Familial Patterns in Hypertension and Coronary Heart Disease

By Caroline Bedell Thomas, M.D.

The family histories of Johns Hopkins medical students were studied in detail and independent evaluations were made of the prevalences of hypertension and of coronary heart disease among the students' parents and grandparents. The hereditary factors in hypertension and coronary heart disease were studied and some interesting patterns of differences in sex inheritance became apparent that need further investigation.

The investigation of genetic factors in hypertension is complicated by the pleomorphic nature of the disorder. Although elevation of arterial pressure is the fundamental attribute of all forms of hypertension, uncertainty exists as to the interrelationship of the various clinical types. For example, essential hypertension and the hypertension secondary to pyelonephritis or toxemia of pregnancy may be etiologically independent. On the other hand, it is possible that such secondary hypertension occurs chiefly in persons who are highly susceptible to hypertension in the first place. Another confusing fact is that disability and death in clinical hypertension due to strokes, heart attacks, and renal failure are more closely linked to atherosclerosis than to elevation of arterial pressure per se.

Accordingly, as a step toward understanding how to predict and ultimately to prevent such cardiovascular catastrophes, we embarked in 1946 on a long-term investigation of the precursors of hypertension and coronary heart disease, using the Johns Hopkins medical students as subjects. The study was based on the hypothesis that the origins of these 2 serious diseases are multifactorial and closely intertwined, so that factors common to both may often be present in the same individual. Not only have we studied the students' physiologic, metabolic, and psychological characteristics, but their family histories as well, to determine the nature of each student's inheritance. By following these subjects over the years, it is our purpose to determine which factors are related to the early onset of hypertension or coronary disease.

Successive classes of medical students have cooperated in collecting data regarding the occurrence of all types of hypertension and coronary disease among their own parents, aunts, uncles, and grandparents. Our method has been previously described in detail. When all the available facts for each relative were assembled, a final rating of "present," "absent," "questionable," or "unknown" was made for hypertension and for coronary disease independently. Our rating for hypertension was based on clinical diagnosis by physicians, rather than on a single blood pressure measurement, the criterion used by Pickering and his co-workers. This was necessary, because the majority of the grandparents in our series were no longer living. The parents' generation was in the mid fifties on the average. Approximately 11 per cent of the fathers and 14 per cent of the mothers were reported to have hypertension, while 9 per cent of the fathers and 2 per cent of the mothers had coronary disease.
The spectrum of cardiovascular disease among the parents of Johns Hopkins students is shown in Table 1. In addition to the categories shown there, approximately 10 per cent of the subjects had a parent with questionable hypertension or coronary disease. Thus, less than two thirds of the students can say that both parents are definitely free from these disorders.

We have previously reported the prevalence of hypertension and coronary disease in 2 successive generations. Figure 1 gives a comparison of the prevalence of these disorders among the offspring of 3 types of mating: Type I, where both marital partners were affected, type II, where 1 partner was affected, and type III, where neither partner was affected. The proportion of affected offspring was greatest where both parents suffered from some form of these disorders, and least where neither parent was affected. According to whether both, one, or neither of the parents was affected, the prevalence in the offspring was 22.2 per cent, 12.3 per cent, and 8.1 per cent respectively. Thus, 2.7 times as many offspring of a type I mating had some form of hypertension or coronary disease as did the offspring of a type III mating, while the rate for type II was intermediate. This descending gradation in prevalence for the 3 types of mating was statistically highly significant.

What if the 3 types of mating are based on one disorder, disregarding the presence or absence of the other? Where matings are based on hypertension, there is a highly significant gradation in the prevalence of hypertension among the offspring (Fig. 2). The prevalence of coronary disease among the offspring of 3 types of mating based on hypertension shows a similar gradation which is not significant. When matings are based on coronary disease, a highly significant gradation in the prevalence of coronary disease among the offspring is found. Again, there is a similar gradation in the number of offspring showing the other disorder—this time, hypertension. Accordingly, whichever disorder we start with, the patterns of gradation of the 2 disorders in the offspring are similar in direction, and the prevalences of some form of the disorders in the offspring show highly significant differences among the 3 types of mating. All of these findings taken together, suggest a genetic interrelationship between hypertension and coronary disease. Our sibling data also point in that direction, but are as yet statistically inconclusive.

