

An initial report is offered in a long-term study to determine whether essential hypertension is conditioned by genetic factors, or by environmental influences in early life, or by a combination of both. Early data indicate familial concentrations when relatives of hypertensives are studied. However, no binding conclusions can be drawn at present.

HYPERTENSION AMONG RELATIVES OF HYPERTENSIVES: PROGRESS REPORT OF A FAMILY STUDY

Frances R. Gearing, M.D.; E. Gurney Clark, M.D., F.A.P.H.A.; George A. Perera, M.D.; and Morton D. Schweitzer, Ph.D., F.A.P.H.A.

THIS STUDY was undertaken in an attempt to answer the following questions: (1) Is primary hypertension more prevalent among the relatives of hypertensive individuals than among the relatives of normotensives? (2) Are there differences in the individual and environmental characteristics of those who develop hypertension and those who do not? (3) What is the relative influence of heredity and environment in the development of this disorder? Interest in these questions has been stimulated by conflicting statements in the literature concerning the role of genetic factors in the development of hypertension. These statements range from positive claims that hypertension is inherited as a Mendelian dominant with a 90 per cent rate of manifestation,^{6,7} to statements that the concept of dominant inheritance is unsupported.⁵

Several family studies have been undertaken in recent years addressed to the question of heredity.^{8,1,9} The methods and conclusions are widely divergent. This is not surprising. Not only does the definition of hypertension vary from one study to the other, but

systolic pressures or single casual pressures are often used, and no clear distinction is made between primary and secondary hypertension. Hearsay evidence and the inclusion of sudden death or cardiovascular accidents as evidence of hypertension are incorporated into some of these studies. Controls are either lacking or inadequate by virtue of selection, and conditions and observations are not the same for hypertensives and controls. In addition to variations in diagnostic criteria and standards of observation, evidence is meager as to whether environmental factors are present which might account for differences in family concentration. Therefore, on the basis of studies such as these, the question of the relative role of heredity and environment in the development of hypertension has not been completely answered to date.

We believe that primary (or essential) hypertension is a specific disease characterized by the repeated finding of a diastolic pressure of 90 mm of mercury or above, in the absence of any recognizable condition which can give rise to an elevated blood pressure. This

disease generally has its onset in the third and fourth decade (rarely if ever after age 50), is twice as common in women as in men, and affects approximately 5 per cent of the population. Its onset is usually insidious, and the majority of the patients have few, if any, symptoms during the uncomplicated phase which may last from a few months to more than 15 years. Complaints are usually minor, such as intermittent nervousness, dizziness, palpitation, or headache.^{3,4}

Since primary hypertension appears to be an important factor (or precursor) in the development of coronary artery, cerebrovascular, and kidney disease,²⁻⁴ there is need to know the part played by environmental and hereditary factors in initiating and perpetuating this condition. Therefore, we have undertaken an investigation of relatives of 100 documented hypertensive individuals, and a control group of relatives of 100 normotensives, all of whom are being examined under similar conditions. We are looking for differences in the prevalence of primary hypertension in the two groups of relatives, as well as for differences in environmental factors among those relatives who have hypertension and those who do not.

Selection of Families

The criteria for an index case are as follows: an individual between the ages of 45 and 65 with documented primary hypertension, who has a living spouse and two or more siblings and offspring over the age of 20 available for examination. The index controls are being matched with the index cases by age, sex, and race. The criteria for index controls include repeated diastolic pressures of 85 or less and systolic pressure of 145 or less, in the absence of any condition known to lower the blood pressure, and the same minimum number of available adult relatives.

We have two sources of index families: the Columbia-Presbyterian Medical Center and the HIP-Yorkville Medical Group. At the Medical Center, we obtain our potential index cases from the Hypertension Clinic (a referral clinic in continuous operation since 1924), from the diagnostic files of the hospital, and from patients attending the major outpatient or Group Clinic. The potential index controls are obtained from the Group Clinic, or from admissions to the hospital for elective surgical or gynecological procedures.

At HIP-Yorkville, the potential index cases are obtained from the physicians' rosters, and the potential controls from the roster of the same physician, in so far as possible. The potential index cases and controls, whatever their source, are screened first for age, marital status, and family size. The second screening is for medical conditions, and we exclude all individuals with clinical evidence of diabetes, thyroid and kidney disease, valvular disease and cerebrovascular disease. The final judgment on medical criteria for acceptance as index persons is made by our senior medical investigator (Dr. Perera). The individuals who meet all of these rather rigid criteria form the starting point of the families in our study.

