SERIAL ELECTROCARDIOGRAMS: THEIR RELIABILITY AND PROGNOSTIC VALIDITY OVER A 24-YEAR PERIOD*

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SUMMARY PAGE

THE PROBLEM

Careful follow-up studies with comparison of serial electrocardiograms is the only way to determine the "normal" or physiologic variability of the electrocardiogram and whether serial changes reflect underlying pathological alterations or are related to physiological variables. For this purpose, the reliability and prognostic validity of serial electrocardiograms were determined in a group of young men who were followed from 24 to 49 years of age.

FINDINGS

Electrocardiographic durations, amplitudes, and vectoral orientations at each of the four evaluations were similar to values from cross-sectional surveys of men at the same ages. The pattern of QRS deflections did not change although there were changes in the amplitude of these deflections. A significant decrease in QRS and T amplitude (ΣQRS and ΣT) was found with increasing aging and did not correlate significantly with weight and blood pressure. The QRS axis moved leftward as the group became older and the change in QRS axis was related to interval weight changes and to blood pressure. The T axis and the QRS-T angle did not change during the 24 years of study. The group subsequently developing coronary heart disease had a greater decrease in QRS amplitude and tended to have a greater leftward movement of the QRS vector, but caution is emphasized in extrapolating these observations to the diagnosis of disease in individual patients. The resting electrocardiogram is a reliable measurement despite minor serial changes in amplitude and vectoral orientation and has limited predictive value in young men.

ACKNOWLEDGMENTS

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INTRODUCTION

The electrocardiogram is generally considered to be a reliable and valuable means of detecting acute myocardial changes, particularly those associated with myocardial infarction. The evidence is less convincing that the resting electrocardiogram can reflect subtle myocardial alteration and thus permit prediction of subsequent development of overt disease. To have predictive value the electrocardiogram must be a reliable measurement with the only alterations resulting from underlying pathological changes, or if there is variability due to physiological factors, these must be identified and separated from pathological changes. It is generally conceded that the wide range of "normal" variation diminishes the predictive value of a single electrocardiogram analyzed by usual techniques, but quantitative evaluation and the availability of serial electrocardiograms have been expected to afford a better definition between "normal" and "abnormal" and to delineate subtle, but prognostically important, alterations. Compilation of electrocardiographic data on healthy individuals provides a quantitative definition of normal ranges (1). Within the broad range of normal values there are probably values that infer considerably different risks of future disease. Careful follow-up studies with comparison of serial electrocardiograms is the only means of determining the "normal" or physiologic variability of the electrocardiogram and whether serial changes reflect underlying pathological alterations or are related to physiological variables.

We have evaluated periodically since 1940 a relatively homogeneous group of initially healthy young men, and the electrocardiograms recorded during these evaluations have provided an opportunity to determine serial alterations and to correlate these changes with physiological and pathological aspects. These men were examined four times from age 24 to age 49 years, and heart disease developed in or abnormal electrocardiograms were obtained from a significant number. These considerations permit an examination of the reliability and the predictive value of serial electrocardiograms in young men. This report catalogues the electrocardiographic values for each examination, relates serial changes in these parameters to nonelectrocardiographic variables, and documents the reliability of various electrocardiographic items. To test the prognostic value, the serial changes during the first three examinations were correlated with the development of disease between the third and fourth examinations.

PROCEDURE

A group of 1,056 healthy young men (mean age 24 ± 2.7 years), physically qualified for naval flight training, were studied extensively in 1940. They were re-examined in 1952, 1958, and 1964. The general aspects of this study, including selection of the group, methodology, and the status of follow-up are reviewed elsewhere (2-6). In 1952, 88 per cent of survivors were examined; in 1958, 96.8 per cent; and in 1964, 84 per cent. Some medical information (exclusive of examination) was obtained on 96 per cent to 99 per cent of the original group during each examination period. An interval history of disease in a subject was usually documented by obtaining copies of

hospital records. Additional medical history was obtained from a medical questionnaire returned by the subjects in 1966.

In 1940 the subjects were evaluated in the fasting state, and leads 1, 2, 3, and CF4 were recorded on photographic paper using a Sanborn Cardiette Conventional 12-lead electrocardiograms were obtained in 1952, 1958, and 1964, although about one fourth of the electrocardiograms in 1958 were recorded with a lead converter system (7). Photographic records were obtained in 1952 and 1958 and direct-writer paper records were obtained in 1964. A standardization of 10 mm = 1 mv was used on all electrocardiograms except those recorded with the lead converter. All subjects were postabsorbtive in 1964, but their feeding status was not controlled in 1952, and the majority were fasting in 1958.

