SPECIAL CLINICS FOR HYPERTENSION— THE ROLE OF THE HYPERTENSION DETECTION —AND FOLLOW-UP PROGRAMME

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Introduction

The role of special clinics in the management of hypertension is almost impossible to assess accurately. Until conventional care becomes better standardized, and until the role of special clinics becomes more clearly defined, one can anticipate that clinics devoted to hypertension will sometimes be shown to be more effective than the conventional system, and at other times to be no more effective. Therefore, the problem of the role of special clinics might best be addressed by determining whether there is evidence that an unusually complete programme aimed at controlling hypertension offers advantages over the conventional care system. Assuming that such advantages are demonstrable, it will then remain for further investigation to determine which elements of the special clinic are critical to the success of that clinic's activities. It will then become possible to determine whether the necessary elements can be introduced into the conventional care system in an efficient and economical manner, or whether the requirements are so specialized that it will be more efficient to retain special clinics. There are numerous examples of both possibilities. Early in medical history virtually all diabetics were seen in special clinics, and now the need has diminished to the point where only unusual problems are seen in special clinics. Conversely, the problems of the blind remain a province for special clinics, simply because the conventional care system is unable to meet the particular needs of those who are affected.

It would therefore seem more appropriate to begin by asking whether there is evidence that a special clinic can produce better results than the conventional care system. The resolution of this question obviously would depend upon the practices throughout the conventional care system, with their variations, but would depend also upon whether it could be demonstrated that special clinics, operating in an optimal fashion, could produce evidence of greater effectiveness than the conventional care system. The latter question was sufficiently compelling that an *ad hoc* committee was assembled by the National Heart,

Lung and Blood Institute of the National Institute of Health, to consider the status of the problem and to make recommendations for the future.

In 1971, there were certain perceptions that were quite uniformly accepted. There was evidence that only about half of hypertensives discovered in household surveys were recognized as such by the medical care system. In addition, of the half who were diagnosed, only half of these in turn were taking medication regularly and had blood pressure levels that would permit the statement that they were under control. There was, therefore, the perception that detection and compliance were such major problems that it would be irrelevant to determine that a given clinic, reaching only a minority of hypertensives, could produce better data than another clinic or another group of practitioners. Furthermore, it was widely recognized that the rates of hypertension in any population were governed in part by the criteria that were used to establish the presence or absence of hypertension. The rates might vary by as much as threefold depending upon whether a single blood pressure determination were used, whether the determining levels were 90 mm Hg or 95 mm Hg, or whether corresponding systolic pressures were used instead of diastolic pressures. Several major epidemiologic studies had demonstrated that individuals with elevated pressures had substantial excess risks of mortality and morbidity from cardiovascular disease, but it was far from clear that the reduction of blood pressure to so-called 'normotensive' levels would confer benefit.

The important Veteran's Administration trial had been published, indicating that lowering of blood pressure of hypertensives would be effective in lowering morbidity and mortality. The benefit seemed to be limited to lowering the rate of stroke and of congestive heart failure; there was little if any effect on rates of myocardial infarction. However, by the nature of the rigorous design used in that study, the majority of individuals in the trial had evidence of end-organ damage and had relatively stable blood pressures at

the hypertensive levels that were studied. Similar observations made in many clinics also suggested that lowering blood pressure of those with evidence of end-organ damage or what was called 'hypertensive disease' would be beneficial. Certainly the selected individuals in these various studies were far from random.

It was therefore unclear at what level of blood pressure intervention might be useful, when the net toxicity of treatment might overcome presumed benefits, or which approaches might offer maximal benefits with the least toxicity and least loss of compliance. Some authorities felt that it was not necessary to treat all hypertensives and that it was sufficient to treat only the ones with the highest blood pressures or to wait until some evidence of end-organ damage had appeared before instituting treatment. Other equally competent authorities felt that the earliest possible intervention held the greatest likelihood of reducing excess morbidity. Taken in relation to this view was the prevailing sense that it might not matter as much as one had hoped how carefully these problems were delineated because most patients would not comply with treatment anyway, and therefore none of the sources of care, whether high specialized or in the conventional care system could expect to have more than a small impact on the general problem of hypertension. In this sense, the conventional medical system was already coping with the problem as well as was possible and there were serious questions whether further interventions and further demonstrations were worthwhile.

