Commentary on Epidemiological Studies and Intervention Trials

Lot B. Page†

Epidemiological studies have proved invaluable for identifying environmental risk factors and gene–environment interactions in the development of hypertension and other chronic diseases. Now, after several decades, the solid contributions of longitudinal and cross-national studies of random population samples are well established. The art and science of clinical trials have achieved a high level of sophistication and have given clear answers to questions of great importance to public health. No other form of experimentation could have provided this kind of data. It has had an incalculable influence on clinical practices and on nonpharmacological approaches to the prevention of disease throughout the world.

Nevertheless, each “generation” of epidemiological studies and clinical trials has raised new questions, and these have often led to new clinical trials. The early studies were designed to answer simple questions about risk factors and effects of interventions in general populations. “High risk populations” (mostly male) were selected and rigid exclusion criteria were adopted to get clear answers in a relatively short time frame. As noted by Remington,1 the design constraints often resulted in considerable loss of power and in event rates no greater than those in the general population.

Results reported at the end of clinical trials and late results in the same (or similar) populations are not always the same. It is evident that some questions cannot be answered within the customary 3–5 year time frame. There are some old unanswered questions, such as the lingering uncertainty about the benefit of antihypertensive treatment on coronary events. There are also some new questions that have arisen from long-term observations of treatment effects.

As noted by Yusuf et al,2 there has been a marked increase in the hospital frequency of congestive heart failure (CHF) in older, treated hypertensive patients. Inasmuch as the prevention of CHF has been a major benefit of treating hypertension, this raises some very important questions. It is possible that late CHF may be the result of occult ischemic heart disease, but there is no clear evidence of this. Perhaps we have been treating the congestion but not the failing myocardium, which goes on to overt manifestations at a later time. Late CHF in older hypertensive patients needs to be definitively studied.

Another concern is the evidence (based on Health Care Financing Administration [HCFA] data) that more and more older hypertensive patients are entering dialysis programs for renal failure due to hypertensive vascular disease.3 Both of these late manifestations of hypertension raise a third question that has not been addressed in large clinical trials. Is it sufficient to simply lower the blood pressure, or is the pharmacological and physiological method of reducing blood pressure the really important issue in the long run?

Perhaps the most important question of all is: Can primary prevention of hypertension be achieved by nonpharmacological means?

All these questions are amenable to study by clinical trials of refined and targeted design. At the same time, it is progressively more difficult to conduct trials because of rising costs and ethical constraints.

Turning to the relation of salt and hypertension, it appears to me that the accumulated evidence of a causal relation is overwhelming. A concept of widely variable hereditary susceptibility seems to fit the facts better than a model of bimodal distribution divided between susceptible and nonsusceptible individuals. Methods for measuring salt intake in populations are still not very satisfactory. In this connection, I would like to call attention to the lithium chloride dilution method devised by Claudia Sanchez-Castillo4-5 that has been applied in epidemiological studies in England and deserves widespread use.

I also want to mention the great contribution that has been made by the INTERSALT study.6,7 This study has provided on a grand scale a confirmation of the findings that have emerged from dozens of other studies in all parts of the world. It has consolidated the importance of sodium, potassium, obesity, and alcohol, all of which are independently related to blood pressure. Two other findings of INTERSALT are worthy of special mention: 1) The age-related upward slope of blood pressure is clearly related to salt intake. This upward slope in adult populations is a prerequisite to primary hypertension.8 2) INTER-
SALT data also show an effect of salt on population blood pressure after deletion of all persons with hypertension. This effect is almost equal in magnitude to that seen when hypertensive patients are included. This finding seems to me especially relevant to public health recommendations, which by necessity are directed to the whole population.

There remain a number of vitally important questions for further research in this area. Among them are the following: 1) What are the genetic markers of susceptibility to hypertension induced either by salt or other dietary or environmental variables? As pointed out by Folkow, the genetic heterogeneity of human populations makes it unlikely that a single gene pattern will account for all cases. However, it is entirely possible that a small number of dominant genes may emerge within a polygenetic framework. Such a model has received support by the study of Motulsky et al on the sodium-lithium countertransport system. 2) What role do anions (especially chloride) play in blood pressure control? This subject has been neglected in the past and is now getting a great deal of attention. Nevertheless, data on humans are still meager. 3) Is susceptibility to salt variable by age and sex? Blood pressure changes with age are nonlinear. There seems to be a "flat place" after attainment of adult size, as noted in virtually all studies that include children and young adults. There are changes of slope of blood pressure that are different in magnitude in different decades of age. What role do calcium, phosphorus, and magnesium play in the development of hypertension, and how are they related to salt sensitivity?

Future studies need to take into account the predicted change in blood pressure over time in different age/sex/race groups. They also need to be designed with sufficient power to overcome the expected effects of regression dilution and undercollection discussed by Paul Elliott.

Epidemiological and intervention studies obviously cannot answer the questions about physiological mechanisms, and there is still a long way to go to understand the nature of the interactions of sodium, potassium, and anions, but epidemiological findings have given strong impetus to laboratory studies of these interactions.

References


KEY WORDS • clinical trials • essential hypertension • salt
Commentary on epidemiological studies and intervention trials.
L B Page

Hypertension. 1991;17:I34
doi: 10.1161/01.HYP.17.1_Suppl.I34

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/17/1_Suppl/I34.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at: http://hyper.ahajournals.org//subscriptions/