Another aspect of our family studies has excited our attention: there appear to be sex differences in the transmission of these 2 disorders. Where the 3 types of mating based on hypertension are considered, the gradation in prevalence among the offspring came chiefly from the female offspring (Fig. 3). Where both parents were hypertensive, the occurrence among the female offspring was 20.7 per cent; where one parent was hypertensive, 13.0 per cent, and where neither parent was hypertensive, 4.5 per cent. The incidences among the male offspring were much more alike: 11.1, 10.0, and 7.9 per cent. Conversely, where the presence or absence of coronary disease is the basis for the 3 types of matings, the gradation in prevalence stemmed chiefly from the male offspring, who showed a 21.2, 8.2, and 4.1 per cent incidence respectively where both, one, or neither of the parents was affected (Fig. 4). Percentage prevalences for the female offspring were much lower and showed little difference: 4.1, 2.4, and 2.6 per cent respectively. Presumably, the difference between men and women in age of onset of coronary disease is a complicating factor in this comparison.
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Pursuing the apparent sex differences in regard to hypertension further, we divided the students’ parents into 4 groups according to sex and the presence or absence of hypertension. Where mothers were hypertensive, their mothers (the grandmothers) had more than twice as much hypertension as their fathers (the grandfathers), namely, 41.7 versus 19.4 per cent (fig. 5). They also had twice as much maternal hypertension as did unaffected mothers (41.7 versus 19.5 per cent), while there was no difference in the prevalence of paternal hypertension (19.4 versus 19.0 per cent). A similar comparison was found in the occurrence of hypertension in fathers of affected and unaffected fathers—28.6 versus 13.0 per cent, nearly a twofold difference. We have also compared the incidence of hypertension in male and female siblings of hypertensive mothers and fathers (fig. 6). Where the probands were women, their female siblings had twice as much hypertension as their male siblings, whereas where the probands were men, their male siblings had nearly twice as much hypertension as their female siblings.

Since the publication of our findings, somewhat similar observations have been made by Allen and Spuhler. In their recent studies of systolic pressure levels among Navaho Indians, they found good correlation between systolic pressures when sisters were compared with sisters and brothers with brothers, but almost none when they compared siblings without regard to sex. In 2-generation comparisons, the father-son and mother-daughter correlations were the highest. They concluded that there is a “sex specific” tendency in the inheritance of blood pressure. These trends agree closely with our findings.

In summary, our studies indicate that both hypertension and coronary disease show a gradation in the prevalence of each disorder in the offspring of 3 types of mating. This gradation is consistent with the Mendelian law of segregation, in that the greatest proportion of affected persons was always found among the offspring of 2 affected parents and the smallest proportion among the offspring of two unaffected parents. The gradation was most marked where the presence or absence of the same disorder was studied in 2 successive generations. However, a less striking gradation in the same direction was noted where

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<th>Parental H+/C+ (GP)</th>
<th>Offspring (P)</th>
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<td>N</td>
</tr>
<tr>
<td>Both parents affected</td>
<td>26</td>
</tr>
<tr>
<td>One parent affected, one parent unaffected</td>
<td>52</td>
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<tr>
<td>Neither parent affected</td>
<td>41</td>
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<th>MATING (GP)</th>
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**Fig. 1** Top. Comparative incidence of hypertension and coronary heart disease (H+/C+) among the offspring of 3 types of mating. GP, grandparents of the medical students; P, parents, aunts and uncles of the medical students. (From Thomas, C. B.: Ann. Int. Med. 47: 539, 1957.)

