High Blood Pressure Control: What Are the Next Steps?

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Hypertension is a very common condition in adults in industrialized communities, and about twice as common in blacks as in whites. It has been shown that hypertension is an important risk factor in cardiovascular disease, and especially in stroke. The benefit of antihypertensive treatment has been demonstrated in Veterans Administration trials. Hypertension is rather easily detected by screening a population.

Given these rather well-verified assumptions, it appears logical to expect that mass screening and treatment of the persons with identified cases should be a productive enterprise. But screening tests for many diseases with the aim of early treatment of the discovered cases have been placed in question by a number of workers, although others enthusiastically endorse them. A few controlled trials of multiphasic screening have failed to show appreciable benefit. Is hypertension an exception; is the uncertainty about the efficacy of screening justified in the case of hypertension? This question, among others, urgently needs to be answered.

Dr. Richard Remington addresses some of these questions in the final paper in this session. Dr. Remington is dean of the School of Public Health at the University of Michigan and an early proponent of randomized field studies on the effectiveness of hypertension control programs.—PHILIP SARTWELL, MD

IN DISCUSSION of 50 years of scientific progress, it is conventional to state that most of our knowledge has been gained recently. Fifty years is often considered the rough equivalent of a geologic age when applied to the advancement of science. This observation applies to statements about our understanding of high blood pressure, its causes, treatment, and epidemiology. After all, can we not properly date the original development of probability sample survey techniques from World War II or thereabouts? Can we not date the entire history of randomized controlled clinical trials from the late 1940s and early 1950s? Is the development of effective drugs for lowering blood pressure not encompassed within the past 25 years? Certainly, all these statements are true, but is it also true that 1929, the year that marked creation of the APHA Section on epidemiology, was really lost in the dark ages of knowledge and attitudes toward high blood pressure?

Literature Review

In searching for an answer to that question, it seemed reasonable to review the relevant literature published during 1929. This proved to be an interesting excursion. The literature is leavened by little savories such as the study by Vincent and Thompson (*1*) published in the

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March 9, 1929, issue of Lancet concerning the effects of music upon human blood pressure. These investigators played music to three groups of volunteers—musical, moderately musical, and nonmusical. The size of the groups was not specified. The musical group showed no response to a change in volume, but their blood pressure fell in response to a change of melody to a "pleasing" type. Other effects of the investigation were mixed. However, the investigators did comment on the difficulty of developing a valid experimental design. They said,

> We venture to suggest also that, since there is so much more music at the present date than in 1914, people have become to a certain extent immune to its effects. This is corroborated by the observation that, with some notable exceptions, professional musicians are not as much affected by music as musical amateurs. The best type of subject is undoubtedly a musical amateur of good taste and emotional susceptibility, who can, and habitually does, enjoy music in a naive manner without the exercise of too much critical faculty. Then, of course, there are corresponding difficulties with the type of music selected for the experiment. It is not to be expected, for example, that a musically sophisticated person will be roused to any very great emotion by the rendering of a Strauss waltz, even if he hears it direct from Vienna. On the other hand, it is not much use to try Holst's 'Planets' on a gentleman who can go into rapture over 'The More We Are Together'.

In 1929, Granger (*2*) reviewed the current conception of essential hypertension, which he defined as a systolic blood pressure of 145 mmHg or above and left ventricular hypertrophy without demonstrable cause, although he noted the hypertension may exist in the early stages without cardiac enlargement. Granger said that no definite cause has been established for the vast majority of cases of elevated blood pressure, a statement no less true in 1979 than it was in 1929. In fact, one landmark contribution of hypertension epidemiology has been to decrease successively the estimated fraction of cases of high blood pressure secondary to some known cause by reporting results of investigations based on well-defined general populations, rather than on selected clinical series. Granger believed that the height of the blood pressure probably was of great moment in determining the prognosis of the disease, a statement also as true today as it was then. He said, "Treatment should be directed mainly toward a regulation of life and habits of the individual, so as to promote rest, freedom from worry and aggravation, and moderate pleasurable exercise. Dietary restrictions are of use only in the obese, or when cardiac or renal incompetence occurs. Drugs have a very small field in this condition." Except for the sentence about pharmacological management, that statement is not bad, even today.

