Panel Discussion on Genetic and Environmental Factors in Human Hypertension

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Dr. Kohlstaedt: The subject assigned to us is highly controversial and before the evening is over we will, I hope, have aroused a considerable amount of discussion. I am basing this on some of the opinions that were expressed during the meeting today. Our discussion is to be on genetic and environmental factors in human hypertension.

We are going to become involved in a controversial subject because we can't disentangle the genetic side from the environmental side of our problem. I think that for many years we have recognized that there is a familial pattern in the incidence of high blood pressure. Any lay person will tell you high blood pressure runs in the family. This may be firmly established, but the genetic certainly is not differentiated from the environmental contribution.

We will begin with one factor which was brought out in the course of the discussion today in one of Dr. Goldblatt's comments. He called attention to the frequency of hypertension and its importance in Negroes in the Virgin Islands. I think it is pretty well recognized that hypertension is also more frequent in the Negro in the United States. Back in 1929 there was an article in the Lancet by Donnison who had studied some of the East Africans. He reported that in this Negro group the blood pressure was lower than in European whites. Not only was it lower, but instead of increasing with age, it decreased.

One member of our panel has in recent months had a very interesting experience with hypertension in Negroes in some of the islands in the West Indies and so we will begin our discussion by calling on Dr. Moser.

Dr. Moser: There have been several studies conducted during the past 20 years that have attempted to establish the fact that certain races do or do not have more hypertension than we have here in the United States. One of the studies mentioned was done by Donnison in East Africa, and there have been other investigations in Africa, mostly on the east coast or the southern part of the continent. These have all indicated that the incidence of hypertension is very low and that there does not appear to be an increase of blood pressure in older individuals. Data also indicate that in some areas blood pressure rises as the level of civilization rises or as the natives become "urbanized." The comparison has been drawn between the African native and the American Negro. As you know, it apparently has been demonstrated that the American Negro has a higher blood pressure than the white person living in the same area. From these comparative studies it has been concluded that since the American Negro has higher blood pressure than his ancestors, some factor must be operating to produce hypertension. The easiest thing to say is, of course, that the American Negro has been put under some stress to which his more primitive ancestors were not subjected. Before these apparent differences are accepted, it must be remembered that the American Negro and the Negroes living in the West Indies came from the West Coast of Africa and are not closely related to the East Africans upon whom the above conclusions are based. There are very few studies that I know of that have been done in Western Africa. It may very well be that results in this area will be identical to those from other portions of Africa, but we must await them before drawing any...
definite conclusions. I think there are factors "other than stress" that must be considered in view of other work that has been done during the past 15 years.

Several attempts to study the problem have been made in other parts of the world. Studies in the islands off Panama have shown that among primitive tribes the blood pressure is lower in both sexes and in all age groups than in comparable age groups in the United States, both white and Negro. Another interesting study was done in Panama where blood pressures in native Panamanians were compared with those obtained in a group of West Indians who had come over to work on the canal and who were living under similar economic and social circumstances. This work revealed a significant difference between the Panamanians and the West Indians. The West Indians had hypertension 7 times more frequently than the Panamanians in the older age groups and 16 times more often in the younger age groups. This is a rather significant finding. Taylor, who did the study, analyzed pathologic data and found that the incidence of pylonephritis and other renal disease in the West Indians was very high as compared to the Panamanians and whites in the same area. Arteriolar nephrosclerosis also was much more frequent in a ratio of 7:1, West Indians to Panamanians. He concluded that the high incidence of hypertension in the West Indians was most probably secondary to the increased renal disease in these individuals. From the discussions today this may be the correct conclusion, but we must also think about it in other terms. It is possible that the West Indians had more hypertension for other reasons and consequently had more secondary arteriolar nephrosclerosis. This is a question I don't believe anyone can answer definitely at this time. The one outstanding fact is that the West Indian people have a great deal of hypertensive cardiovascular disease. This suggests that there has been a change, either dietary, psychic, renal or unknown in these people since they left Africa many years ago to account for the outstanding difference in the incidence of this disease in the West Indians as compared to the incidence among their ancestors in Africa (assuming that studies will reveal little or no hypertension in West Africa).

It has been known for many years in Jamaica and in Nassau in the British West Indies that there is a great deal of hypertension. Almost everyone on the Islands has a relative that has "the high blood," died of hypertension, or has had a "stroke." On the basis of these impressions and with the help of many practicing physicians in Nassau we attempted to set up a preliminary study in an effort to establish the incidence of hypertension on the Islands, to determine whether or not it existed throughout all age groups and finally, if possible, to discover some lead concerning the etiology of the disease.*

I hesitate to report our results in view of their very preliminary nature, but perhaps the data we have may be of some interest. There had been an attempt to study this problem in the Bahamas several years ago by Humphries who collected data on approximately 400 natives both on New Providence, the major island of the Bahamas, and on the smaller out-islands. The information from this small group revealed that 40 per cent of all the natives on Nassau had systolic blood pressures of over 150 mm. Hg regardless of age. On the out-islands 60 per cent of the natives had hypertension as defined by this systolic blood pressure level.

