

HOW EARLY CAN THE TENDENCY TOWARD HYPERTENSION BE DETECTED?

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The detection of the earliest stages in the development of a chronic disease is useful for many reasons. The natural history of the disease can best be defined if the time of onset is more clearly delineated. It is reasonable to assume that etiologic studies are best conducted as close to the time of onset as is possible. It seems reasonable to assume also that treatment will be most effective in the earliest stages of the disease rather than in later stages, when tissue changes that are perhaps irreversible may already have occurred.

In the case of the studies of blood pressure, several observations made during the last decade or two suggested the basis for the present approach. It was demonstrated by Miall and Oldham, following many clinical indications, that the blood pressure of an individual was reflected in his first-order relatives within the limits of a regression coefficient of approximately 0.3–0.4.^{1,2} This observation followed a relation that was predicted by Pickering and his associates.³

Inasmuch as these observations were made in adults, it was reasonable to ask how early in life this familial relation could be demonstrated. The value of finding such a familial relation early in life seemed to be augmented by the recent observations by Miall and Lovell that in adults the greatest determinant of rise in blood pressure was the level of blood pressure attained at the beginning of a longitudinal survey. Thus, those with the highest pressures had the greatest rise in pressure over subsequent years, suggesting that the phenomenon of rising pressure was already established and moving in a defined direction for most individuals in a population.

Because the familial aggregation effect of blood pressure seemed to be readily reproducible and was demonstrable in adults aged 16 to 65, it was decided to seek a familial relation in individuals younger than 16 years of age.

Relatively few studies of blood pressure have been carried out in children because of the notion that blood pressures in children are unreliable and difficult to obtain, especially when taken in the clinic or doctor's office.

The present report is preliminary, but presents a study of familial aggregation of blood pressure in children aged 2–14 years. The data were gathered with a portable blood pressure recorder that minimizes observer variation.

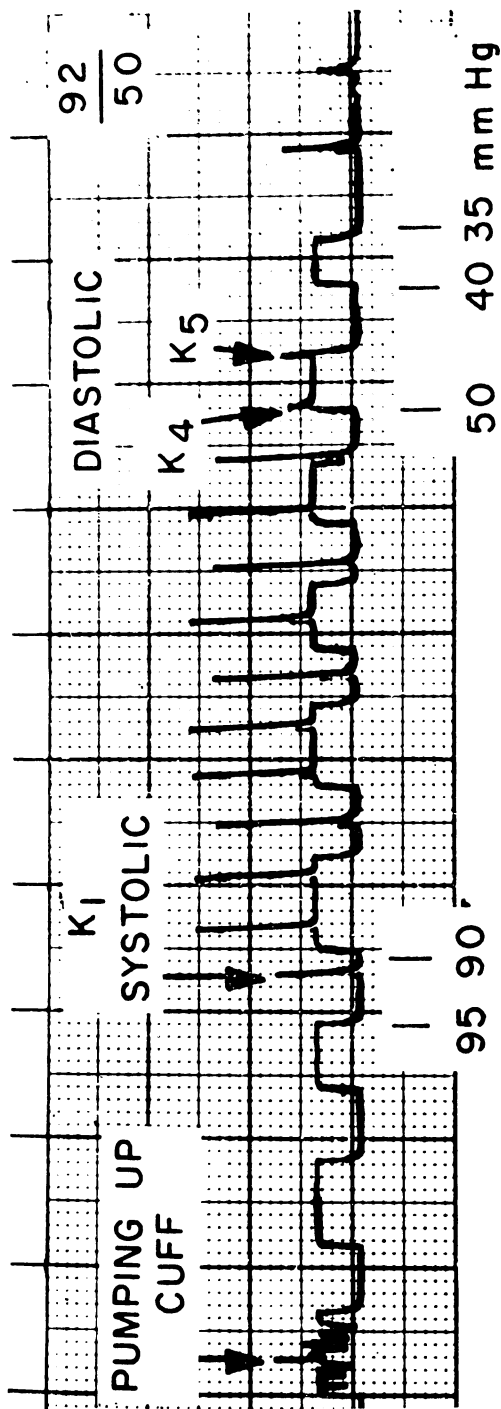
The population that was studied represented the children of 300 women who had been studied initially during a pregnancy occurring in the years 1956–1960. During this time, 200 bacteriuric women were identified, 100 of whom were treated to remove the bacteriuria; the remaining 100 were given a placebo. An additional 100 women were nonbacteriuric controls obtained by a random process from all of the nonbacteriuric women registering for prenatal care at the same time that the bacteriurics were identified.