Methods and Procedures

Following the selection of index families, permission is obtained to invite all adult family members to the Medical Center for an examination and interview. (Adult relatives includes spouses, siblings, and offspring, siblings' spouses and siblings' offspring.)

Each member of these families is then contacted by letter, telephone, personal interview, or a combination of these procedures, in order to encourage participation in the study. Appointments are made to suit convenience. The ma-

Table 1—Diagnostic Classification

1. Primary Hypertension (as defined above).
2. Secondary Hypertension—Systolic hypertension alone, or clear evidence of an underlying condition known to produce an elevated blood pressure.
3. Normotensive.
4. Borderline—Diastolic pressures persistently between 86- and 99, or a labile blood pressure with diastolic pressures varying from 80 through 100 on repeated readings.
5. Probable Hypertension—Individuals under 45 with occasional diastolics 90 or above, needing follow-up observations on blood pressure and urinalysis in six months or a year before a definite diagnosis can be established.
6. Possible Hypertension—Individuals in older age groups with borderline readings, a vague history, possibly slight proteinuria, in whom information is needed concerning previous blood pressure readings and urinalyses as well as information in regard to possible medication and other conditions, prior to attempted classification as either primary or secondary hypertension.

Majority of the examinations are carried out in the early evening (after work) or on week ends. Medical examinations are performed by selected members of the resident staff of the Columbia-Presbyterian Medical Center or by a qualified physician from the HIP-Yorkville Medical Group. The examination includes the basic elements of a routine medical examination with particular emphasis on the taking of three blood pressure readings: one casual, at the beginning of the examination, one sitting in the course of the examination, and a third in the supine position after five minutes' rest. The fundi are examined, and the findings are recorded in accordance with the Keith-Wagener-Barker classification. The urine is tested for protein and sugar, and if protein is present, a microscopic examination is made. These examinations are done without the examining physician knowing whether the subject is related to a hypertensive or normotensive.

The classification of all subjects is the responsibility of the senior medical investigator who performs this task without knowledge of the subject's background. In other words, he does not know whether a subject is related to a hypertensive or a normotensive. To further guard against possible bias, the name of the subject is deleted prior to classification, and the family history is not included in the protocol presented to him. The classification may be any one of the six possibilities shown in Table 1.

Only an approximate 70 per cent of our subjects could be classified into one of the first three categories on the basis of initial physical findings and medical history. The remaining 30 per cent have required additional information or further examination, or both, prior to classification. A small number continue to defy classification despite repeated follow-up.

At the time of the examination, a detailed interview is carried out with each subject by an experienced interviewer. This interview covers such items as ethnic origin, education, diet patterns, salt preferences and intake, smoking and alcohol consumption, occupation, family size, and many others. Questions are formulated in an attempt to differentiate those individual and environmental characteristics which have been suggested as important in the development of hypertension. The examination requires about 30 minutes, the interview from 45 to 90 minutes.

Results

At this time we present some preliminary results dealing with two of the original questions: (1) Does primary hypertension "run in families"?, and (2) Is there evidence of genetic factors?