In our study we utilized a questionnaire which included name, age, race, family history, body configuration, number of pregnancies, other diseases and occupation. These were distributed to 5 groups of physicians and in this way we hoped to get representatives of different patient groups. Casual blood pressures were taken utilizing the disappearance of sound as the diastolic reading. Prisoners who were under constant observation,

*Dr. Murcott, Chief Medical Officer in Nassau, the Bahamas and Drs. Lorenz, Adderly, Erdley, Etkoff and others assisted in this study. Dr. Malcolm Hale, resident physician at the Princess Margaret Hospital in Nassau was particularly helpful in collecting the data included in this report.
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Figure 1: Top. Percentage of systolic blood pressures over 150 mm. Hg.

Figure 2: Middle. Percentage of diastolic blood pressures over 100 mm. Hg.

Figure 3: Bottom. Systolic blood pressures of various populations.

Laborers who received physical examinations before being sent to the United States, a group of consecutive patients in a private physician’s office and a group of inpatients and outpatients of the Princess Margaret Hospital in Nassau comprised the individuals studied. In this way a broad sampling of the population was obtained.

Figure 1 shows the percentage of patients in our study who had blood pressures over 150 mm. Hg. This and subsequent figures are based upon results in approximately 1,000 cases, a number admittedly too small to arrive at definite conclusions but enough to suggest some trends. Certainly, we do not present these figures as statistically significant. As can be seen, a large percentage of West Indians have high systolic pressures when compared to Master’s statistics on white people in the United States. Over 50 per cent of the West Indians over the age of 39 years actually had systolic hypertension by our usually accepted criteria. Admittedly, the factor of anxiety at the time the readings were taken enters into a consideration of these figures. A more important criterion of hypertension is, of course, the diastolic blood pressure. Figure 2 compares the percentage of individuals in our series who had diastolic blood pressures of 100 mm. Hg or more with those in Master’s series. For example, from age 30 to 35 more than 20 per cent of the males and approximately 30 per cent of the females in the Bahamas had diastolic pressures over 100. In the older ages 50 per cent of the females and 25 to 40 per cent of the males showed similar findings. Some age groups were omitted from the figures in the Bahama studies because of insufficient numbers in that particular age grouping.

Figure 3 compares our study to that of Saunders in the Virgin Islands and that of Master in the United States. It is to be observed that blood pressures in the Saunders’ study are quite similar to ours with the exception that in the younger age groups blood pressures appear to be higher in the Bahamians. If we compare blood pressure figures obtained on the American Negro we would
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find that they fall somewhere in between Master's figures and the other 2 studies, but do not approach the high levels noted in the Bahamians at any age or sex. From these preliminary data we certainly have not established the true incidence of high blood pressure in the Bahamians, but it is, I believe, significant that 30 to 40 per cent of all people over the age of 40 had what we would consider diastolic hypertension (over 100 mm. Hg). If we take above 90 mm. as an acceptable criterion for diastolic hypertension, we would note in the age groups over 40 that this condition is present in 60 to 70 per cent of these people. I believe that this group of individuals presents a challenge since it appears that the incidence of hypertension is higher here than in most parts of the world.

A visit to the hospital wards in Nassau, definitely confirms the impression that cerebral vascular accidents are extremely common, that malignant hypertension is not uncommon, and that the death rate from hypertension is very high. We attempted to perform urine examinations on all of the patients whose blood pressures were taken, but in this we were not particularly successful, even in hospitalized patients. In the few specimens that were examined, and especially in a group with systolic pressures over 180, albuminuria was very rare. Microscopic examinations were unsatisfactory, so that at this time we are unable to draw any conclusions regarding the renal status of these patients.

The most interesting finding of the entire study to date, and one that may have some bearing upon the reasons for the apparently large percentage of individuals with hypertension in the Bahamas, has to do with their salt intake. An analysis of the water supply in Nassau and several of the outer island groups revealed that the well water was significantly high in its sodium content. In New York City and Detroit, for example, the average quantity of sodium in the water is .3 mg. per 100 ml. In the hospital water in Nassau the amount is 129 mg. per 100 ml., and on Eleuthera, one of the other islands, it is 210 mg. of sodium per 100 ml. If you assume that people consume between 2 and 2.5 L of water in their food and drink daily, the Bahamians have an intake of 3.5 to 5.5 Gm. of sodium per day in water alone. If you put this in terms of sodium chloride intake it means approximately 7 to 10 Gm. of sodium chloride per day, exclusive of the quantities of salt in the food. In a standard publication on drinking water there is only one city listed in the United States where the sodium content of the water approaches that of any well water in the Bahamas and this water is listed as unpalatable for drinking. It is of interest that the Bahamians drink a great deal of water because of a constant thirst. Sodium excretion studies done to date have been limited, but suggest an average excretion of 12 Gm. or more of sodium chloride daily. This is something that we plan to study in some detail. It may have absolutely no bearing on the fact that these people have hypertension, but it may provide some lead to the etiology.

