Screening of the Coronary Prone by Study of Offspring

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THE INCREASED likelihood of coronary heart disease developing in persons with elevated levels of serum cholesterol, blood pressure, body weight, and certain electrocardiographic abnormalities has been repeatedly shown in retrospective and prospective studies (*1*). Other studies have revealed significant associations between fathers and their children for cholesterol and blood pressure levels and ponderal index values (*2–4*). These observations raise the question of whether it is possible to identify or screen coronary-prone middle-aged men by studying their children.

To evalute this procedure, the so-called coronary risk factors should be measured on both fathers and children. The frequency of predicting the presence of coronary heart disease factors among fathers by examining their children's values for these characteristics could then be quantified. Furthermore, if such a procedure were to be practical, a "captive" population of children whose fathers are at risk should be selected. Eleventh grade students seem to be ideal for this purpose as they are a captive, relatively stable population, and their fathers are mostly 35 to 55 years old.

The feasibility of such a procedure was demonstrated in a pilot project involving 100 student-father pairs (*2*). Briefly, the pilot study revealed significantly positive associations between the students and their fathers for serum cholesterol and blood pressure levels and ponderal index values. In addition, predominantly high levels of all variables combined (blood lipids, blood pressure, glucose, uric acid, skinfold thickness, and ponderal index) of the students predicted all the fathers with ST–T abnormalities. Also, three-fourths of the fathers with a history of coronary heart disease or with elevated levels of relative body mass and two-thirds of the

Table 1. Relationships between children's and fathers' distributions for a selected characteristic

Father's distribution	Children's distribution		
	Lower	Middle	Upper
Lower	*a*		*b*
Middle			
Upper	*c*		*d*

$P = \frac{a+d}{a+b+c+d}$. Null situation, $P = 0.50$.

fathers with high blood pressure levels were identified by their offsprings' high levels of all variables combined.

The response rate, field procedures, and findings of the pilot study were sufficiently promising to justify the design of a more definitive study. This report, based on 501 student-father pairs, is an evaluation of the effectiveness of predicting the coronary risk status of fathers using their offspring's characteristics.

Methods and Materials

Seven hundred 11th graders in a suburban high school near Buffalo, N.Y., and their fathers were invited to participate in this study. Serum cholesterol, blood pressure, uric acid, skinfold thickness, height, and weight measurements were determined for 501 students and their fathers (a participation rate of 71 percent). In addition, the fathers were questioned (in a standard fashion) by a physician to assess a history of myocardial infarction or angina pectoris.

The standard 12-lead ECG was interpreted by two physicians, independently, according to criteria used in the National Health Survey (*5*). Left ventricular hypertrophy was diagnosed when the maximum R wave (V5 or V6) plus the S wave (V1 or V2) were greater than 35 mm. (*6*). Disagreements, which occurred with approximately 25 percent of the readings, were resolved by jointly reexamining the tracings.

Single blood pressure readings in 5 mm. intervals were recorded from the left arm with the subject seated; the fifth phase for diastolic blood pressure was used. The ponderal index, a measure of relative body mass, was calculated from the formula: height $\div \sqrt[3]{\text{weight}}$. The fasting serum cholesterol level was determined by the technique of Abell (*7*). A Lange skinfold caliper was used to determine triceps (arm) skinfold measurements.

The ordac method of analysis was used to express the relationship between children and their

Table 2. Distribution of fathers according to age groups

Age (years)	Number	Cumulative percent
35–39	34	7
40–44	148	36
45–49	153	67
50–54	104	88
55–59	40	96
60–75	20	100
Total	[1] 499	...

[1] 2 fathers did not give their ages.