**Fig. 2** Middle. Comparative incidence of disorders among the offspring of 3 types of mating based on (1) hypertension and (2) coronary disease. GP as in figure 1. P, S in figure 2 is the same as P in figure 1; both indicate the parents and their siblings, i.e., the aunts and uncles of the medical students. (Adapted from figure 8, Thomas, C. B., and Cohen, B. H.: Ann. Int. Med. 42:90, 1955.)

**Fig. 3** Bottom. Sex differences in the inheritance of hypertension (H+). (From Thomas, C. B., Am. J. M. Sc. 224: 367, 1952.)
hypertension was considered in one generation and coronary disease in the other, in either of the 2 possible sequences. Certain sex differences in the familial appearance of hypertension and coronary disease were noted. In regard to hypertension, the mothers and sisters of hypertensive women had more than twice as much hypertension as their fathers and brothers. On the other hand, the fathers and brothers of hypertensive men had almost twice as much hypertension as their mothers and sisters.

These findings are presented as areas for further exploration. Most of the studies discussed were based on material from our first 5 classes only. Conclusions derived from such a limited series will doubtless require some modification, but the trends seem unmistakable. As our numbers grow, the familial patterns will gradually emerge with sharper definition and increasing variety.

**Summary**

Studies have been made of the prevalence of hypertension and of coronary heart disease in 2 successive generations of subjects.

The greatest proportion of affected persons was always found among the offspring of 2 affected parents and the smallest proportion among the offspring of 2 unaffected parents. This finding is consistent with the hypothesis that hypertension and coronary heart disease are hereditary disorders, at least in part.

While the most striking correlations were seen when the prevalence of the same disorder was studied in 2 successive generations, similar but less striking correlations were found when hypertension was investigated in one generation and coronary disease in the other.

The female relatives of hypertensive women were found to have more than twice as much hypertension as their male relatives, while the male relatives of hypertensive men had almost twice as much hypertension as their female relatives.

**Summario in Interlingua**

Esseva studiate le prevalentia de hypertension e de morbo cardiaci coronari in 2 successive generationes de subjectos.

Le plus alte proportion de subjectos afficite esseva semper trovate inter le prole de 2 afficite parentes. Le plus basse proportion de subjectos afficite esseva semper trovate inter le prole de 2 non-afficite parentes. Iste constatatation concorda con le hypothese que hypertension e
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morbo cardiac coronari es disordines herediteri, al minus in parte.

Le plus frappante correlationes eseva constatate quando le prevalentia del mesme disordine eseva studiate in 2 generationes successive. Simile, ben que minus frappante correlationes eseva constatate quando hypertension eseva investigate in un generation e morbo coronari in le alte.

Le consanguineos feminin de feminas hypertensive monstrava un incidentia de hypertension plus que duo vices illo de lor consanguineos mascule. Le consanguineos mascule de masculos hypertensive monstrava un incidentia de hypertension plus que duo vices illo de lor consanguineos feminin.

REFERENCES


There is strong circumstantial evidence to show that blood cholesterol levels are causally associated with atherosclerosis and that these levels may be partly controlled by diet. Neither of these propositions has been proved but enough is known to suggest the value of wider testing to determine their validity. In this study the use of vegetable oils made it possible to provide much the same kinds of food to which people were accustomed and the pattern developed makes use of ordinary foodstuff, is easily prepared, and is widely acceptable. This diet reduces serum cholesterol levels in normal people and in many hypercholesteremic people and may be more effective than a simple low-fat diet. The key lies in the use of a modified unsaturated vegetable oil in combination with low saturated fat foods. The principal source of fat was a mixture of 94 per cent cottonseed, 15 per cent monostearin, 1.5 per cent distearin, and 1.5 per cent tristearin. It was tested first over a 21-day period in 4 active young physicians and later by study continued for 6 to 24 months in 16 patients with atherosclerosis. The results suggest its use in a broader test relating blood cholesterol levels with atherogenesis. It is pointed out that there is much to be learned before we can recommend such a pattern as a proper modification of the American bill of fare which chance and choice and custom have approved.

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