One last comment about the diet; we have been unable to carry out a careful study of average diets, but some facts are worth mentioning. The native diet is very high in carbohydrates (grits, rice and peas) and almost everything is fried in salt pork oil. It is of interest to note that a pound of salt pork has 8.1 Gm. of sodium. On the basis of this we would expect that our further studies will show these people to be ingesting a very high quantity of sodium chloride and I feel that this group of people should certainly be submitted to a continuing, careful study. We plan to pursue the investigation of blood pressures, diet and renal abnormalities during the next few years and hope that we may have an answer to this very interesting problem of West Indian hypertension in the not too distant future.

Dr. Kohlstaedt: Thank you very much, Dr. Moser. In this study we have become involved in the problem of susceptibility to disease. We have as a panelist this evening a man who is an expert in the field of epidemiology, particularly with relation to infectious disease.
DR. FRANCIS: In a 1951 summary of the published studies of the occurrence of hypertension in this country and elsewhere, Mor-sell\textsuperscript{11} stated that none of the studies reviewed was based on a scientific sample of the country as a whole or any subdivision of it. In a large proportion of instances the blood pressure readings are those of very special aggregations which cannot be deemed representative of anything but themselves. Moreover, they constitute primarily surveys which at most could give some idea of the prevalence of hypertension in the groups. Because of the varying procedures and criteria for diagnosis of what was termed hypertension these data cannot be cumulated to gain an approximation of the country-wide experience. There is no meeting ground between the studies. One time surveys of this nature provide little information as to the incidence of the disorder, the rate of development, or the natural history and course.

This is not to say that the studies to date have been of no value, for they have given rise to a number of impressions or suggestive relationships, some of which approach a level of acceptability. These relate to the distribution of hypertension by age, sex and certain racial or cultural characteristics. As has been pointed out, the evidence of familial aggregation has also been gaining in credibility.

The epidemiologic method can be used to approach many different phases of the problem. A first desire is to obtain adequate identification of those who develop the disease and their selective group characteristics by age, sex, race, occupation, socioeconomic, genetic and constitutional status, and way of life. If there are groupings which distinguish these persons from others of a representative population, that information can direct attention to other individuals of similar characteristics who do not show overt evidence of the disturbance but who may be in the preparatory stage. In brief, the purpose is to define groups of special incidence, hence susceptibility, in which investigations as to causative factors can be concentrated. It would be wise to record the blood pressures and to follow the course of all levels of subjects rather than seeking in advance a specific cut-off point labeled as abnormal.

From the general discussions of the problem, it is apparent that essential hypertension is considered a progressive biological disturbance. One can consider the working hypothesis that it originates in one basic defect, whether that defect derives from a single cause or whether it is a disorder which can be set in process by a variety of injuries. Let's assume that something serves as a starter and subsequently the difficulty is aggravated or actually perpetuated by other and varied insults. There exist then a number of points at which the progress of the disease may be interrupted. Epidemiologic investigations can study the factors involved in any part of the development process. With the major interest in approaches to prevention, it is apparent that, after establishing a sound foundation as to the occurrence of disease, epidemiology should concentrate on pushing investigation further toward the origins of the disorder in the search for correlations which might disclose causative influences in the community and in the way of life. This requires extended, detailed, and continuous application of what Osler called "that most difficult of all the arts, the art of observation." It means continued surveillance of the population to record the progression of changes from apparent normality, through the benign, the accelerated and terminal steps, unless they can somehow be averted.

If exposures, habits, or familial relationships are found which are highly and selectively correlated with incidence, the possibility exists that these harmful influences can be intercepted or dissipated, even though their mode of action is not known; in the meantime their nature can be carefully investigated. Moreover, group variations may point to multiple, primary, or precipitating causes exhibited by collections of cases in different age, social, or occupational groups.

These prolonged observations are difficult. What leads are there then through which to search for observable susceptibles? The re-
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ports from the Bahamas by Dr. Moser suggest that in this population the entire process is being telescoped into a short span which is very inviting for investigation of susceptibles and the causative influences in that situation. The familial aggregations need immediate attention to establish their nature, if genetic or if related to common exposures by a family group. It would be interesting to know how age distribution in multiple families is related to known toxic exposures such as streptococcal infections or common relationships in behavior, habits, harmful social exposures. In this search for susceptibles a need is quite apparent for new methods for detecting the susceptible. There are indications that if one considers possibilities, like the cold-pressor test in which Hines has been interested,\textsuperscript{12} it may be possible to devise tests which will provide a basis for finding susceptibles or hyperreactors, the subclinical cases who will become hypertensive. For these purposes and this outlook a different orientation in research is needed. The urge here is to avoid fixation upon end results and to move toward knowledge of origin and preventive outlook.

In the course of these studies knowledge may be acquired which will clarify the alternative questions posed by Goldring:\textsuperscript{13} (1) Does vascular (arteriolar) disease precede and account for the elevated blood pressure, or (2) is vascular disease a direct consequence of increased blood pressure, or (3) are vascular disease and elevated blood pressure unrelated, and merely concomitant expressions of a common cause? The epidemiologic studies should comprise a representative population or sample, concentrating upon recording of pressures without commitment to arbitrary diagnosis and then observe them to see what happens over a period of time by continued surveillance.