In considering a large trial of the efficacy of treating hypertensives in the general population, there was also concern about the design of such a study. Many members of the *ad hoc* committee felt that it was no longer possible, in the American setting, to conduct a placebo trial, since a substantial number of physicians already felt that all hypertensives, by whatever definition, should receive treatment. I have written about this thorny problem elsewhere and shall not enter into it now (Kass, 1978).

Suffice it to say that the committee, after much deliberation, recommended a trial with certain characteristics. The trial should be large enough to demonstrate an effect on the gross mortality experience of the populations, rather than a cause-specific effect, if efficacy of the treatment were demonstrable. The trial should involve community based screening for hypertension rather than selected populations such as inpatient or outpatient hypertensives. The trial should compare treatment offered by the conventional care system as opposed to an optimal method in which detailed efforts were made to overcome the problems of compliance. The trial should have rigid criteria of definition of hypertension, of the goals of treatment, of the assessment of morbidity and toxicity, of approaches to treatment and was to

be supervised by external and internal committees that had the right to intervene if there were evidence of prohibitive toxicity or of adverse consequences of any treatment.

Because of the problems of assessing morbidity when one group was to be seen frequently and another group to be seen variably, it was agreed that mortality should be the only firm end point for the study and that analyses involving end points other than mortality would necessarily be less definitive.

The trial that emerged has been amply described elsewhere (Hypertension Direction and Follow-up Program Cooperative Group, 1976, 1977). Therefore only a few characteristics will be stressed here and no attempt will be made to offer completeness. A few points that are relevant to some of the data will be summarized.

Methods

Fourteen clinical centres throughout the United States were selected, and a Data Coordinating and Analysis Centre, a Centre for the Analysis of Electrocardiograms, and a Centre for Standardization of Biochemical Studies were also chosen. Of the target populations that were presented by each centre, some 89% were screened, and 158,096 persons, of both sexes, age 30–69 years, were screened for hypertension. The first screen occurred in the home in all but one of the centres, the exception being a large industrial population that was screened at the work place. An active attempt was made, in selecting the populations, to overrepresent the proportion of blacks in the study compared with the ratios for the country at large, because of the well-known excess risk in blacks of hypertension and its consequences.

The first screening required a mean diastolic pressure of 95 mm Hg, and those with this level or higher were invited to return for a second screening at the clinic. Those with a blood pressure of 90 mm Hg or above in the second screening were entered into the study, regardless of whether they had previously been diagnosed as hypertensive or whether they were at the time taking antihypertension medication. Those satisfying the blood pressure criteria were randomized between the two forms of care: referred and stepped care.

Individuals in the referred care category were advised that they had elevated blood pressures, and were urged to visit their physicians. They were informed that a letter with all relevant findings would be sent to their physicians. Free clinics were available in each community for those who did not have the resources for private care and there were arrangements for free medication as needed. In addition, each person in the trial was visited at the end of the first, second, fourth, and fifth years, in their homes, by a nurse who recorded blood pressure and other

relevant data and who was instructed, if the blood pressure was 90 mm Hg or above, to urge the patient to return to the source of care for more attention. In these respects referred care was more stringent than usual care.

The stepped care patients were treated according to a strict protocol. Those patients whose entry blood pressures were 100 mm Hg or higher were to be brought to a goal of 90 mm Hg and no patient was to be considered at goal unless this criterion was strictly met. Those with entry pressures between 90 and 100 were to be brought to a goal 10 mm Hg below the entry pressure. It should be emphasized that many patients were therefore brought to goal pressures of 80–90 mm Hg. When it is realized that the mean blood pressure differences between stepped and referred care were in the order of 5 mm Hg, it should be evident that the goal of treatment may have played an important role in the outcome of the trial.

Treatment in the stepped care group consisted of initial treatment with chlorthalidone (or spironolactone, if necessary), with each step representing the addition of another drug if the patient had not responded after a requisite number of visits to the earlier step. Step 5 permitted the clinician complete discretion in the use of antihypertensive drugs. About 85% of all stepped care participants were controlled in steps 1 and 2 with chlorthalidone alone or with chlorthalidone plus reserpine or plus methyldopa. Stepped care also consisted of vigorous efforts to retain compliance. Patients were given free care for their hypertension and free drugs. Missed visits were followed by telephone or mail reminders and home visits if necessary. Free transportation to the clinic was available for those who needed it and clinic hours were adjusted to make them as convenient as possible, including evening and weekend clinics.