All blood pressures were taken in the homes, and the present data were obtained from the first 83 families found during the first eight months of the followup study, during which time 326 children aged 2–14 years were studied.

All pressures were taken from the left arm after the patient had been resting in a chair for five minutes or longer. The appropriate cuff size was used, based on the recommendations of the American Heart Association. The blood pressure was taken three times in succession, and the mean of the three readings was recorded. All pressures were taken by a single observer who was using a newly developed instrument.

This instrument was developed by Kass in collaboration with Professor E. Mollo-Christensen of the Massachusetts Institute of Technology. It records on tape the Korotkoff sounds of an individual through a microphone, along with a simultaneous calibration scale. The tape can be played back later. The instrument weighs about 18 pounds and consists of an ordinary mercury sphygmomanometer that has been wired at five-millimeter intervals to produce the calibration scale. As the mercury falls, contact with these electrodes activates an oscillator, which generates a high-pitched signal at alternative five-

FIGURE 1. SAMPLE READ-OUT TAPE (SPEED: 5 MM/SEC)



millimeter intervals. The blood pressure is taken in the usual manner and the observer hears the sound through attached earphones.

At a later date, when the tape is played back through a single-channel recorder such as an electrocardiograph, a pattern such as that seen in Figure 1 is produced. The square waves in this illustration were set with the lowest reading at 35 millimeters of mercury. Each battlement represents five millimeters of mercury. The spikes represent the Korotkoff sounds, superimposed on a battlement pattern. The first sound therefore represents the systolic pressure, and the muffled sound, seen by a substantial change in the amplitude of the spike, represents the fourth phase of the Korotkoff sounds, or diastolic pressure. In the example given in Figure 1, the blood pressure is 92/50. This method minimizes observer error and digit preference, and the readout can be checked later by several independent observers. The accuracy of this instrument has been tested in several laboratories, and the correlation between ordinary indirect sphygmomanometry and the machine is around 0.9.⁵

Illustrative of the reproducibility of the method is the finding that when a series of tapes was read and later reread in random sequence by the same observer, the standard deviations of the difference between the two sets of readings were 1.8 mm Hg for systolic and 1.7 mm Hg for diastolic pressures. Duplicate readings agree within 2 mm Hg.

When blood pressures were taken in the home, it was customary to perform the blood pressure reading on the mother and then on the children. Only those children on whom readings could be obtained have been included in the analysis. In 80 per cent of the families, all children of ages 2-14 had their blood pressures recorded, and in another 17 per cent all but one child were studied. Of the 347 children of the 83 mothers studied, only 21 were not recorded. Eight of these were found, but readings were not obtained, because of either refusal of the child, machine failure or electrical interference resulting from excessive motion by the child. Four children were in state institutions, seven were out of state and two could not be located.

The mean blood pressures and standard errors, plotted against age in two-year age groups for boys and girls, are seen in Figure 2. A slight steady rise with age is seen for both systolic and diastolic pressures. These data are similar to those reported by Moss and Adams.⁶

To adjust for age and sex, blood pressures were expressed in standard deviation units (SDU), where SDU = observed recorded pressure for

an individual – mean pressure for his two-year age and sex group ÷ standard deviation of the blood pressures in that age and sex group.