Table 3. Distributions of six selected variables among fathers, by age

Father's variables	35—44 years		45—49 years		50 years or more	
	Number	Percent	Number	Percent	Number	Percent
Diastolic blood pressure (mm. Hg.)	182	100.0	153	100.1	164	99.9
35–75	38	20.9	24	15.7	35	21.3
80	49	26.9	33	21.6	23	14.0
81–87	22	12.1	24	15.7	22	13.4
90	33	18.1	35	22.9	32	19.5
91–130	40	22.0	37	24.2	52	31.7
Systolic blood pressure (mm. Hg.)	182	100.0	153	100.0	164	100.1
80–110	42	23.1	21	13.7	27	16.5
115–120	57	31.3	44	28.8	28	17.1
125–130	35	19.2	38	24.8	32	19.5
135–145	30	16.5	24	15.7	39	23.8
150–230	18	9.9	26	17.0	38	23.2
Uric acid (mg.)	178	99.9	147	100.0	159	99.4
2.0–5.0	32	18.0	32	21.8	31	19.4
5.1–5.5	36	20.2	29	19.7	31	19.8
5.6–6.1	36	20.2	35	23.8	33	2.80
6.2–6.8	36	20.2	27	18.4	35	22.0
6.9–11.0	38	21.3	24	16.3	29	18.2
Arm skinfold (mm.)	182	100.0	153	100.1	164	100.1
2–11	32	17.6	31	20.3	37	22.6
12–15	29	15.9	24	15.7	40	24.4
16–19	39	21.4	39	25.5	36	22.0
20–23	42	23.1	31	20.3	35	21.3
24–44	40	22.0	28	18.3	16	9.8
Ponderal index	182	100.0	153	100.0	161	100.1
10.1–11.9	38	20.9	39	25.5	34	21.1
12.0–12.2	30	16.5	35	22.9	32	19.9
12.3–12.5	48	26.4	24	15.7	33	20.5
12.6–12.8	35	19.2	28	18.3	35	21.7
12.9–14.6	31	17.0	27	17.6	27	16.8
Cholesterol (mg. per 100 ml.)	178	100.0	147	100.0	159	100.1
88–210	37	20.8	30	20.4	21	13.2
212–230	34	19.1	27	18.4	34	21.4
232–244	36	20.2	34	23.1	26	16.4
246–268	40	22.5	26	17.7	33	20.8
270–352	31	17.4	30	20.4	45	28.3

NOTE: Totals reflect only those people for whom measurements were obtained.

fathers (2, 8). Ordacs are ordinal age-corrected scores. To obtain ordacs, each frequency distribution for a selected characteristic was divided into thirds (lower, middle, and upper) within the three age groups 35–44, 45–49, and 50 or older. Fathers in the lower third of the distribution for their age group were assigned a score of 1, fathers in the middle third a score of 2, and fathers in the upper third a score of 3. The distributions for these same characteristics were similarly divided and scored for boys and girls.

The ordac method permitted examination of relationships between fathers regardless of age and children regardless of sex. The relationships between father-child pairs can be measured as shown in table 1.

Let p be the proportion: $p = (a + d) \div (a + b + c + d)$. If there is no association for a selected characteristic between fathers and their children, then p will equal 0.50 (since we expect equal frequencies in the four corner cells a, b, c, and d). In the non-null situation, that is in the presence of association, p will not equal 0.50. If p exceeds 0.50, then the association is positive. The sum of the four corner cells $(a + b + c + d)$ can be considered the number of cases in which both the father's and child's characteristics differ from average. Then p is the proportion of those cases in which both the father and child have characteristics that are higher or lower than average.

The proportion p can be viewed as an overall measure of the aggregation of the characteristic in fathers and their children. The cells in the middle of table 1 are not used in the computation of p. Since the middle cells designate average values, their exclusion does not appreciably affect the aggregation of a characteristic between fathers and their children. A 95 percent confidence interval can be computed for p to determine if observed associations are statistically significant. The variance of p is equal to $1 \div [4(a + b + c + d)]$. The 95 percent confidence interval is $p \pm 1.96 \sqrt{\text{variance}}$.