Although the hypertension clinics limited themselves to the care of the hypertensives and referred patients to the conventional care system for other medical care problems, it was inevitable that advice was sought by patients on other medical matters. Such advice usually consisted of friendly referrals to other sources of care, unless the problem was judged to be trivial. All patients for whom it was relevant were advised to discontinue smoking and to lose weight. Unhappily, after 5 years, the rates of change of smoking habits and the rate of loss of weight, in the referred and stepped care groups were virtually identical.

This brief sketch of the background and design of the trial does not do justice to the extensive and detailed protocols, but serve as a basis for the following discussion.

Results

Several of the most important findings of HDFP will

be summarized. Detailed analyses of these various points will be found in the publications from the group.

1. There were 5,485 persons in stepped care and 5,455 in referred care. As can be expected when such large groups are randomized, the two groups were quite comparable in the many criteria of comparison that were analyzed.

2. Approximately 71% of individuals were in stratum 1, with diastolic blood pressures (DBP) of 90–104 mm Hg at entry, 19% were in stratum 2 (DBP 105–114 mm Hg) and 10% in stratum 3 (DBP 115+ mm Hg). It is often forgotten that, although the relative risk of excess morbidity and mortality is obviously greatest in those with the highest pressures, the total number of morbid events is much greater in the so-called 'mild' hypertensive group, simply because of its size. Therefore, although clinicians have understandably been most impressed by the 'severe' hypertensives, from the point of view of action to lower the excess mortality and morbidity ascribable to hypertension it is the 'mild' group that makes the greatest contribution to excess morbidity ascribable to hypertension and therefore needs much attention.

3. Mortality from all causes was reduced in SC (stepped care) as opposed to RC (referred care) by 16.9%, by 20.3% in stratum 1, by 13.0% in stratum 2, and by 7.2% in stratum 3. Presumably the lower difference between the groups as blood pressures rise represents the greater concern and effectiveness of the conventional care system for those with higher blood pressures and suggests that the greatest effect of SC was due to greater preoccupation with stratum 1 than is commonly the case in conventional practice.

4. The cumulative mortality curves for SC and RC show a steady and progressive difference for each year of the study and this difference is found in all strata.

5. With respect to cause-specific mortality, a word of explanation is needed first. All information on causes of death on death certificates, coroners' and hospital autopsy data, etc., were made available to a nosologist who was unaware of the SC and RC status of the patient. A single cause of death was then given by a nosologist. The cause specific data were analysed from this single cause of death. Therefore all of the following information should be taken in relation to this rather arbitrary approach.

6. Deaths from cerebral vascular disease were about 45% lower in SC than in RC groups and from acute myocardial infarction were 26% lower in SC.

7. On the other hand, there were 14% fewer deaths in SC than RC for all noncardiovascular causes, with renal disease, malignant disease, gastrointestinal disease, and respiratory disease all being lower in SC than in RC. This difference may represent a greater likelihood of better medical care

in SC than in RC, accounting for much of the observed difference between these groups. Alternatively, the difference may represent greater lethality ascribed to the underlying diseases when hypertension was also present and was inadequately treated. I favour the second hypothesis simply because medical care has not yet been shown to be a significant factor in mortality experience of large populations, except perhaps for the implications of the present study on hypertension. The arbitrary constraints on the nosologist must inevitably have led to some downgrading of the effect of hypertension in many cases in which there were other serious disorders. In all events, the effect of SC is even greater in the 'mild' hypertensives as will be seen below and this effect is of such a magnitude as to overcome any presumed effects of improved medical care apart from management of hypertension.

8. Persons with target organ damage (defined as left ventricular hypertrophy by electrocardiogram, or a history of myocardial infarction, or a history of stroke, or a history of intermittent claudication, or serum creatinine greater or equal to 1.7 mg/100 ml) had a reduction in mortality of about 21% whereas those without such evidence had reductions of 17% in SC compared with RC.

