertension (cited above) was largely the consequence of inadequate treatment, as suggested by this study, it also gives some sense of the magnitude of the pool of undertreated hypertensive patients in this urban setting from which it derived. Clearly, the social forces relating to this deficiency as identified in the paper by Bennett and Shea are of paramount importance.

REFERENCES

1. Bennett NM, Shea S: Hypertensive emergency: Case criteria, sociodemographic profile, and previous care of 100 cases. Am J Public Health 1988; 78:636–640.
2. US Public Health Service and Health Care Financing Administration: International Classification of Diseases, 9th Rev. Clinical Modification. DHHS Pub. No. (PHS) 80-1260. Washington, DC: Govt Printing Office, September 1980.
3. Keith NM, Wagener HP, Barker NW: Some different types of essential hypertension: their cause and prognosis. Am J Med Sci 1939; 197:332–343.
4. Kincaid-Smith P: Malignant hypertension: mechanisms and management. Pharmacol Ther 1980; 9:245–269.
5. World Health Organization: Arterial hypertension. WHO Tech Rep Ser 1978; 628:57.
6. Bulpitt CJ: Prognosis of treated hypertension 1951–1981. Br J Clin Pharmacol 1982; 13:73–79.
7. McGregor E, Isles CG, Jay JL, Lever AF, Murray GD: Retinal changes in malignant hypertension. Br Med J 1986; 1:233–234.
8. Koch-Weser J: Hypertensive emergencies. N Engl J Med 1974; 290:211–214.
9. Brown JJ, Davies DL, Lever HF, Robertson JIS: Plasma renin concentration in human hypertension III: Renin in relation to complications of hypertension. Br Med J 1966; 1:505–508.
10. Perera GA: Hypertensive vascular diseases: Description and natural history. J Chronic Dis 1955; 1:33–42.
11. Hayreh SS, Servis GE, Virdi PS, Marcus ML, Rojas P, Woolson RF: Fundus lesions in Malignant Hypertension III. Arterial blood pressure, biochemical, and fundus changes. Ophthalmology 1986; 93:45–59.
12. Hayreh SS, Servis GE, Virdi PS, Marcus ML, Rojas P, Woolson RF: Fundus Lesions in Malignant Hypertension IV. Focal interstitial periarteriolar transudates. Ophthalmology 1986; 93:60–73.
13. Hayreh SS, Servis GE, Virdi PS, Marcus ML, Rojas P, Woolson RF: Fundus Lesions in Malignant Hypertension V. Hypertensive optic neuropathy. Ophthalmology 1986; 93:74–87.
14. Byron FB: The pathogenesis of hypertensive encephalopathy and its relation to the malignant phase of hypertension; experimental evidence from the hypertensive rat. Lancet 1954; 2:201–211.
15. Volhard F, Fahr T: Die Brightsche Nierenkrankheit Klinik, Pathologie, und Atlas. Berlin: Julius Ringer, 1914.
16. Jones DB: The renal vascular lesions of severe and malignant hypertension: A light immunofluorescent microscopy, transmission and scanning electron—microscopy study. Clin Sci Mol Med 1976; 51:S27–S29.
17. Mandal AK, Bell RD, Nordquist JA, *et al:* Anatomic pathology and pathogenesis of the lesions of small arteries and arterioles of the kidney in essential hypertension. Pathol Annu 1977; 12:331–371.
18. Johnson JG, Lee S, Acchiardo S, *et al:* Normal plasma renin activity in malignant hypertension. J Clin Invest 1973; 52:43a.
19. Kincaid-Smith P: Understanding malignant hypertension. Aust NZ J Med 1981; 11(Suppl I):64–68.
20. Kaplan NM: Primary aldosteronism wih malignant hypertension. N Engl J Med 1963; 269:1282–1286.
21. Johansson B, Strandgaard S, Lassen NA: On the pathogenesis of hypertensive encephalopathy: the hypertensive "breakthrough" of autoregulation of cerebral blood flow with forced vasodilation, flow increase, and blood-brain barrier damage. Circ Res 1974; 34(Suppl I):167–174.
22. Chester EM, Agamanolis DB, Banker BQ, *et al:* Hypertensive encephalopathy: A clinicopathologic study of 20 cases. Neurology 1978; 28:928–939.
23. Isles C, Brown JJ, Cumming AMM, *et al:* Excess smoking in malignant-phase hypertension 1979. Br Med J 1979; 1:579–581.
24. Petitti DR, Klatsky A: Malignant hypertension in women aged 15 to 44 years and its relation to cigarette smoking and oral contraceptives. Am J Cardiol 1983; 52:297–298.
25. Gudbrandsson T, Hansson L, Herlitz H, *et al:* Malignant hypertension—Improving prognosis in a rare disease. Acta Med Scand 1979; 206:495–499.
26. Suk-Hee Y, Whitworth JA, Kincaid-Smith PS: Malignant hypertension: Aetiology and outcome in 83 patients. Clin Exp Theory Prac 1986; A8(7):1211–1230.
27. Kincaid-Smith P, McMichael J, Murphy EA: The clinical course and pathology of hypertension with papilledema 1958. Q J Med (new series) 1958; 27:117–153.
28. Perera GA: The accelerated form of hypertension: A unique entity? Trans Assoc Am Physicians 1958; 71:62–67.

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