In 1929, several reports of an epidemiologic or quasi-epidemiologic type appeared. For example, Alvarez (*3*) reported analyses of blood pressure levels in 6,225 prisoners and 422 guards at the San Quentin prison. In this paper, Alvarez criticized the existing standards for normal blood pressure—for example, those arising from insurance data. He said such standards are based

on highly selected groups—for example, accepted risks for insurance. Alvarez argued the need for random sampling, and suggested that a booth be set up on a street corner with blood pressure measurements taken on the first 10,000 men and women passing the booth. As noted earlier, we should not be too critical of Alvarez, since probability sampling techniques for human populations were developed only some 15 to 20 years later. Alvarez explored black and white differences and noted that the blood pressure of blacks rose faster with age than it did for whites. He also commented that Mexicans showed no tendency toward rising blood pressure with age. He found no effect of habitual alcohol use on blood pressure and said, "Many will rejoice to hear that the pressures of those men (habitual alcohol users) were no different from the abstainers." He looked at drug use, tobacco, weather, obesity, and height, and made the interesting observation that first-degree murderers had higher blood pressure levels than the other prisoners. He also noted that prison guards at San Quentin had much higher blood pressures than did their charges.

Scientists who published in 1929 had a very modern interest in blood pressure variability. For example, Diehl (*4*) studied 100 male students at the University of Minnesota, taking their systolic blood pressure readings mornings and evenings on 6 consecutive days. He found that the evening readings were higher by approximately 10 mm and that "Study of the individual cases shows that in some subjects the difference between morning and evening pressures is consistently great enough for the one to be considered normal and the other hypertension, and that in other cases the variation from day to day in the same person is sufficiently great for the pressure to be considered normal on one day and hypertension on a subsequent day." He also said, "A positive correlation was not found between the height of the blood pressure and its variability." We could find more recent studies of the concept of labile hypertension, for example, that, although published 40 years later, may have reached conclusions 40 years less sophisticated than Diehl's. Furthermore, crude as it was, his result about the lack of correlation of blood pressure level and variability was a precursor of things to come much later.

We are still talking about obesity and blood pressure, but in 1929 Hartman and Ghrist (*5*) were also talking about it. They studied the files of 2,042 Mayo Clinic patients, aged 15 and over and classified them by the accepted standard of the day, 6 classes of underweight and overweight and found a significant association between obesity and systolic blood pressure level. Hartman and Ghrist suggested that measurement error may have been responsible for the lack of a relationship with diastolic blood pressure.

In 1929, discussions of the possible role of dietary sodium chloride in producing or sustaining elevated blood pressure were no less intense than they were in 1979. Albeit in a small case series, Berger and Fineberg (*6*) varied sodium chloride intake in 11 hypertensive patients. Their literature citations make it abundantly clear that one could find support for any shade of opinion concerning the role of dietary salt, a situation as true today as it was 50 years ago.

One continuing theme that has plagued epidemiologists working in high blood pressure research is the determination of diastolic blood pressure. In 1929, investigators either ignored disastolic pressure completely, reporting their results only for systolic, or, if they did report diastolic, they substantially downplayed its importance—and for the right reason, difficulty of measurement.

My entry into the field of high blood pressure research was almost 25 years ago, half the period spanned by this landmark session. My interest was in diastolic measurement, and I designed an elaborate multiple Latin square experiment in an attempt to control for observer, participant, and order of observation. These results were reported at the APHA meeting in Atlantic City in 1959. I managed to convince myself that fourth-phase diastolic blood pressure was a more precise index than fifth phase. I have lived to regret that judgment. I have participated in decisions to use fifth phase as the sole diastolic index in large-scale investigations, such as the Hypertension Detection and Follow-up Program. But this issue never seems to die. Just as measurement of diastolic blood pressure was a major concern of investigators in 1929 and a matter of interest in 1959, it continues to be discussed by the American Heart Association. The draft of the latest version of the booklet, "Recommendations for Human Blood Determination of Sphygmomanometers" has just been made available. It has not been released, but after much debate and in the face of substantial differences of opinion, the AHA will recommend converting its current diastolic standard from fourth phase to fifth phase, albeit with several caveats.