9. Blacks had an 18% reduction in mortality for males and 21% for females. White males had a reduction of 15% and white females had no overall change in mortality for SC compared with RC. The latter data are of particular interest with respect to stratum 1 (90–104 mm Hg) in which there was a striking difference between SC and RC for females which were then overcome by a reverse effect in the higher blood pressure strata. This is discussed below.

10. In stratum 1, white males had a reduction of 20%, black males of 11%, white females of 29%, and black females of 26% in mortality for SC over RC.

11. If stratum 1 is further subdivided, the reduction for all persons in mortality was 22% for those in the 90–94 mm Hg category, 23% for 95–99 mm Hg and 14% for 100–104 mm Hg.

12. If target organ damage was present as defined above, in the 90–104 mm Hg group, the reduction in mortality was still 22% and if such damage was absent there was a reduction in mortality of 25% for SC over RC in this mildest group of hypertensives. Corresponding reductions were seen in each subdivision of stratum 1 when broken down by 5 mm Hg intervals.

13. When target organ damage was absent, there was almost 26% reduction in mortality for those entering with DBP of 90–94 mm Hg, 16% for those with 95–99 mm Hg, and 24% for those with 100–104 mmHg at entry.

14. Whether a patient was or was not receiving hypertensive medication at entry, patients were randomized only according to the presenting blood pressure. However, in retrospect, those in all strata

who had been receiving such medication at the time of entry into the trial had a 12% decrease in mortality for SC over RC after 5 years compared with 21% reduction in those not previously treated. In the 90–104 mm Hg stratum, the reductions in mortality were 22% for those who were receiving treatment at the time of entry compared with 20% for those who were not receiving treatment. The evidence favours the view that it is the level of blood pressure at the time of screening and not the presence or absence of prior treatment that was the major determinant in the outcome.

15. Overall, for all patients in all strata who were not receiving antihypertensive medication, and who were free of evidence of target organ damage, the reduction in mortality for SC over RC was 25% and for such individuals in stratum 1, the reduction was almost 29%.

16. In the case of stroke there were similar reductions in SC over RC for both sexes, both races, and in all blood pressure strata. For example, in the absence of end organ damage and of antihypertensive medication, the reduction in rate of stroke was over 48% for all groups in all strata and in the presence of end-organ damage the reduction was still 21%. When these differences were adjusted for age, sex and race, the overall difference in rate of stroke for all groups for SC over RC was about 53%. In fact, the SC group experienced a reduction in rate of stroke such that the final observed rate was comparable to the overall rate of stroke for all persons in the United States. The risk had essentially been normalized.

These are merely glimpses of the data and their careful perusal in appropriate detailed publications from HDFP will be necessary. Certain anomalies remain. There was little effect in young males, the effect in white females was paradoxical in that the lowest stratum of hypertension experienced substantial benefits whereas in the higher strata referred care seemed to do a bit better than stepped care. In many instances these anomalies may simply reflect small numbers and as the categories became more delimited, the numbers became so small that there are analytical difficulties. Similarly, in analyses of end points other than mortality, problems arise in ascertainment since SC received more intensive contact with their therapists than did RC.

There is much to be sorted out but the overall lessons seem unquestioned. There is a distinct benefit from SC over RC and the benefit is greatest in the lower levels of elevated pressure. In part this benefit probably represents diminished likelihood that RC participants with 'mild' elevations of blood pressure received treatment. In part also, the goals of treatment as set up by the HDFP protocol were more demanding than is the usual clinical teaching about the goals of therapy. Much work will be needed to sort out the implications of these different possi-

bilities. These unsettled problems should not detract from the fundamental message that is implicit in these data about the natural history of hypertension and the role of contemporary therapy in altering the course of the disorder.

To return to the initial theme of the role of special clinics, it becomes evident that stepped care has produced quite striking effects compared with the conventional care system. Precisely which elements of stepped care are critical are a matter for conjecture. Compliance rates were high, the goals of treatment were more rigidly set than is usual, and every effort was made to provide optimal care in a convenient and effective setting. The degree to which the conventional care system can supply these attributes, and the degree to which each of these attributes is individually necessary, are subjects for further study. It must suffice at this point to say that an optimal system of care produces such striking reductions in mortality and morbidity from cardiovascular disease that the implications of the data cannot be disregarded.