FIGURE 2. MEAN BLOOD PRESSURE OF CHILDREN

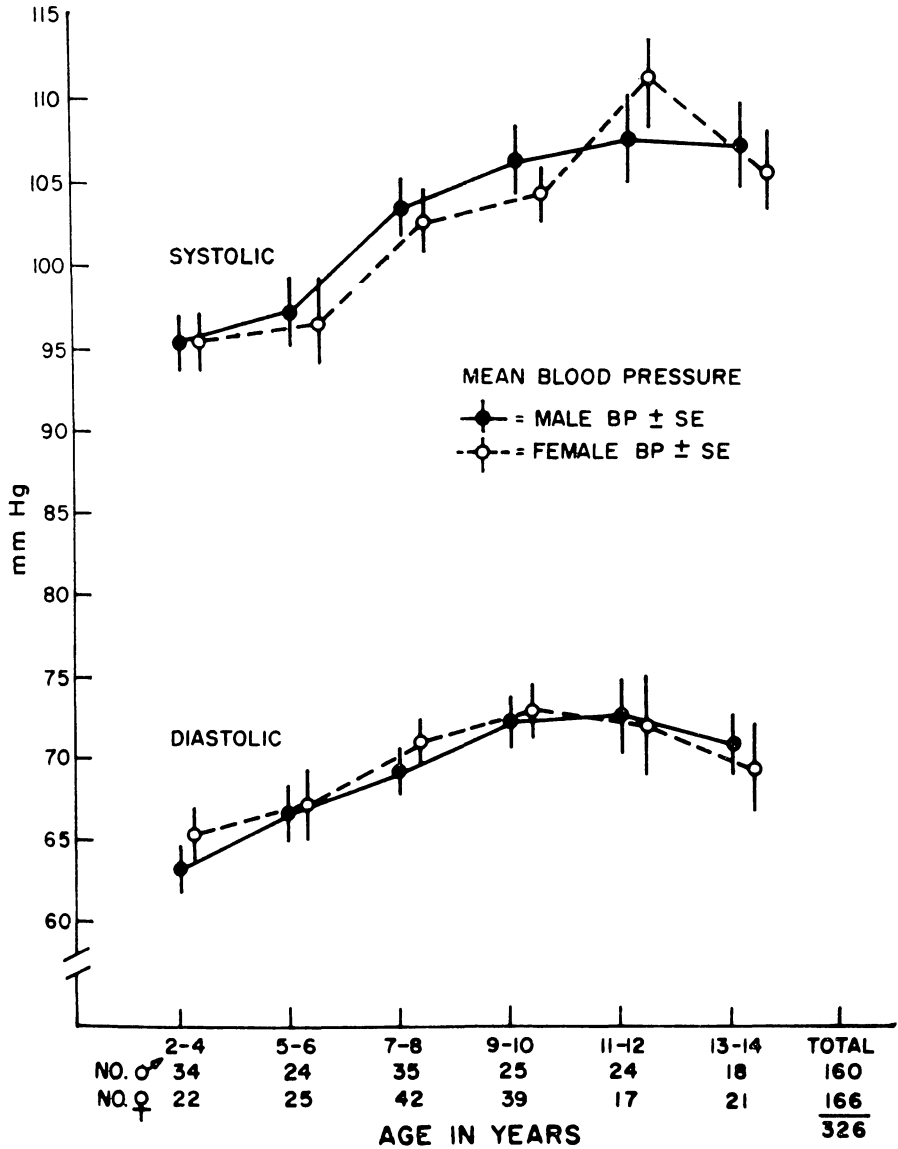


TABLE 1. ANALYSIS OF VARIANCE, ENTIRE GROUP

<i>Systolic</i>	<i>Degrees of Freedom</i>	<i>Systolic Sum of Squares</i>	<i>Mean Square</i>	<i>F Score</i>
Among families	82	168.86	2.059	3.448*
Within families	243	145.13	0.597	
<i>Diastolic</i>				
Among families	82	144.13	1.758	2.514*
Within families	243	169.88	0.699	

* $p < .01$.