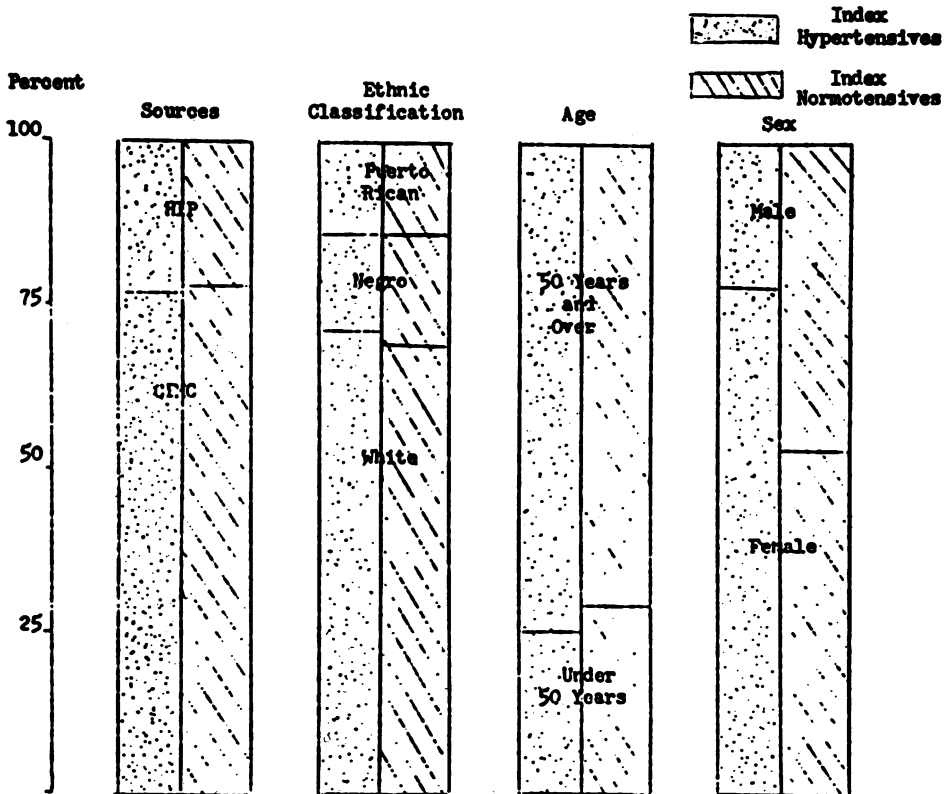
The following data are based on 533 relatives in 125 families. Figure 1 characterizes our index cases and controls

in this "first run." The majority of the index families, both hypertensive and normotensive, were obtained from the Columbia-Presbyterian Medical Center, as shown in Column 1. The ethnic distributions in the two groups are the same (within 2 per cent): 70 per cent white, 15 per cent nonwhite, and 15 per cent Puerto Rican. The age distributions are similar in the two groups with an average age at 55 and 56 years. The matching of normotensive and hypertensive indexes by sex has presented difficulties. Our goal is to achieve a female-to-male ratio of approximately 2:1 in both groups in order to reflect the occurrence in the general population. As noted in the last column in

Figure 1, male hypertensives and female normotensives who meet the criteria of this study have been more difficult to find. In the past few months diligent effort has reduced this discrepancy. The two groups are similar in family size, with an average of 7.5 live-born siblings per family, and an average of 2.9 live-born offspring. (Data not shown.)

Table 2 shows the characteristics of the examined relatives in the two groups of families. Sex composition is approximately equal. Age distributions are likewise very similar. Differences of 3 per cent or less exist in each age group. The men are from three to four years older than the women in both groups. The education levels are also similar in

Figure 1—Characteristics of Index Persons



NOTE: Information from 66 Index Hypertensives; 59 Index Normotensives.

Table 2—Characteristics of Subjects

	Relatives of Index Hypertensives	Relatives of Index Normotensives		
Subjects	275	258		
Sex				
Women	53%	54%		
Men	47	46		
Age Distribution*				
20-29 years	19%	16%		
30-49 years	44	44		
50 years and older	37	40		
Education				
No secondary school	28%	26%		
Some secondary school	50	52		
Some higher education	22	22		
Unknown	(19)	(15)		
Nativity of Parents				
United States and Canada	31%	25%		
Europe	53	53		
Caribbean Area	15	22		
Other	1	—		
Unknown	(8)	(8)		
* Average Ages (Years)	Mean	Standard Deviation	Mean	Standard Deviation
Women	42±1.1	12.7	43±1.2	13.7
Men	46±1.3	14.5	46±1.3	13.8

the two groups of families. There is a considerable proportion of college-trained individuals in each group (22 per cent). If the offspring are considered separately, the percentage of those having some higher education increases to 32 per cent. (This breakdown is not shown.) Ethnic origin, measured by nativity of parents, shows that the percentage of parents born in

Europe in each group is identical (53 per cent). The percentage of parents born in the Western Hemisphere is 46 per cent vs. 47 per cent. There is an excess (7 per cent) of parents of normotensives born in the Caribbean area, and a corresponding excess of United States and Canadian-born parents in the hypertensive group.