A double Master two-step test was performed on each subject in 1958 and 1964. In 1964 a Harvard step test with three minutes and four minutes of exercise (20 steps/min on a 20-inch step) were carried out on all subjects in the fasting state (8). Post-exercise tracings (leads 1, 2, 3, aVF, V2, V4, V5, and V6) were recorded on two 4-channel Sanborn recorders at the following intervals: immediately, 1, 2, 3, and 5 minutes after exercise.

Measurement of electrocardiographic durations and amplitudes followed the recommendations of the Committee on Electrocardiography, American Heart Association (9). Measurements on records from 1940, 1952, and 1958 were made to the nearest 0.2 mm by one observer (W.R.H.) and checked by another (R.K.O.). The measurements on records from 1964 were made by two other observers (A.O. or R.E.M.). For inclusion in this analysis it was necessary that the original ECG and either the 1952 or 1958 record be available and technically adequate. Only records having correct standardization displayed on the tracings were used for comparison of amplitudes, although all records otherwise technically satisfactory were used for measurement of vectors and intervals. Electrocardiograms with bundle branch block, unequivocal myocardial infarction, and Wolff-Parkinson-White syndrome were excluded from the group having comparison of measurements.

The QRS and T vectors were estimated by two examiners (W.R.H. and R.K.O.) using the technique described by Grant (10). The vectoral analysis of the 1964 tracings were performed by two other observers (A.O. and R.E.M.) using the same techniques. The initial QRS vector (termed "initial 0.04 vector") was estimated from the initial 0.04 second of each of the frontal leads and the terminal QRS vector (termed "terminal 0.04 vector") estimated from the remainder of the complex. This terminal portion varied normally from 0.02 to 0.04 second. A piece of celluloid with ruled lines at 0.04-second intervals was found to be helpful in making these estimates.

Data were coded and analyzed with an IBM 1620 computer using standard statistical methods (5). The measurements from the first three examinations (1940, 1952, and 1958) were correlated with clinical and laboratory data from these examinations, with the interval changes in these parameters, and with the development of

cardiovascular disease during the interval between the first three examinations and the last examination in 1964. Coronary heart disease was the major category of cardiovascular disease, and the following categories were made to describe the presence of disease: 1) "Definite," unequivocal clinical and electrocardiographic events, de novo development of Minnesota Code I, 1 (11) or documented evidence of myocardial death with compatible history and ECG findings; 2) "Probable," positive clinical history as evaluated by two or more examiners or "ischemic" ST depression greater than 1.0 mm on post-exercise electrocardiogram (corresponding to Minnesota Code: XI, 1); 3) "Indeterminate," a less definite history or post-exercise ST depression of 0.5 to 1.0 mm (corresponding to Minnesota Code XI, 2-5); 4) "Normal," no detectable evidence of cardiovascular disease.

RESULTS

INTERVALS AND AMPLITUDES

The ages of the men at each examination were similar, and the results are reported for the mean age at each interval. The PR interval increased significantly from age 24 to age 36 and from age 36 to age 42 despite an increase in the heart rate (Table I). The QRS duration did not change significantly. The QT interval (corrected for rate) decreased significantly between ages 24 and 36 but did not change significantly thereafter. These values at each age are similar to those from cross-sectional electrocardiographic surveys.

Measurements of Q, R, S, and T waves for three ages are presented in Table II. The upper (97.5%) and lower (2.5%) limits are included as suggested by Simonson (1). Although small in magnitude, the decreases in Q amplitude in lead 2 (Q_2) are statistically significant ($p < 0.001$). The mean amplitude of Q_1 increased during the interval, but the wide variability, indicated by the standard deviation and range, precluded this change from being statistically significant. All changes in R amplitude were statistically significant ($p < .05$ to $p < .001$). The decrease in S_1 from age 24 to age 42 was also significant ($p < .001$). The diminution in T amplitude in all leads was significant between ages 24 and 36, but only the decrease in T_3 was significant between ages 36 and 42 ($p < .05$ to $p < .001$).