One of the defects of Pickering’s considerations\textsuperscript{14, 15} is that it constitutes a survey of conditions at a moment in time without information as to how these situations would change, or what the progress is in persons with different levels of pressure. Study of group behaviors and characteristics may also give valuable indications as to multiple etiologies.

This conference might well be a starting point for an advisory group to offer its services in the planning and conduct of epidemiologic studies so as to obtain the greatest amount of valid information from the undertakings.

Dr. Kohlstädt: We have mentioned the role of heredity and Dr. Neel is our geneticist. Would you care to comment on the place of inheritance and what help a geneticist can contribute to this problem.

Dr. Neel: The question of the role of heredity in hypertension is sufficiently controversial that there are certain preliminary points I am anxious to bring to your attention before attempting to contribute to any specific questions to which the panel might be asked to address itself.

To begin with, it must be pointed out that from the standpoint of the geneticist hypertension is a somewhat messy trait to work with. Three difficulties are outstanding. First, the papers of Hamilton, Pickering, Fraser-Roberts and Sowry\textsuperscript{14, 15} have recently emphasized that blood pressure is a continuously distributed variable. The point at which we draw a line and say ‘‘this is hypertension’’ is entirely arbitrary. With respect to another continuously distributed variable, stature, we would scarcely consider classifying all individuals as ‘‘tall’’ and ‘‘not tall,’’ and yet that is exactly what most genetic studies in the field of hypertension have in effect done. The geneticist is at his best when he is working with a clearly defined and discontinuous trait, such as albinism or phenylketonuria. Continuously distributed traits, on the other hand, present analytic problems difficult to meet even in experimental material. Second, there is the lability of blood pressure. Students of the genetics of body stature are not confronted with the spectacle of their subjects suddenly shooting up 3 inches or shrinking 2 as they approach with anthropometer in hand. This lability of the blood pressure cannot help but complicate genetic studies. Finally, there is the fact
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that the mechanisms which regulate blood pressure levels are still poorly understood. All studies on heredity in hypertension try to exclude from the series individuals with hypertension for such organic reasons as chronic pyelonephritis or polycystic kidney. But at a time when we recognize that such apparently "clean" entities as cystinuria or diabetes insipidus or ovalocytosis are actually genetically heterogenous, it takes a brave man to maintain that the entity termed essential hypertension is not etiologically heterogenous. Indeed, this is the clear implication of the concept of blood pressure as a continuously distributed variable.

In general, I subscribe to the point of view developed by Pickering and his collaborators regarding the etiology of hypertension—that it is the end result of the interaction of certain essentially unknown environmental variables and a genetic predisposition, the latter determined by multiple genes. However, for a variety of reasons, I am not satisfied that their studies provide us with a valid estimate of the relative contributions of the two components and, even if they did, the findings on an English population could not be automatically transferred to other populations. The problem of hypertension being what it is, it is a matter of some practical importance to identify both these genetic and environmental components as soon as possible; herein lies the only approach to that understanding of the disease which must precede rational therapy. Our tranquilizers, our ganglionic blocking agents, our sympathectomies, are all admissions of defeat in that failing to adjust the carburetor because we do not understand its workings, we now put a little sand in the fuel line to cut down on the flow of gasoline to the carburetor.

There is reason to suspect that the frequency of hypertension, however arbitrarily defined, is increasing. There is something about the avalanche of progress, dietary change and so forth with which our culture is confronted that brings out the hypertensive in us. But we of the United States and Europe have been making biological adjustments to our changing culture for centuries and, so to speak, may have developed a relative immunity to environmental "hypertensinogens." In my opinion, the big breakthrough in our understanding of hypertension will come from the study of societies where a rapid transition from stone age to atomic age culture is in progress. Here, if ever, is the chance to isolate and identify the genetic and environmental precipitants of hypertension to which we of the western world have already made a partial adjustment which may tend to obscure the basic mechanisms involved.

A single example which tends to complement Doctor Moser's presentation will suffice. In a visit to the Gold Coast several years ago I had the privilege of making rounds with the chief of medicine of the large governmental hospital in Accra. His service was divided into two subservices, one accommodating the African of some education employed by the government or in business, the other designed for the African relatively fresh from the bush and working in the city, usually as unskilled labor. I was told that among admissions to the ward for the acculturated, hypertension and its complications was one of the very serious problems, while the same entity was seldom if ever seen on the adjacent ward. My informant fully recognized the need for the objective verification of this clinical impression. We are all familiar with the evidence to the effect that hypertension is more frequent and more severe in the American Negro than in the American Caucasian. The African will be forced to telescope into a brief period biological adjustments which have extended over centuries in the western world. In my opinion, here and under similar conditions in other parts of the world, lie the best opportunities for defining both the environmental and genetic components of hypertension.

Dr. Kohlstädt: Mr. Moore has been involved in reviewing data and statistics for some time in his present position at the National Heart Institute. Mr. Moore, I think you told me that you had a chance to look at some of the data that has been under discus-
sion, particularly with relation to Dr. Pickering's concept of the distribution of, shall I say blood pressure, rather than hypertension, in a population. Will you give us some ideas regarding this problem?