Table 3 shows the diagnosis of subjects according to the classification in Table 1. Of the 533 subjects, 94 per cent have been classified into one of the first three categories (Primary Hypertension, Secondary Hypertension, Normotensive) as a result of approximately 700 examinations. Six per cent or 33 individuals still remain in one of the last three categories despite additional medical information and examination.

Table 4 shows the occurrence of hy-

Table 3—Diagnosis of Subjects

Primary hypertension	100	19%
Secondary hypertension	30	6
Normotension	368	69
Borderline	21	4
Probably hypertension	6	1
Possibly hypertension	8	1
Total	533	100

Table 4—Primary Hypertension in Relatives of Hypertensives and Normotensives

	Relatives of Hypertensives	Relatives of Normotensives	P
All Subjects			
Hypertensives %	22.5	14.7	<0.01
n	(275)	(258)	
Women			
Hypertensives %	25.5	16.7	<0.05
n	(145)	(138)	
Men			
Hypertensives %	19.2	12.5	(0.051)
n	(130)	(120)	
40 years and older			
Hypertensives %	30.4	21.1	<0.05
n	(161)	(156)	
Under 40 years			
Hypertensives %	11.4	4.9	<0.05
n	(114)	(102)	

Table 5—Comparison of Spouses, Siblings, and Offspring

	Relatives of Hypertensives	Relatives of Normotensives	P
Spouses			
Hypertensives %	17.5	17.3	—
n	(63)	(52)	
Siblings			
Hypertensives %	44.6	24.1	<0.01
n	(92)	(87)	
Offspring			
Hypertensives %	9.4	4.6	(=0.06)
n	(85)	(87)	

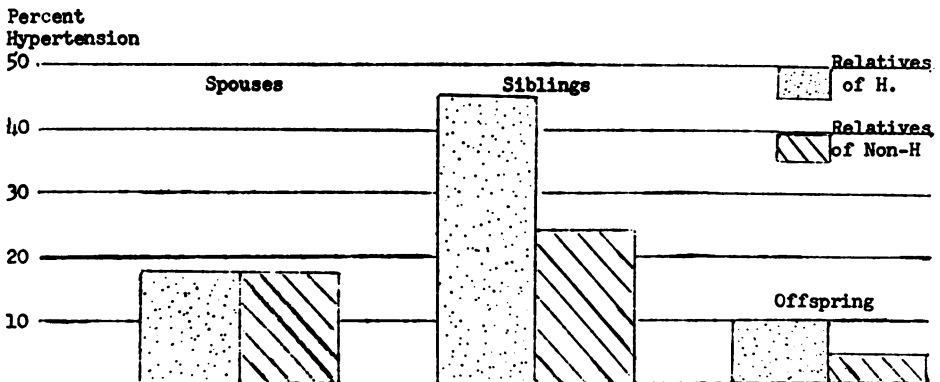


Table 6—Association of Primary Hypertension in Parents and Children

Parents	No. of Children	Primary Hypertension	
		No.	%
Both normotensive	46	2	4
One hypertensive	62	5	8
Both hypertensive	8	2	25

pertension in the two groups of examined relatives. We have observed a prevalence one and a half times as great among relatives of hypertensives as among relatives of normotensives. This is true for men and women taken separately, and for relatives under and over 40 years of age. The differences are significant at the 5 per cent level except for men ($p=0.051$). Among the relatives under 40 years of age, the observed difference (11 per cent vs. 5 per cent), although significant at the 5 per cent level, represents only 17 hypertensives. This observed difference is sufficiently noteworthy that we hope to be able to make further observations on these younger people to confirm or exclude the possibility that the age onset of hypertension may be earlier in the relatives of hypertensives than in the relatives of normotensives.

Table 5 shows the prevalence of hypertension among spouses, siblings, and offspring. Among spouses, there is no difference in the two groups. Among siblings, however, hypertension occurs twice as frequently among siblings of hypertensives than among siblings of normotensives (44 per cent vs. 24 per cent). This difference is significant at the 1 per cent level.

Twice as many hypertensives were observed among children of hypertensives as among children of normotensives (9.4 per cent vs. 4.6 per cent). This difference falls short of statistical

significance ($p=0.06$). Since these figures are based on only 12 hypertensive individuals, and many of these children are still at risk because of their age, it is clear that one will need to have a larger number of subjects. In addition, there is need to follow the normotensive children in both groups for several years to see which ones may develop hypertension as they grow older.