One of the things that makes high blood pressure a fitting subject for a landmark session in epidemiology in the intertwining of methodological developments with substantive findings. Perhaps no other health problem so well illustrates the interaction of epidemiologic and statistical methodology with important steps in improving our understanding of substantive issues.

The assessment of average blood pressure levels and of the prevalence of hypertension in populations has

had an interesting evolution over the last 50 years. From Alvarez's booth on a street corner, we have progressed substantially to the 1939 investigations of Robinson and Brucer (*7*) who studied a large group of people who were accepted for life insurance in the Chicago area. Statistical defects of this study were summarized by Treloar (*8*). Master and co-workers (*9*) studied the blood pressure records of 74,000 people who applied for work in American factories during World War II and published their results in 1950. Hamilton and co-workers (*10*) surveyed pressures of a group of British clinic patients who were being treated for conditions not known to be related to blood pressure. Comstock (*11*) was one of the earliest investigators to use probability sampling techniques in an attempt to assess community blood pressure levels (1957). He also provided an extensive analysis of blood pressure differences between blacks and whites. In 1961, Johnson and Remington (*12*) published the results of a probability sample survey of the population of Nassau, Bahamas. This site was chosen because of the unusually high concentration of sodium chloride in the drinking water; despite this apparent excess intake of sodium chloride, they found that systolic and diastolic blood pressure distributions by age, sex, and race, were similar to those reported by Comstock. Boe and co-workers (*13*) selected blood pressures from the adult population of the community of Bergen, Norway, in yet another population study.

In recent years, the National Health Examination Survey has presented blood pressure distributions from a stratified, heavily clustered, multistage probability sample of the noninstitutionalized U.S. population (*14,15*). It is fascinating to watch the joint evolution of population estimation techniques and prevalence estimates of hypertension over 50 years.

High blood pressure research has been the subject of a series of prospective, longitudinal studies, including investigations in Framingham, Tecumseh, Albany, Chicago, Minneapolis, and Los Angeles. The results of these studies, summarized in the final report of the U.S. Pooling Project (*16*), demonstrated that elevated blood pressure is a major and independent risk factor for coronary heart disease, stroke, and all causes of mortality—the latter association was established many years earlier from life insurance data.

With the advent of effective pharmacological agents for lowering the blood pressure beginning in the midfifties and continuing to this day, case-control study methodology has been applied in an attempt to assess the contribution of antihypertensive agents to the production of breast cancer, for example. In 1974, reports of such association were published (*17–19*). Other investigations, however, have failed to confirm this association, and the weight of scientific opinion now appears to favor the view that selection artifacts and other biases may have been largely responsible for the reported effects (*20*).

It is difficult to imagine a more influential set of investigations than those of the Veterans Administration Cooperative Study Group on Antihypertensive Agents (*21,22*). Their randomized, controlled, double blind, multicenter clinical trials among U.S. war veterans established the efficacy of pharmacological management of the established hypertensive patient, by showing a significant reduction in major morbidity and mortality in patients treated with combination antihypertensive therapy as compared to randomly allocated patients receiving a placebo. New pharmacological agents had been developed and tested rapidly from the midfifties onward, but the major endpoint of all these investigations was a reduction in blood pressure. They showed that the life-saving potential of such reductions, suggested by life insurance and longitudinal studies identifying elevated blood pressure as a risk factor for all causes of mortality, was largely achieveable by pharmacological control.

Investigations of high blood pressure have now passed to the intervention phase. The Hypertension Detection and Follow-up Program (HDFP) reported its findings in the *Journal of the American Medical Association*, December 7, 1979 (*23,24*). This study, an

ecological intervention trial, was concerned with elevated blood pressure in its natural physical, biological, and social environment. Approximately 160,000 persons were screened in 14 communities nationwide. Those in the target age range, 30–69 years, whose diastolic blood pressure was at or above 95 mmHg were invited to a second-stage screening at the clinic. Those whose pressure was 90 or above were then randomized into stepped- versus referred-care groups. In the wake of the studies by the VA group, researchers felt that it was impractical to block effective treatment of control patients by the administration of a placebo, and therefore, referred-care participants were assigned to care by their own physicians. Participants in the stepped-care group were treated with the minimum number and dosage of drugs required to reduce their diastolic blood pressure to a predetermined goal.