Values for ΣQRS and ΣT at the three ages (Table III) were similar to those described by Simonson (1) in cross-sectional studies of young men. The decreases in ΣQRS and ΣT between 24 years and 36 years were significant ($p < .001$), but no significant difference were found from 36 years to 42 years. The decrease in ΣT during this interval was also not statistically significant. The changes in ΣQRS correlated with the changes in ΣT ($r = 0.38$, $p < .001$).

Table I

Electrocardiographic Intervals in the Same Group of Young Men Followed for 24 Years

Mean Age (years)	Cardiac Rate (beats/min.)	PR Interval (seconds)		QRS Interval (seconds)		QT Interval (seconds)	
		mean	S.D.	mean	S.D.	mean	S.D.
24	63	0.154	±0.020	0.088	+0.017	0.385	+0.036
36	74	0.160	±0.021	0.086	±0.013	0.360	±0.029
42	71	0.167	±0.044	0.087	±0.012	0.365	±0.033
48	74	0.163	±0.023	0.082	±0.014	*	*

*Not measured

Table II

Mean, Standard Deviation, and Upper (97.5%) and Lower (2.5%) Ranges for Q, R, S, and T in the Standard Limb Leads

Wave	Age	Lead 1				Lead 2				Lead 3			
		Mean	S.D.	Upper Limits	Lower Limits	Mean	S.D.	Upper Limits	Lower Limits	Mean	S.D.	Upper Limits	Lower Limits
Q	24	0.2	0.4	1.4	00	0.5	0.5	1.5	00	0.7	0.8	2.9	00
	36	0.2	0.3	1.0	00	0.3	0.4	1.5	00	0.7	1.0	3.5	00
	42	0.3	0.5	1.3	00	0.3	0.5	1.7	00	0.8	1.2	4.5	00
R	24	5.6	2.6	11.5	1.7	11.4	4.1	20.3	4.3	7.2	4.3	16.9	0.9
	36	5.8	2.5	11.9	1.8	9.2	3.6	17.5	3.3	4.8	3.7	14.1	0.1
	42	6.3	2.7	12.1	1.9	8.7	3.7	17.3	2.7	4.1	3.6	13.3	00
S	24	1.2	1.1	3.5	00	0.9	1.1	3.9	00	0.7	1.4	4.3	00
	36	1.0	1.0	3.3	00	0.9	1.1	3.9	00	0.9	1.6	5.7	00
	42	0.9	0.9	3.5	00	0.9	1.2	4.1	00	1.0	1.8	6.5	00
T	24	2.5	0.9	4.5	1.1	3.4	1.2	6.1	1.3	0.9	1.2	3.3	-1.6
	36	1.9	0.8	3.8	0.4	2.4	0.9	4.4	0.8	0.6	0.9	2.2	-1.5
	42	1.8	0.9	4.0	0.4	2.4	1.4	4.7	0.5	0.4	0.9	2.3	-1.4

Table III

ΣQRS and ΣT for Standard Leads with Upper (97.5%) and Lower (2.5%) Ranges

Age	N	ΣQRS (mm) Mean	S.D.	Upper Limits	Lower Limits	ΣT (mm) Mean	S.D.	Upper Limits	Lower Limits
24	435	28.23	8.18	45.3	22.1	6.76	2.36	11.8	5.2
36	372	23.52	6.75	40.5	18.7	4.88	1.87	8.8	3.5
42	431	23.12	6.93	39.2	18.6	4.63	2.22	9.0	3.2
48	423	20.10	5.49	31.9	10.9	5.16	1.77	8.8	2.1

VECTOR CHANGES

The cumulative percentage distributions of the frontal QRS and T vectors and the frontal QRS-T angle are plotted in Figures 1-3. The mean orientation of the QRS vector moved leftward with increasing age, but the most striking change was the increase in the number of individuals with vector orientation more leftward (i.e., having a smaller value) than +30°. At 24 years, only 10 per cent had this leftward orientation but at 36 years, 30 per cent had this orientation, and 38 per cent at 42 years of age. In contrast to the QRS vector changes, the frontal T vector and the frontal QRS-T angle changed little with age and the distribution of values did not change significantly. The cumulative frequencies for QRS vector, T vector, and QRS-T angle at age 48 were almost the same as plots of these values at age 42 and were not plotted because of their coincidence with these curves. Changes in QRS vector correlated with changes in T vector ($r = 0.24$, $p < .001$) as might be expected from the absence of significant change in the QRS-T angle.