Table 6 shows the results of mating combinations. Twice as many hypertensives are observed among the children when one parent is hypertensive, than when both parents are normotensive. To date we have examined only eight children whose parents are both hypertensive, and two of these have hypertension. As the study continues, and the number of children resulting from each mating combination increases, it is our hope that meaningful comparisons among these groups can be made.

Comments

From these data it might appear tempting to conclude that heredity accounts for the familial concentration we have observed. This would be going beyond the evidence. From the present data, we are unable to tell whether hypertension is conditioned by genetic factors, or related to characteristics referable to environmental influence in early life, or a combination of both.

Information bearing on possible environmental factors is currently being obtained in the interview with each subject concerning health, activities and attitudes during early life. Analysis of these factors will be possible when data have been collected on a sufficiently large sample to permit comparisons between individuals with stated characteristics, and without them, as well as between families with differing characteristics.

This is only a progress report of a long-term study. We believe that family

studies such as these may lead to the clarification of genetic hypotheses, and we hope, in time, to answer some of the questions which have been posed.

REFERENCES

1. Hamilton, M.; Pickering, G. W.; Roberts, J. A. F.; and Sowry, G. S. C. The Aetiology of Essential Hypertension: I, II, IV. *Clin. Sc.* 13:11,37,273, 1954.
2. Perera, G. A. Arterial Hypertension. In Cecil and Loeb, A Textbook of Medicine (10th ed.). Philadelphia, Pa.: Saunders, 1959, p. 1188.
3. ———. The Natural History of Primary Hypertension. From Conference on Arterial Hypertension. New York Heart Association, 1960.
4. Perera, G. A.; Clark, E. G.; Gearing, F. R.; and Schweitzer, M. D. The Family of Hypertensive Man: Progress Report of a Long-Range Study Program. *Am. J. M. Sc.* 241:18, 1961.
5. Pickering, G. W. High Blood Pressure. New York, N. Y.: Grune and Stratton, 1955.
6. Platt, R. Heredity in Hypertension. *Quart. J. Med.* 16:111, 1947.
7. ———. Essential Hypertension, Incidence, Course, and Heredity. *Ann. Int. Med.* 55:1, 1961.
8. Søbye, P. Heredity in Essential Hypertension and Nephrosclerosis: Genetic-Clinical Study of 200 Propositi Suffering From Nephrosclerosis. Copenhagen, Denmark: Munksgaard, Nyt Nordisk Forlag, Arnold Busch, 1948.
9. Thomas, C. B., and Cohen, B. H. The Familial Occurrence of Hypertension and Coronary Artery Disease, With Observations Concerning Obesity and Diabetes. *Ann. Int. Med.* 42:51, 1955.

Dr. Perera is professor of medicine, Columbia University College of Physicians and Surgeons; Dr. Clark is professor of epidemiology, Dr. Gearing is assistant professor of epidemiology, and Dr. Schweitzer is associate professor of epidemiology, Division of Epidemiology, Columbia University School of Public Health and Administrative Medicine, New York, N. Y.

This paper was presented before the Epidemiology Section of the American Public Health Association at the Eighty-Ninth Annual Meeting in Detroit, Mich., November 14, 1961.

The investigation reported in this paper was supported in part by Research Grant H-4020 from the National Heart Institute, Public Health Service.

Training in Epidemiology

A multidiscipline course in Principles of Epidemiology will be offered at the Public Health Service's Communicable Disease Center, Atlanta, Ga., January 14-18, 1963, as a part of the continuing program of the center's Training Branch.

Designed to provide public health workers with a basic understanding of how epidemiological technics can be used in an approach to the solution of problems in the preventable disease field, the course is offered for the following categories of public health personnel: physicians, dentists, veterinarians, nurses, laboratory workers, environmental health personnel and other members of the public health team. Participants will be selected on the basis of professional education and experience and current responsibility in public health programs at all levels of government. Preference will be given to persons whose professional tasks involve the application of epidemiological procedures, and registrants will be expected to attend all sessions of the course.

Further information and application forms may be obtained from: Communicable Disease Center, Atlanta 22, Ga. Attention: Chief, Training Branch.