TABLE 2. CLASSIFICATION BY BACTERIURIA STATUS OF MOTHER

<i>Group</i>	<i>Number of Families</i>	<i>Number of Children</i>
Entire group	83	326*
Ever bacteriuric	59	232*
Never bacteriuric	24	94*
Bacteriuric now	17	71*
Not bacteriuric now	66	255*

* Analysis of variance, $p < .01$.

Using this device, those individuals whose standard deviation units are positive tend to run blood pressures higher than the mean for their own age and sex group, and those with negative values are below the mean. This method permits the study of familial aggregation by the technique of analysis of variance. When the variance of blood pressure scores of these children is compared, the variability of blood pressure within families is significantly less than the variability among families. The data are presented in Table 1. The familial aggregation or clustering of blood pressures is found for both systolic and diastolic pressures, and even in this relatively small sample the p value for the difference in variability within and among families is less than 0.01.

It is not expected that bacteriuria in the mother would have any influence on familial aggregation of blood pressure, because bacteriuria had been previously found not to be familial.⁷ Similarly, because the rate of bacteriuria in girls of this age is approximately one per cent and the finding is exceedingly rare in boys,⁸ it was not anticipated that bacteriuria would influence the findings in the children or in the

families. Nevertheless, the families were analyzed on the basis of the bacteriuria status of the mother to see if these predictions were true. Table 2 indicates that each group exhibited significant familial aggregation, and that the presence or absence of bacteriuria in the mother did not influence the familial blood pressure effect.

As a demonstration of the strength of the familial relation one child from each family with two or more children was selected at random as a propositus, and the regression of the child's siblings on the propositus was calculated using standard deviation unit scores. The degree of this relation was expressed as the regression coefficient. Table 3 shows that for the entire group in the series, the regression coefficient is 0.46 for systolic and 0.28 for diastolic pressures. The table also presents similar data gathered by Miall, *et al.*,⁹ using relatives of all ages. The results seen in the present study of children are in the same range as those observed by Miall in his study of adults and their relatives.

The familial aggregation occurs at all levels of blood pressure (Figure 3). Mean childhood pressures were calculated for each of the 83 families. By weighting for family size, one would expect these means to be normally distributed if no intrafamilial clustering was present. The expected distribution for systolic pressures is represented by the clear spaces, and the observed distribution is seen in the stippled area. Fourteen families fall at the extremes when only four would be expected without familial aggregation. The observed distribution is significantly different from the expected distribution at the one per cent level by chi-square. A similar relation is observed for diastolic pressures, but the figure is not presented here.

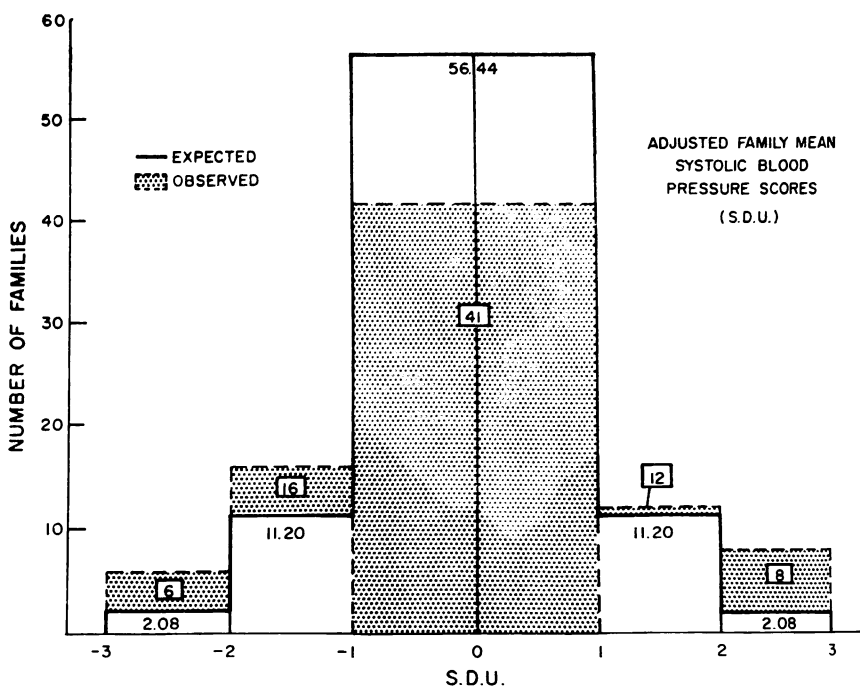
The data suggest a familial influence on blood pressure that is measurable in childhood between ages 2 and 14. The effect is seen