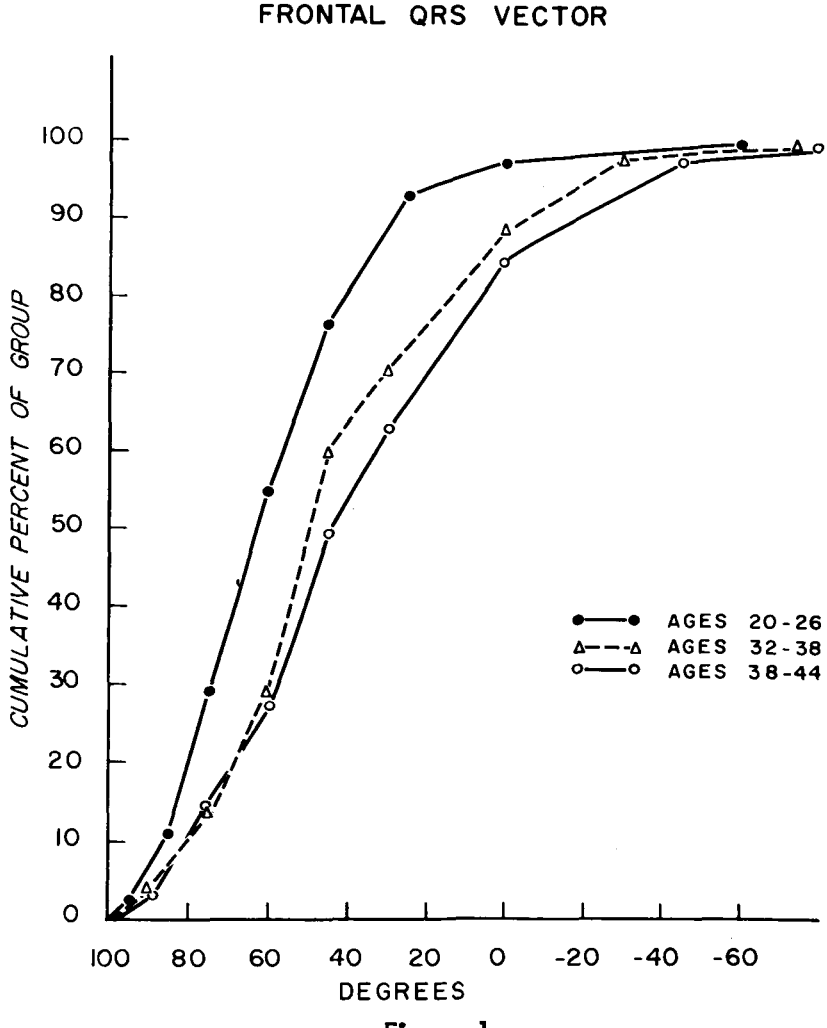

Figure 1

The frontal QRS vector changed significantly between each of the three examinations. The distribution of QRS vector orientation at ages 44-50 was similar to that at ages 38-44 and was not plotted.

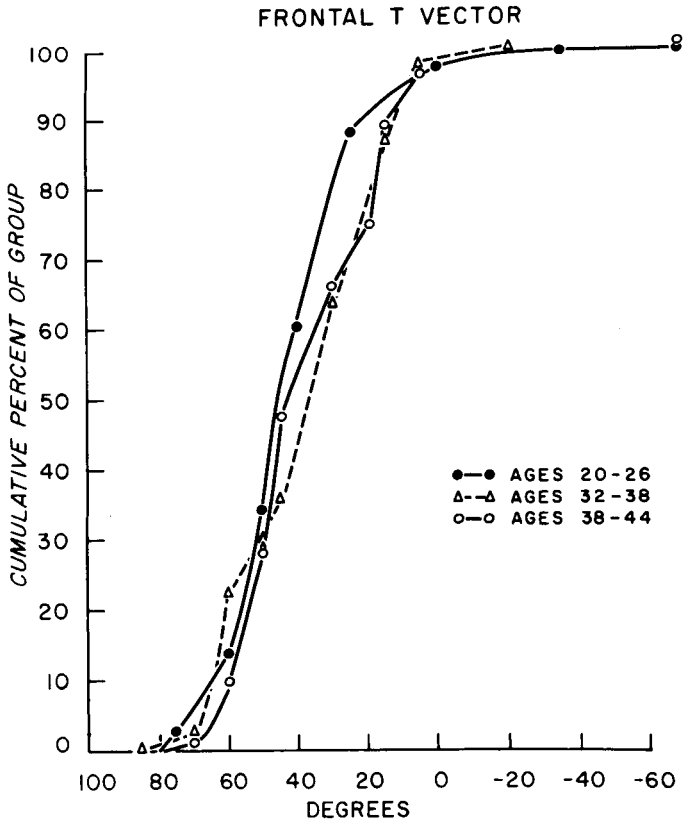

Figure 2

The frontal T vector did not change significantly during the period of study. The T vector orientation was not plotted for ages 44-50 but is the same as that for ages 38-44.