Mr. Moore: I am sometimes of the opinion that clinical researchers have much the same faith in the magic of statistics that we laymen have in the magic of clinical medicine. This is particularly impressed upon me when I see some of the large-scale surveys of blood pressure and the deductions that are made from the curves that come out of these studies.

Three large population surveys of blood pressure have been reported in recent years. First, there is the study by Master and his colleagues, published in 1950, but based on blood pressure records taken among job applicants during World War II. Those job applicants presumably were ambulatory and some medical examiner took a blood pressure or several blood pressures, and recorded one of them on an entrance physical examination form. It is difficult to ascertain what blood pressure was recorded, but 50,000 or more were assembled and some 15,000 of them went into Master's studies. The second study, by Pickering and his colleagues, was based upon a population of patients who attended a number of hospital clinics of various types excluding, however, those associated with the care of hypertensive diseases. The third and most recent study is by Bøe and colleagues in Bergen, Norway. This was based on a community survey in which approximately 96 percent of the population had blood pressure readings taken under fairly standardized conditions. I will also refer to a study which my colleagues in the National Heart Institute have been conducting since 1946 in the town of Framingham, Mass. There we have had under study a large sample of the adult population of the town, numbering approximately 5,000 men and women in the ages 30 through 59. All of these studies, even though not all of them are based on the same sampling principles, yield curves of distribution of blood pressures which have many similarities although conclusions about mean blood pressures differ.

There are 3 facts important in terms of the kinds of deductions made from curves of population blood pressure, some of which have been referred to by the preceding speakers. The first is that the distributions of systolic and diastolic blood pressures in an adult population are continuous ones, and this continuity is found in each age and sex group. By continuous I mean that if the percentage of the population is plotted against blood pressure level from low to high, either systolic or diastolic, there are no clean breaks in the curve. Secondly, there are obvious sex differences, with pressures for females being lower than for males in the thirties, about the same in the forties, and considerably higher at later ages. Finally, there is a tendency for these frequency distribution curves, for either sex, to become flatter and to shift to the right as older age groups are plotted (fig. 4). In statistical terms we say that these curves at older ages are skewed to the right—they have a humping on the right side of the curve. The curve of blood pressures for a group of men in their thirties is approximately statistically normal; it is symmetrical, bell-shaped, and has certain specifiable mathematical characteristics. At later ages the curve for systolic blood pressures can be made normal by applying a logarithmic transformation. The statistical normality of the distribution of blood pressures among men in their thirties and the skewing of the distribution to the right among men in their fifties is well illustrated in figure 4, based on unpublished data from the Framing-
ingham study. These features are not generally true for diastolic pressure and this fact may, in itself, be of importance.

The type of normality which the statistician refers to has nothing whatever to do with biological normality, and I feel that one has no right to make any inferences about the biological normality or non-normality of a blood pressure observed at any point on the scale from purely statistical considerations. It is my feeling that the position which has been taken by Master and his associates, that some point on the curve of blood pressures can be marked down and the population above that point be termed abnormal or hypertensive, is not defensible on any purely statistical grounds, even though this point is defined in terms of standard deviations from the mean. Only if there is some concept of assessing the group above a certain level in terms of some biological characteristic independent of the blood pressure or, alternatively, if data are available from a longitudinal study which permits follow-up of the population to find out whether something different happens to the group of persons who are at the upper end of the curve over some period of time succeeding the original measurement, is it permissible to set any particular level of blood pressure as abnormal or to call any group in the population above that level abnormal.

The continuity of the blood pressure curve suggests that it is, in fact, probably impossible on any grounds to find any single cutting point on the curve which clearly distinguishes one class of people as different from all the people on the other side of that point. I assume that this is what Pickering means when he says that hypertension is a quantitatively and not qualitatively distributed variable; that blood pressures have an even distribution throughout the population and that there is in fact no point at which you can distinguish between a "hypertensive" and a "nonhypertensive" group. This suggests that any survey at a single point in time does not permit one to learn about the consequences of "high blood pressure" for a population. One must have longitudinal surveys. This is, as a matter of fact, what the National Heart Institute is attempting to do in the Framingham study where we have a large group of people, a sample from the total population including persons at all levels of blood pressure, who are returning to the clinic for examination every 2 years.

There are some problems of method, mentioned by Dr. Neel, which I would like to discuss for a moment from the statistical point of view. Generally speaking, for the purpose of characterizing a total population and for the purpose of establishing differences between two population groups, a single determination of systolic and diastolic blood pressure taken under standard conditions will be sufficient. With sufficiently large numbers, the mean, standard deviation and general shape of the curve can be established with a high degree of reliability. The surveys which yield the curves which I have described have all been based on a single, casual blood pressure. For the purposes of studies of that type, I think the use of casual blood pressures is in fact advisable—superior either to the use of a so-called basal blood pressure, or allowing the investigator to characterize an individual by the blood pressure recording which he thinks to be "typical." I doubt that any investigator is capable of setting up a situation in which he can objectively choose, out of the multitude of blood pressures that he might take on an individual, the single one which best characterizes the individual. The alternative of choosing a "basal" blood pressure is seldom feasible in large-scale investigations.