For this study, the ponderal index distribution was reversed so that its classification into low, medium, and high categories corresponds to low, medium, and high relative body mass. This reversal allows for comparability as well as for combining the ponderal index scores with other variables.

Results

Examinations were completed on 501 student-father pairs. The age range of students was 15–20 years for 253 boys and 248 girls.

Table 4. Distribution of six selected variables among children, by sex

Child's variables	Boys		Girls	
	Number	Percent	Number	Percent
Diastolic blood pressure (mm. Hg.)	244	100.0	243	100.0
35–60	31	12.7	52	21.4
65	28	11.5	53	21.8
70	77	31.6	68	28.0
75	45	18.4	40	16.5
80–90	63	25.8	30	12.3
Systolic blood pressure (mm. Hg.)	244	100.0	243	100.1
80–105	15	6.1	67	27.6
110	16	6.6	59	24.3
115	39	16.0	49	20.2
120	60	24.6	45	18.5
125–175	114	46.7	23	9.5
Uric acid (mg.)	244	100.0	234	100.0
2.0–3.9	3	1.2	87	37.2
4.0–4.6	26	10.7	81	34.6
4.7–5.2	59	24.2	42	17.9
5.3–5.9	80	32.8	18	7.7
6.0–8.6	76	31.1	6	2.6
Arm skinfold (mm.)	244	100.0	243	100.0
2–5	85	34.8	7	2.9
6–8	91	37.3	21	8.6
9–11	37	15.2	45	18.5
12–14	18	7.4	74	30.5
15–44	13	5.3	96	39.5
Ponderal index	244	100.0	243	100.0
10.1–12.4	44	18.0	57	23.5
12.5–12.8	47	19.3	50	20.6
12.9–13.1	47	19.3	55	22.6
13.2–13.4	52	21.3	42	17.3
13.5–14.6	54	22.1	39	16.0
Cholesterol (mg. per 100 ml.)	244	100.0	234	100.0
88–160	66	27.0	36	15.4
162–178	59	24.2	45	19.2
179–194	51	20.9	45	19.2
196–212	39	16.0	62	26.5
214–294	29	11.9	46	19.7

NOTE: Totals reflect only those people for whom measurements were obtained.

Fathers ranged in age from 35–75 years (table 2). The distributions of the six selected variables for the fathers according to their age and for their offspring according to sex are given in tables 3 and 4. Positive associations were observed between age of adults and levels of cholesterol and blood pressure and skinfold thickness. Girls had lower levels than boys for blood pressure and uric acid. Cholesterol levels, ponderal index, and skinfold thickness were higher among girls than among boys. The age and sex relationships of these characteristics were generally similar to those in other studies. (*9*).

The levels of the six selected variables among fathers and their children in the upper third of their distributions can be determined from these tables. For example, fathers 35–44 years with a diastolic blood pressure of 90 or more formed the upper third of the distribution of this variable. In some instances it will be necessary to interpolate between the values shown in tables 3 and 4 to obtain the level of a particular variable that corresponds to the upper third of the distribution.

Table 5 summarizes the relationships between children and fathers for the six selected characteristics. A positive statistical association between fathers and their children was evident for each of the variables with the exception of systolic blood pressure. Even for systolic pressure, however, a tendency toward aggregation was observed.

The sensitivity and specificity of using a child's measurements to predict his father's are shown for each of the six variables in table 6. Sensitivity indicates the proportion of fathers in the upper third of their distributions (positives) who would be correctly identified using their children's measurements. Specificity refers to the proportion of fathers in the lower two-thirds of their distributions (negatives) who would be correctly identified. The sensitivity of the children's measurements varied from 47 percent for fathers with high levels of diastolic blood pressure to 35 percent for fathers with high levels of systolic blood pressure. The percent specificity ranged from 69 to 76 for the six variables.