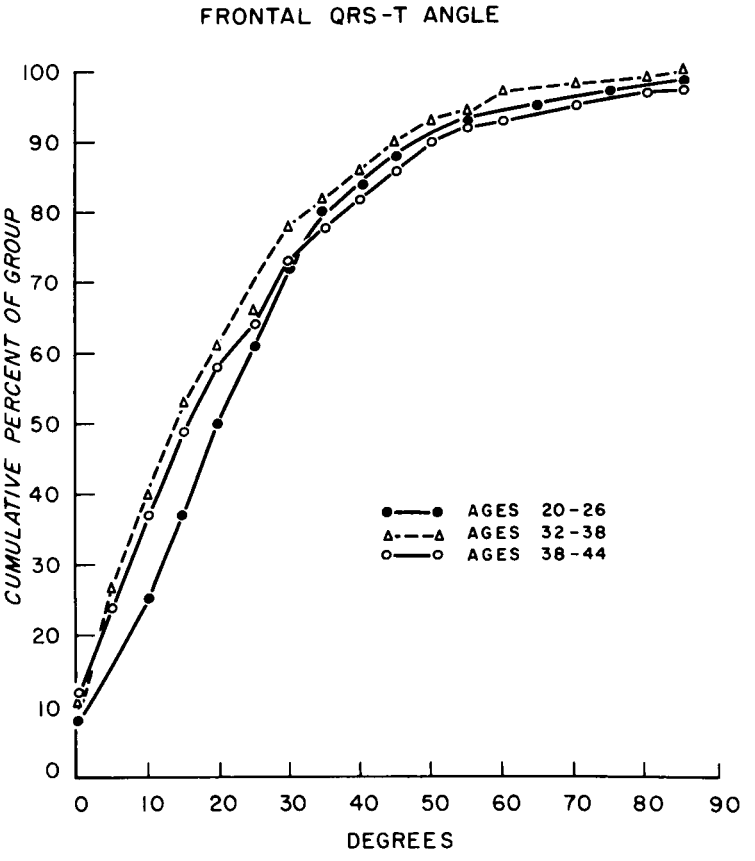

Figure 3

The frontal QRS-T angle did not change significantly during the period of study despite changes in the QRS vector.

Although determination of the initial and terminal QRS vectors are subject to inaccuracies from failure to record all leads simultaneously and arbitrary division of the initial and terminal portions, these estimates provide another means of evaluating vector shifts. The changes in the initial QRS vector paralleled shifts in mean QRS vector, but the variability was considerably greater: $46.7^{\circ} \pm 24.3^{\circ}$ at age 24, $39.2^{\circ} \pm 44.5^{\circ}$ age 36, and $33.6^{\circ} \pm 24.8^{\circ}$ age 42. There was a similar change in terminal forces: $53.3^{\circ} \pm 80.4^{\circ}$ at age 24, $32.2^{\circ} \pm 85.3^{\circ}$ at age 36, and $28.9^{\circ} \pm 81.6^{\circ}$ at age 42.

INTRAINDIVIDUAL VARIATIONS IN ELECTROCARDIOGRAPHIC COMPLEXES

The reliability of the electrocardiogram was determined by assessing the changes occurring in the electrocardiograms of each individual during each interval. There were minor variations in the Q, R, and S waves but few major alterations, as illustrated by the absence of major changes in Q waves (Table IV). The appearance and disappearance of all Q deflections, regardless of amplitude, are recorded in the category of "any Q lost or gained," but only significant deflections (greater than 2 mm or more than 1/4th of succeeding R wave) are recorded under "significant Q lost or gained." It is apparent that many minor Q deflections may appear or disappear in leads 1 and 2, but the gain or loss of sizeable Q deflections in these leads is unusual. However, in lead 3, Q waves of significant amplitude may often disappear and, more frequently, appear during the age interval, 24 to 42 years. As indicated by the greater standard deviation and increased upper limits for Q_3 (Table II), the Q wave in this lead, when present originally, often increases with age.