If, instead of establishing the characteristics of a large population at a given moment in time, it is desired to study the development of hypertension in individuals and its association with other characteristics, a single blood pressure reading may not be sufficient. In a survey based on the study of individual changes in blood pressure, statistical considerations suggest that the individual should be characterized by the mean of a number of blood pressure recordings, preferably taken by different observers and over some time
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span. In this fashion it is possible to take into account the type of individual variability which Dr. Neel mentioned, a variability which may depend on the time of day, perhaps on a reaction to the investigator who takes the blood pressure, and also on the peculiar cyclical swings which characterize some individuals.

With data of this type in hand, it is clearly possible to sort out groups of individuals in the population who fall into various ranges of blood pressure from low to high, even though the distribution is a continuous one. I am sure that it will be found on later follow-up that groups at various levels are characterized by different risks of developing some of the essential manifestations of hypertension, or by changes in certain other measurable physiologic characteristics. Only by this type of study is it possible to say how much more "abnormal" are those groups characterized by higher blood pressures, and I am confident that such a study will show a continuum of risk over the whole range of pressures.

We have, in fact, found this in our Framingham population in a 4 year follow-up with a group of men aged 45 to 62.17 At several stages of blood pressure level from low to high, the risk of a coronary attack steps up in quite even steps. This appears to be relatively independent of the risk which is associated with the cholesterol level. We find progressive steps down to a point where it is possible to identify a group of men in the lowest third of the population with respect to the blood pressure level and find on follow-up that they have a measurably lower risk of coronary disease than the higher groups. Surprisingly, the men with concomitantly low blood pressure and low serum cholesterol had a risk of developing coronary disease less than that of the total population of women in the same age group.

Dr. Kohlstaedt: We would like to throw the discussion open and accept some questions from the floor. Dr. Perry, would you mind saying a word about your experience in West Africa?

Dr. Perry: Let me say in defense of what follows that my primary purpose was not to obtain blood pressures but rather to obtain autopsy tissues. I attempted to go to the most primitive areas in which autopsies were performed. I wanted human beings who were as unspoiled by civilization as possible, but such people are not ideal for obtaining blood pressure data. I can confirm that Dr. Williams' findings in Uganda2 apply to a hospital population in nearby Ruanda Urundi where I found some 500 people with an average blood pressure very close to 105/65 mm. Hg. In French Equatorial Africa, which is somewhat closer to the area where the American Negro has his ancestry, the mean blood pressure was also low. This survey also represented a hospital population—there was no way of getting any other kind of survey. Furthermore, people in both of these areas all had chronic diseases which might well be expected to affect blood pressure. They all had syphilis, they all had schistosomiasis, they all had malaria, and all of them were malnourished. It was impossible to find any group who did not have these diseases. Laboratory work was so limited that the incidence of underlying renal disease could not be determined. Hypertension is a disease that has an age incidence, yet these people are too primitive to have any idea how old they are. A meaningful comparison of the incidence of hypertension in Equatorial Africa and elsewhere is therefore impossible. Only a clinical impression is possible. Nonetheless, I think that if one makes all allowances, he comes to the conclusion that there is almost no chance that these people have as high an incidence of hypertension as Negroes in the West Indies have. I do not think one can go beyond that.

Dr. Kirkendall: I rode from the airport with Dr. Moser. He mentioned that the Bahamians had quite a lot of sodium in their urine and he thought their diet was very high in sodium chloride. I remembered that Dr. Herbert Pollack of New York University had conducted a nutritional survey in Formosa on the Chinese soldiers there, and that he had found these people ate 20 to 30 Gm. of salt a
day. I could not recall whether he had commented on the incidence of high blood pressure in this population. This afternoon I went to the library and looked up that series of articles and, in a brief review of the material, I could find no blood pressure recorded and no comment on the incidence of arterial hypertension. It was a very careful nutritional study, and undoubtedly the figures for the salt ingestion are correct. I wonder if someone in this audience has first-hand information of this particular survey and, if they do, whether they found the incidence of high blood pressure in the Chinese soldiers on this diet to be high.

Dr. Rodbard: I bring second-hand knowledge. Dr. Takeo Kuroyanagi of the University of Tokyo who has been working with us at the University of Buffalo Chronic Disease Research Institute has told us that cerebrovascular episodes are quite common in the population of Japan and the islands of the Pacific. Being a seafaring people who depend to a large extent on salted fish, the Japanese are exposed to essentially the same dietary and salt ingestion patterns as the Formosans. This also may suggest a tie between high salt intake and hypertension.

Mr. Moore: There is some information which I think will be published shortly, that will clearly indicate that the Japanese male population has a level of blood pressures about equivalent to that of the white American male population. The national vital statistics certainly show that the rate of cerebral vascular accidents in Japan among males is as high as, or conceivable a bit higher than, the rate in the United States, although the coronary rate for Japanese is about a fourth that found among white American males.