Assuming that high scores may cluster within individual persons, a combined score was derived for the six variables. For all six characteristics a child's score could range from 6 to 18. The sensitivity and specificity of the children's combined score levels in predicting coronary-prone fathers is shown in table 7. Fathers in the upper third of the distribution of the six variables combined were considered to be coronary prone. Using children with a combined score of 12 or higher permits the correct identification of two-thirds of the coronary-prone fathers and one-half of the remaining fathers. Generally the more children examined, the greater the sensitivity and the less the specificity.

The sensitivity and specificity of using a combined score based on blood pressure, ponderal index, and skinfold measurements of children to predict coronary-prone fathers is shown in table 8. Blood pressure, ponderal index, and skinfold of children

Table 5. Relationships between fathers and children, according to selected characteristics

Children's characteristics	Father-child aggregation
Diastolic blood pressure	0.60(±.06)[1]
Systolic blood pressure	.56(±.80)
Uric acid	.67(±.07)[1]
Arm skinfold	.60(±.07)[1]
Ponderal index	.71(±.07)[1]
Cholesterol	.62(±.07)[1]

1 Statistically significant at the 5 percent level.
NOTE: ( ) = 95 percent confidence interval.

Table 6. Sensitivity and specificity of using children's characteristics to predict fathers with high levels for six selected variables

Children's characteristics	Fathers in upper third (sensitivity)		Fathers in lower two-thirds (specificity)	
	Number	Percent	Number	Percent
Diastolic blood pressure	158	47	327	69
Systolic blood pressure	153	35	332	73
Uric acid	147	46	315	72
Arm skinfold	153	39	332	73
Ponderal index	153	46	329	76
Cholesterol	154	41	308	72

Table 7. Sensitivity and specificity of using children's combined score on six variables to predict coronary-prone fathers

Children's combined score for 6 variables	Number of children	143 coronary-prone fathers (percent sensitivity)	305 non-coronary-prone fathers (percent specificity)
6 or more	448	100	0
7 or more	446	100	1
8 or more	434	97	3
9 or more	412	92	8
10 or more	372	86	18
11 or more	318	76	32
12 or more	245	65	50
13 or more	185	51	63
14 or more	123	33	75
15 or more	77	30	86
16 or more	52	15	90
17 or more	22	6	95
18	7	2	99

Table 8. Sensitivity and specificity of using children's combined score for four variables to predict coronary-prone fathers

Children's scores for 4 combined variables[1]	Number of children	146 coronary-prone fathers (percent sensitivity)	323 non-coronary-prone fathers (percent specificity)
4 or more	469	100	0
5 or more	455	98	3
6 or more	410	91	14
7 or more	351	79	27
8 or more	275	64	44
9 or more	186	47	64
10 or more	117	34	79
11 or more	60	17	89
12	21	7	97

[1] Systolic and diastolic blood pressure, ponderal index, and skinfold measurements.

Table 9. Sensitivity and specificity of using scores of 245 children with a combined score of 12 or more to predict fathers with coronary disease or ECG abnormalities

Fathers' characteristics	Number of fathers	Percent sensitivity
History of angina pectoris	17	41
History of myocardial infarction	9	78
ST–T abnormalities	36	45
Left ventricular hypertrophy	66	55

were selected for this index because of their general availability. Coronary-prone fathers are again defined to be those fathers in the upper third of the distribution of the six variables combined. Children with a score of 8 or higher for the four variables combined allowed the correct identification of two-thirds of the coronary-prone fathers and 44 percent of the other fathers.

Fathers with histories of coronary heart disease or selected electrocardiographic abnormalities were similarly analyzed (table 9). Seven out of nine (or 78 percent) of fathers who gave histories of myocardial infarction were identified through their children who had combined scores of 12 or higher.

Comment

The identification of coronary-prone adults through a study of coronary risk factors among their children appears to have practical application. The relatively high participation rate of 71 percent would support this conclusion even if little or no aggregation between risk factors in fathers and their children were observed. The aggregation of risk factors in fathers and their children can be viewed as a bonus. From the scores of children in the upper half of the distribution for the six risk variables combined, two-thirds of the coronary-prone fathers were correctly identified rather than the 50 percent expected by chance alone. The relative ease of obtaining particularly blood pressure, ponderal index, and skinfold measurements for school children lends credibility to this method of screening which is quick, simple, and inexpensive.