The purposes of the investigation were to determine whether pharmacological management of the mild hypertensive produced life-saving results, to determine whether treatment of the younger hypertensive and the female hypertensive was efficacious, and whether hypertensives could be identified, brought under care, and kept under such care. The basic design of the study has been described (*25*).

According to HDFP, the percentage of hypertensives detected, treated, and controlled in the United States has increased two- to threefold since 1972 (*26*). Other studies have replicated this finding.

Intervention trials designed to determine indications for pharmacological management of the mild hypertensive patient have begun in Britain and Australia, as well as in other countries.

Next Steps

With respect to the next steps in high blood pressure control particularly in the community, I believe that a major priority continues to be improvement of the level of detection, treatment, and control of hypertensives in communities throughout the United States. Even though a two- to threefold increase in the rate of such control has occurred, that increase was based on such a low level before 1973 that much work remains to be done. We must seek to improve community blood pressure control efforts, to expand the frequency with which hypertension is detected, bring increased percentages of hypertensives under pharmacological and nonpharmacological control, and expand the vigorous management of the blood pressure to achieve levels within the normal range.

We must investigate the possibilities for nonpharmacological intervention in mild high blood pressure. Clinicians need advice from epidemiologists concerning indications for management of their patients with mild hypertension. Younger patients in particular must now be consigned to lifelong management by using drugs, each of which produces adverse reactions. We should investigate nonpharmacological intervention, including dietary salt restriction, increased physical activity, weight reduction, control of alcohol intake, and other intervention techniques including relaxation and biofeedback. Each of these potential interventions is at the earliest stages of development as an effective antihypertensive modality. Basic research is needed to determine the potential efficacy and acceptability of each. Parallel with this research, multifactor intervention efforts might go forward, directed toward reduction of blood pressure as the primary endpoint. Such trials would not require large numbers of participants and should provide an opportunity for factorial design and experimentation with various delivery techniques.

Parallel with the need for investigation of nonpharmacological control of mild hypertension is the need to study the efficacy of primary prevention of high blood pressure. High-risk and borderline hypertensive patients should be investigated to determine the efficacy and acceptability of the series of intervention methods noted earlier—dietary sodium chloride restriction, weight control, limitation of alcohol intake, and increased physical activity.

However, a number of unanswered fundamental questions concerning hypertension remain. We must remember that approximately 98 percent of all cases of elevated blood pressure are not secondary to any known cause. In spite of a flood of basic research directed at hypertension immunology, elucidation of neurogenic and humoral mechanisms, and other potential etiological pathways, our ignorance remains in many respects as profound as it was in 1929. Those of us who work in epidemiology and biostatistics can, if invited, or if uninvited but aggressive, contribute much to improve our colleagues' experimental designs and data analytic techniques in the basic sciences. From my assessment of the literature, for example, on the physiological effects of sodium chloride, I have a strong impression that the basic scientists really need help.

Are there distinct subentities of clinical hypertension such as low renin hypertension? Many colleagues not only believe that these entities exist, but also that their presence has important therapeutic implications. Finally, as I noted earlier, we need much more investigation of the role of salt, alcohol, and physical activity in elevated blood pressure. No less important is our lack of understanding of the factors responsible for the twofold increase in hypertension prevalence of U.S. blacks over U.S. whites. We are not able, in this latter in-

stance, to partition adequately the hereditary from the environmental influences.

Fifty years ago, a group of colleagues were forming an epidemiolgy section of the American Public Health Association. A group of other colleagues were puzzling over the enigma of hypertension, its causes, prognosis, and treatment. Fifty years from now others, many not yet born, will be asking and answering equally fundamental questions. What will be the content of the 100-year landmark session on high blood pressure? Will the percentage of cases of high blood pressure due to a known cause be increased above its current level? Will drug treatment still be virtually the only method of intervention to control the life-limiting effects of blood pressure elevation?

We may have passed a landmark in American epidemiology in our improved understanding of community control of high blood pressure, but I would urge that we view it merely as a milestone, with many more mile-markers lying beside a long road ahead. In the past 50 years, we have truly pushed back the frontiers of ignorance, though not as much as we would like to believe. Yet, the more we learn, the more there is to know. Certainly, no landmark passed in these 50 years justifies complacency, a reduction of investigative efforts, or a decreased allocation of resources to improve the health of the people through high blood pressure control. Public health demands such efforts, and epidemiology can contribute to the efforts.