Summary

The hypertension detection and follow up pro-

gramme of the National Heart, Lung, and Blood Institute has been briefly described, and the basis given for dividing the participants into two groups, one referred to the conventional care system (referred care) and the other referred to intensive care in special clinics in which treatment was administered according to protocol in a series of graded steps in response to the therapeutic effect observed with the preceding steps (stepped care). Substantial reductions in mortality from all cardiovascular causes, including acute myocardial infarction, stroke, and other major evidences of mortality and morbidity were observed. The effect was uniform for all groups, irrespective of presence or absence of target organ damage and irrespective of race, age, and sex. Although a certain number of anomalies exist in the data, as might be expected from a study involving some 11,000 participants, the overall implication that a carefully graded and carefully developed programme of therapy confers major benefits to a population, in terms of morbidity and mortality, seems warranted. The degree to which the conventional care system can provide similar care to the hypertensive population, and experience similar benefits, represents a major challenge for the immediate future.

Appendix

The fourteen clinical centres and four coordination and service centres of the cooperative group, their institutions, and primary staff that contributed to these data are:

- Atlanta, Georgia—Emory University: Elbert P. Tuttle, Jr, M.D.; Neil, B. Shulman, M.D.; and Jabir I. Sawaya, M.D.
- Baltimore, Maryland—University of Maryland: George Entwisle, M.D.; Aristide Apostolides, Ph.D.; and Richard Hebel.
- Birmingham, Alabama—University of Alabama: Harold W. Schnaper, M.D.; Albert Oberman, M.D.; and Myra C. Johnson.
- Boston, Massachusetts—Harvard University and Brigham and Women's Hospital: Edward Kass, M.D., Ph.D.; James O. Taylor, M.D.; and B. Frank Polk, M.D.
- Chicago, Illinois—Northwestern University: Jeremiah Stamler, M.D.; Rose Stamler, M.A.; and Flora C. Gosch, M.D.
- Davis, California—University of California at Davis: Nemat O. Borhani, M.D.; Dean T. Mason, M.D.; and James E. Price, M.D.
- East Lansing, Michigan—Michigan State University: Sandra A. Daugherty, M.D., Ph.D. and Robert M. Daugherty, Jr., M.D., Ph.D.
- Evans County, Georgia—Evans County Health Department: Curtis G. Hames, M.D.; Siegfried Heyden, M.D., Ph.D.; and H.E. Tyroler, M.D.
- Georgetown, Washington, DC—Georgetown University: Lawrence M. Slotkoff, M.D., Ph.D.; Socrates Fotiu,

M.D.; and Won Ro Lee, M.D.

- Jackson, Mississippi—University of Mississippi: Herbert G. Langford, M.D.; Myra Tyler, M.D.; and Tairo Morino, M.D.
- Los Angeles, California—Cedars-Sinai Medical Centre: Morton H. Maxwell, M.D.; Andrew J. Lewin, M.D.; and Roger Detels, M.D.
- Minneapolis, Minnesota—Mount Sinai Hospital and University of Minnesota: Reuben Berman, M.D.; Richard Crow, M.D.; and Curtis Davis, M.D.
- New York, New York—Albert Einstein College of Medicine: M. Donald Blaufox, M.D., Ph.D.; Sylvia Wassertheil-Smolter, Ph.D.; and Jeanne Hotchkiss, M.D.
- Salt Lake City, Utah—University of Utah: C. Hilmon Castle, M.D.; Joyce Johnson, M.D.; and Erving Ershler, M.D.
- Coordinating Center, Houston, Texas—University of Texas: C. Morton Hawkins, Sc.D., Gary Cutter, Ph.D.; and Robert Hardy, Ph.D.
- Central Laboratory, Chicago, Illinois—Northwestern Memorial Hospital: Agostino Molteni, M.D., Ph.D.; Kenneth A. Schneider, M.D.; and Dolores Bagnola.
- ECG Centre, Minneapolis, Minnesota—University of Minnesota: Ronald J. Prineas, M.B., Ph.D. and Henry Blackburn, M.D.
- National Heart, Lung, and Blood Institute, National Institute of Health—Bethesda, Maryland: Thomas P. Blaszkowski, Ph.D.; James H. Ware, Ph.D.; and Wallace R. Williams, Ph.D.

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