The usefulness of this method of screening fathers should be dependent upon the aim of identifying coronary-prone adults. In an etiological study of the disease, the identification of only a portion of the coronary-prone patients may be misleading. Since the characteristics of the coronary-prone fathers not identified are unknown, possible biases may render interpretations difficult, especially in terms of causality.

On the other hand, the identification of a large portion of coronary-prone adults through a captive child population may provide an ideal group at risk for testing the efficacy of primary preventive measures. The well-defined nature of this group of fathers as well as its accessibility and apparent motivation would provide many of the essential elements required in achieving the aims of preventive trials.

The presence of a limited but measurable association between risk factors in fathers and their children points to the desirability of further research in this area to improve the sensitivity and specificity of prediction.

REFERENCES

(*1*) Epstein, F. H.: The epidemiology of coronary heart disease. A review. J Chronic Dis 18: 735–774 (1965).

(*2*) Ibrahim, M. A., et al.: Coronary heart disease: screening by familial aggregation. Pilot study. Arch Environ Health 16: 235–240 (1968).

(*3*) Deutscher, D., Epstein, F. H., and Keller, J. B.: Relationships between familial aggregation of coronary heart disease and risk factors in the general population. Amer J Epidem 89: 510–520 (1969).

(*4*) Winkelstein, W., Jr., Kantor, S., Ibrahim, M. A., and Sackett, D. L.: Familial aggregation of blood pressure. Preliminary report. JAMA 195: 848–850, Mar. 7, 1966.

(*5*) Coronary heart disease in adults, U.S., 1960–62. PHS Publication No. 1000, Ser. 11, No. 10, U.S. Government Printing Office, Washington, D.C., 1965.

(*6*) Ostrander, L. D., Jr.: Epidemiological study of the electrocardiographic diagnosis of left ventricular hypertrophy. Circulation 33: 270–282 (1966).

(*7*) Abell, I. L., et al.: A simplified method for the estimation of total cholesterol and demonstration of its specificity. J Biol Chem 195: 357–366 (1952).

(*8*) Priore, R. L.: The ordac method of making age adjustments in data. J Chronic Dis 17: 241–263 (1964).

(*9*) Johnson, B. C., Epstein, F. H., and Kielsbeng, M. O.: Distributions and familial studies of blood pressure and serum cholesterol levels in a total community—Tecumseh, Michigan. J Chronic Dis 18: 147–160 (1965).

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Blood pressure, skinfold thickness, ponderal index, cholesterol, and uric acid values were determined for 501 high school students. Similar determinations were made for their fathers. Additional information on the fathers was obtained from a 12-lead electrocardiogram and an inquiry into the presence of angina pectoris or myocardial infarction.

A significant positive association between fathers and their children was observed for five of the six variables examined. The sensitivity of the children's diastolic blood pressure for predicting whether their father's levels of diastolic blood pressure were among the upper third of the distribution of these values was 47 percent. The corresponding sensitivities of other variables were 35 percent for systolic blood pressure, 46 percent for uric acid, 39 percent for skinfold thickness, 46 percent for ponderal index, and 41 percent for cholesterol. The percent specificity ranged from 69 to 76 for the six variables.

Children with a combined score of 12 or higher for the six variables permitted the correct identification of two-thirds of the coronary-prone fathers and one-half of the noncoronary-prone fathers. Similar results were obtained when only four selected variables of the children were combined.

Seventy-eight percent of the nine fathers with histories of myocardial infarction were identified through their children's high levels of combined variables, as were 41 percent of the 17 with angina pectoris, 45 percent of the 36 with electrocardiographic evidence of ST-T abnormalities, and 55 percent of the 66 with left ventricular hypertrophy.