References

1. Vincent, S., and Thompson, J. H.: The effects of music upon the human blood pressure. Lancet 1: 534–537, Mar. 9, 1929.
2. Granger, A. S.: The present conception of essential hypertension. JAMA 93: 819–824, Sept. 14, 1929.
3. Alvarez, W. C.: The blood pressure in 6,225 prisoners and 422 guards. Proc Staff Meetings Mayo Clinic 4: 321–323, Mar. 6, 1929.
4. Diehl, H. S.: The variability of blood pressure, morning and evening studies. Arch Intern Med 43: 835–845, June 1929.
5. Hartman, H. R., and Ghrist, D. G.: Blood pressure and weight. Arch Intern Med 44: 877–881, December 1929.
6. Berger, S. S., and Fineberg, M. H.: The effect of sodium chloride on hypertension. Arch Intern Med 44: 531–542, October 1929.
7. Robinson, S. C., and Brucer, M.: Range of normal blood pressure. A statistical and clinical study of 11,383 persons. Arch Intern Med 64: 409 (1939).
8. Treloar, A. E.: Normal blood pressure. Arch Intern Med 77: 848 (1940).
9. Master, A. M., Dublin, L. I., and Marks, H. H.: The normal blood pressure range and its clinical implications. JAMA 143: 1464, Aug. 26, 1950.
10. Hamilton, M., Pickering, G. W., Roberts, J. A. F., and Sowry, G. S. C.: The aetiology of essential hypertension. I. The arterial pressure in the general population. Clin Sci 13: 11 (1954).
11. Comstock, G. W.: An epidemiologic study of blood pressure levels in a biracial community in the southern United States. Am J Hyg 65: 271 (1957).
12. Johnson, B. C., and Remington, R. D.: A sampling study of blood pressure levels in white and Negro residents of Nassau, Bahamas. J Chronic Dis 13: 39–51, January 1961.
13. Boe, J., Humerfelt, S., and Wedervang, F.: The blood pressure in a population. Acta Med Scand [Suppl] 321: 1–336 (1957).
14. National Center for Health Statistics: Blood pressure of adults by age and sex, United States, 1960–62. PHS Publication 1000, Series 11, No. 4, June 1964.
15. National Center for Health Statistics: Blood pressure levels of persons 6–74 years, United States, 1971–74. DHEW Publication No. (HRA) 78–1648, Series 11, No. 203, September 1977.
16. The Pooling Project Research Group: Relationships of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: Final report of the pooling project. J Chronic Dis 31: 201–306, April 1978.
17. Boston Collaborative Drug Surveillance Program: Reserpine and breast cancer. Lancet 7882: 669–671, Sept. 21, 1974.
18. Armstrong, B., Stevens, N., and Doll, R.: A retrospective study of the association between use of rauwolfia derivatives and breast cancer in English women. Lancet 7882: 672–675, Sept. 21, 1974.
19. Heinonen, O. P., Shapiro, S., Tuominen, L. and Turunen, M. I.: Reserpine use in relation to breast cancer. Lancet 7882: 675–677, Sept. 21, 1974.
20. Reserpine: No changes advised for now. JAMA 242: 224, July 20, 1979.
21. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mmHg. JAMA 202: 116–122, Dec. 11, 1967.
22. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mmHg. JAMA 213: 1143–1152, Aug. 17, 1970.
23. Hypertension Detection and Follow-Up Program Cooperative Group: Five year findings of the hypertension detection and follow-up program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. JAMA 242: 2562–2571, Dec. 7, 1979.
24. Hypertension Detection and Follow-Up Program Cooperative Group: Five year findings of the hypertension detection and follow-up program. II. Mortality by race-sex and age. JAMA 242: 2572–2577. Dec. 7, 1979.
25. Hypertension Detection and Follow-Up Program Cooperative Group: The hypertension detection and follow-up program. Prev. Med 5: 207–215 (1976).
26. Hypertension Detection and Follow-Up Program Cooperative Group: Blood pressure studies in 14 communities, a two-State screen for hypertension. JAMA 237: 2385–2391, May 30, 1977.