Dr. Grollman: There are several papers which are pertinent to what has been said. The paper by Dubois, published in 1912, but rarely referred to, indicates that in French Equatorial Africa the incidence of hypertension in the native Negro is practically that of the Negro in this country. There is also a report which indicates that the incidence of hypertension in the American Negro living under the pastoral surroundings of the South is as great as that of the Negro living under the hectic conditions of Chicago. Apparently, environment does not have much to do with it. In connection with Master’s work which has been quoted so often, it is unfortunate that in much of his earlier data elevations in systolic and diastolic pressures are lumped together as “hypertension,” without appreciation of the fact that a high systolic and normal or slightly elevated diastolic pressure merely reflects the existence of arteriosclerosis and not of hypertensive disease.

It seems to me that in any study involving heredity we must consider two factors: (1) the congenital tendency for the disease to appear, and (2) the possibility of acquiring it as a result of external factors. In this connection the paper of Taylor, quoted by Dr. Moser, cites the fact that hypertension does not exist among the San Blas Indians, but, when these San Blas Indians migrate to the mainland of Panama, hypertension does occur. However, in each instance where autopsy data were available, there was acquired pyelonephritis in the Indians who developed hypertension. In the islands where they live under good sanitary conditions with the ocean surrounding their huts, pyelonephritis is rare. We can thus account for this apparently environmental influence on the incidence of hypertension on a renal basis, which should please Dr. Goldblatt.

Dr. Stamler: A few other studies on this problem should be mentioned. First of all there is the work Dahl and Love have been doing in Brookhaven, N.Y. They divided a population under study into three groups on the basis of habits of salt use at the table—those who routinely salt all their food without tasting it, those who taste and then selectively salt, and those who never add salt at the table. This last group had a lower salt intake and a lower prevalence of hypertension than the other two. This would seem to be a very important finding, if confirmed by more extensive studies, particularly in view of multiple animal experimental and human therapeutic studies on salt and hypertension.
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Since no discussion of this type is "up to snuff" without mention of the Eskimo, may I call attention to 2 papers suggesting that renal and hypertensive diseases were rare in Eskimos, at least prior to gross acculturation.23, 24 Prior to succumbing to the "blessings" of white man's flour, sugar, and canned goods, Eskimos subsisted overwhelmingly on animal foods, with or without fish. They knew nothing of the practice of adding salt to food and when first exposed to it regarded it as one of the many peculiarities of the white man. Is this a significant factor in the apparent rarity of hypertension in Eskimos? In posing this question, one must of course note the paucity of data on blood pressure in Eskimos, particularly prior to acculturation, and one must also warn against loosely interpreting correlation to mean cause-and-effect relationship.

Next it is worth stressing again that the most definitive, striking epidemiologic fact about hypertensive disease in the United States is its far greater prevalence and incidence in the Negroes than in the whites.25 Is this a resultant chiefly of more extensive pyelonephritis in the Negroes than in the whites?26 Is it a by-product of nutritionally induced renal damage early in life, as in choline deficiency27 or from salt feeding?28 Is it a consequence of psychologic stress and strain and frustration resulting from discrimination experienced by Negroes in the contemporary American culture? Or do all of these etiologic factors operate synergistically? Clearly this is a fruitful lead for epidemiologic research to pursue actively.

Finally, may I briefly summarize the contrasts in the epidemiologic patterns of hypertensive disease and atherosclerotic disease. Hypertensive disease is far more frequent in Negroes than in whites in the United States; atherosclerotic disease, particularly coronary disease, is not. Hypertensive disease is more prevalent in middle-aged American women than men; the opposite is the case for atherosclerotic disease, particularly coronary disease. Whereas hypertension, including hypertensive cerebrovascular disease, occurs with a high frequency in Japan and in Africa (e.g., the Bantu of South Africa), atherosclerotic disease, particularly coronary disease, is rare in these peoples and countries.29 Epidemiologic and other studies on the etiology of hypertensive disease must focus on the basis for these contrasting findings.

Dr. Moser: I had a chance to speak to Dr. Louis Dahl just before coming out here and, although he has not published his figures on sodium excretion, in these 3 groups, the high sodium excretors or high sodium intake people in his series still take in less sodium than the West Indians. In reference to your comment about malnutrition and tropical diseases, it was pointed out to me that there were practically no tropical illnesses in any of the Northern islands of the West Indies. Most of the Bahamians and most of the people on the Islands are fairly well nourished. They have a very high carbohydrate intake. It is true that they do not eat much protein, but there are few cases of malnutrition. This certainly is not the experience in the African population and it may be that if there were fewer tropical diseases and better nutrition in these people the incidence of elevated blood pressure might be higher. I wonder if this is what might happen when the African migrates to the United States or other places?

Dr. Kohlstaedt: I think that in the latest article by Dahl and Love21 they also included the matter of body weight and found that when you had a high salt intake and overweight you were pretty sure to develop hypertension. Dr. Francis, do you have any comment?