TABLE 3. STRENGTH OF THE FAMILIAL RELATION

Source	Number	Regression Coefficients	
		Systolic	Diastolic
Present series			
Sib-sib	242	0.46	0.28
Miall*			
Sib-♂ sibs	563	0.299	0.186
Sib-♀ sibs	525	0.306	0.317
All relatives	2218	0.286	0.225

* Clinical Science, 33, 271-283, 1967.

FIGURE 3. ADJUSTED FAMILY MEAN SYSTOLIC BLOOD PRESSURE SCORES



at all levels of blood pressure. The bacteriuria status of the mother does not influence this effect.

These data are obtained from a low socioeconomic group in a large municipal hospital. No attempt has been made to identify environmental or genetic factors that might be responsible for this familial association. It is not known precisely at what age in life the familial effect is first manifest, but clearly the implication is that this is manifest either *in utero* or during the first two years of life.

Therefore, the demonstration of a familial influence on blood pressure in early childhood should direct toward children further investigation into the nature and etiology of hypertension.

One of the important issues raised by the several studies of hypertension has been the relative influence of genetic and environmental factors. An argument that suggests strong environmental influences is herein presented.

Large-scale studies have given many indications that hypertensives tend to have fewer offspring than nonhypertensives.^{10,11} The implica-

tions of the diminished fecundity of those with elevated blood pressures have not been explored fully in the past. Clearly, hypertensives are at a reproductive disadvantage when compared with nonhypertensives. Therefore, over a period of successive generations, hypertensives should breed themselves out of existence if the effect is caused by a dominant gene. The fact that hypertension exists may indicate either that the disease is relatively new, or that it is governed by a dominant gene that has not yet had time enough to dilute itself out of existence. This seems improbable. Alternatively, it could be argued that the disease is caused by a dominant gene, but has associated with it a balanced polymorphism that may overcome in some manner the reproductive disadvantage dominated by the influence of the dominant gene. This hypothesis, though tenable, has no supporting data, and no possibilities have been advanced to indicate that such balanced polymorphism that would overcome the reproductive disadvantage does in fact exist. The third possibility, therefore, would be that the disease is not governed by a dominant gene, but is familial because of an environmental influence that can be passed along in a familial setting.

The last hypothesis is consistent with the environmental studies of Miall and Oldham who calculate that most of the blood pressure effect is explained on the basis of environmental influences.^{2,11}

The environmental effect, taken with the earlier data, would, therefore, suggest the possibility that the tendency toward elevated pressures above the mean for an individual's age group is established on the basis of environmental influences exerting their effects either during the developmental period or during the early years of life.

Should these indications be confirmed by additional studies of childhood populations, it would suggest that the search for etiologic agents in the environment should be limited to these conditions. The possibility must also be considered that treatment given early in life might significantly alter the familial relation.

It should be stressed that these observations not only are preliminary, but they also make an inference that requires sustained study for substantiation. The inference is that the familial aggregation herein demonstrated will reflect itself by a continuous tendency for those families with the highest blood pressure to continue to be families with highest blood pressure in later life. Only a prospective study can indicate whether this suggestion is valid. The present epidemiologic data, however, are highly suggestive of the fact that this will be the case, and they make continued investigation appear to be worthwhile.

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