Dr. Francis: I would like to make only 2 comments on what Dr. Stamler has said. First of all, when he said that there is a difference in the incidence of hypertension between the males and females in the United States, there are no data with which he can make that generalization. These are again spotty examinations of groups which cannot be put into a general picture of what is the case in the United States, but I do think that this is one of the leads where the evidence is sufficiently
strong in a given direction that it ought to be validated in a very well founded study.

Vital statistics are of no value because these illnesses are not reportable. The recent compilations say that of all the deaths in 1955 from arteriosclerosis and hypertension, 11 per cent were from hypertension. Now I do not know who decides that, but the statistics do not mean a thing. Secondly, when you come to the question of what is the basic defect, what is the basic insult, what is the original disturbance that gives rise to hypertension, then the various factors that Dr. Stamler mentioned could be multiplied. This is where I think you have the need for a very great concentration of research. Finally, I would only emphasize again the fact that to talk about this disorder one is going to have to work on a graduation of disturbance rather than upon arbitrary distribution if we hope to find out what happens to different peoples with different levels of blood pressure, to determine whether the blood pressure is the primary, secondary, or the incidental phenomenon in the disease process.

Dr. Kohlstaedt: Dr. Neel informs me that he has a perfect plan for a study of the epidemiology of hypertension. Dr. Neel, if you will give us that perfect plan we can go home.

Dr. Neel: The perfect plan I jokingly mentioned to Dr. Kohlstaedt before this meeting is the kind of project an investigator draws up only if he is absolutely certain he will have nothing to do with its execution. Having dutifully waded through a dozen or so of the references, I couldn’t resist the temptation to draw up a rather grandiose scheme. Assuming unlimited funds and personnel, I would suggest as a starter, the following 2 alternative programs. You will note that both of these studies deal with the “retrorenal” etiology of hypertension rather than the “postrenal” factors with which the symposium has largely been concerned. 1. Select 2 or more areas where representatives of several racial groups are living under comparable socioeconomic circumstances. Obtain a blood pressure on every member of the population. Obtain also a urine specimen, for the purpose of excluding from the study all individuals, no matter what the blood pressure level, with evidence of congenital or acquired renal disease other than the nephrosclerosis of hypertension. A complete medical appraisal of all individuals included in the study would of course be most desirable. Correct all blood pressures to a standard pressure that nullifies the effects of age and sex on the reading. Analyze the findings, either in terms of correlation, regression, or analysis of variance on an intrafamily and interfamly and racial basis. This will result in a valid and unbiased estimate of familial versus nonfamilial factors in several populations. Finally, on a properly selected sample of normotensive and hypertensive families, obtain detailed psychologic, dietary, and other studies designed to determine how much of the intrafamily resemblance which will almost certainly be observed is truly genetic, and how much nongenetic. This is, of course, a very large order, but when one considers the effort going into the study of hypertension, a study of this magnitude is not out of the question. 2. As an alternative approach, select an area with a homogenous population where a rapid cultural transition is in progress; parts of Africa come to mind. Insofar as possible, assemble 2 subsamples, one living as in the past, the other in transition. Make essentially the same observations as for the other type of field study. Any difference between the 2 groups will indicate how much environmental factors alter blood pressures under these conditions. Furthermore, if the data are kept in terms of family units, one can also analyze for intrafamily similarities and so get at the question of genetic determinants in response to environmental change.

Summary

The high incidence of hypertension in the Negro in the West Indies and United States and the infrequency of the disease in the African Negro were the focal point of Dr. Moser’s presentation. The coincidence of a high salt intake in the Bahama population which he studied was emphasized as a possible “lead” for further study.
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Dr. Francis emphasized the value of a longitudinal and complete epidemiologic study in uncovering etiologic factors in hypertension. A definition of hypertension should not be based on any arbitrary blood pressure, but frequency distribution curves for an entire population should be studied together with selective group characteristics which might lead to a definition of susceptibles. Then a follow-up program might be devised which would identify the factors involved in the appearance or progression of hypertensive disease in the susceptible individual or the mild case. From this standpoint the situation in the Bahamas, where the life history of the disease was telescoped into a shorter time span, seemed ideal.

Dr. Neel emphasized the almost certain heterogeneity of the hypertensive trait, as proposed by Professor Pickering, and other difficulties in making genetic studies in this field: variations in blood pressure readings, effects of acquired diseases, and environmental influences such as the acculturation process at work in certain African populations.

Prof. Moore reviewed the current surveys of the incidence of hypertension in certain populations. These support the concept of a continuous distribution of the blood pressure, of varying sex incidence depending on the age of the sample, and of a tendency to find an increase in the proportion of hypertensive subjects in older age groups. The failure of diastolic blood pressure to follow these patterns was an interesting and unexplained phenomenon. The value of longitudinal studies as in the Framingham survey, was demonstrated by the evidence of the reduced life expectancy which even mild degrees of hypertension imposed on the individual.

In subsequent discussion, further information about blood pressure in East African populations was contributed by Drs. Perry and Grollman, and on blood pressure and dietary habits and diseases of Japanese, Eskimo, Central American, and Formosan populations were discussed by Drs. Kirkendall, Rodbard, Grollman, Stamler and Moser.

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