Similar analysis of S deflections revealed slightly greater variation with increasing age than that noted for Q deflections. Of the 540 individuals at risk from 24 to 42 years of age, 59 individuals lost significant S deflections (30 of these in lead 3) and 72 individuals gained S deflections (43 of these in lead 3). There was, however, little change in electrocardiograms with an $S_1\ S_2\ S_3$ pattern. At 24 years, records from 42 of 601 (7%) subjects had an $S_1\ S_2\ S_3$ pattern, defined as S deflections in leads 1, 2, and 3 greater than 3 mm and more than 1/4th of the preceding R deflection. Only three of these tracings lost the $S_1\ S_2\ S_3$ pattern during 24 years of follow-up and this pattern developed in only one individual's record during that period.

The T wave was the most variable part of the electrocardiogram. Despite the continuous decrease in the mean T wave amplitude on follow-up examinations during the 24 years, there was considerable intraindividual variability between examinations. The variability was greatest in lead 3 but the variability in leads 1 and 2 was considered to be of greater interest because of the prognostic significance often attributed to T wave changes in these leads. There were 423 individuals with technically adequate tracings at 24, 36, and 42 years of age that permitted comparison of changes. In approximately half of these individuals (201), the direction of change of T_1 was opposite during the two periods, 24 years to 36 years and 36 years to 42 years; in 130 individuals it decreased during the first interval and increased during the second while the reverse situation obtained in 71 individuals. In the remainder (222 individuals) the direction of change was the same during both periods (151) or did not change appreciably during these intervals. Thus, in almost half of this group there was an apparently haphazard

Table IV

Intraindividual Variations of Q Waves on Serial Electrocardiograms

Age Interval	Number at Risk	Any Q Lost			Significant Q Lost*			Any Q Gained			Significant Q Gained*		
		Q_1	Q_2	Q_3	Q_1	Q_2	Q_3	Q_1	Q_2	Q_3	Q_1	Q_2	Q_3
Age 24 to 36	495	51	28	47	2	4	26	28	6	11	3	1	26
Age 36 to 42	623	29	27	32	5	1	18	38	18	19	3	1	19
Age 24 to 42	540	45	37	54	5	1	11	15	2	38	2	0	23

*Significant Q is defined as a Q wave greater than 2 mm or greater than 1/4 the following R wave.

variability of the T wave in lead 1. The changes in lead 1 were representative of the variability encountered in lead 2.

PHYSIOLOGICAL FACTORS ASSOCIATION WITH AMPLITUDE AND VECTOR CHANGES

The changes in amplitude and vector orientation were correlated with various parameters measured during the 24 years of study (Table V). Weight changes were related to interval change of the QRS and T vectors, but weight was not related to changes in ΣQRS and ΣT. The changes in mean QRS vector (age 24 to 42) and initial 0.04 QRS vector and the QRS vector orientation at age 42 were significantly different for each of the weight increments ($p < .05$ to $p < .01$). The change in terminal 0.04 QRS vector and the QRS-T angle were not related to weight changes.

The interval change in ΣQRS (age 24 to 42) did not correlate significantly with the change in frontal QRS vector ($r = -.04$, $p > .20$), but there was a significant correlation between the change in ΣT and T vector change ($r = -.11$, $p < .01$). Small, but significant, correlations were found between QRS vector shifts and blood pressure and Sf 20-400 lipoproteins. However, these latter variables were also related to weight. When the variance due to weight was removed, blood pressure was found to have a small independent correlation with changes in QRS vector, but the relationship to the Sf 20-400 lipoproteins was the result of the correlation between these lipoproteins and weight.

PREDICTION OF QRS VECTOR, T VECTOR, ΣQRS, AND ΣT

Electrocardiographic data from the first examination and nonelectrocardiographic parameters from all examinations were used to construct expressions that would predict theoretical vectoral and amplitude values for each individual at age 42, and thereby permit comparison of predicted values with observed values. Individuals in whom heart disease subsequently developed were eliminated from this analysis. The most important determinant of the absolute value of any electrocardiographic parameter at age 42 was the absolute value observed at age 24. Nonelectrocardiographic variables contributed little to determination of electrocardiographic items. The following expression was derived to predict the QRS vector orientation at age 42 by utilizing electrocardiographic data at age 24 and all other nonelectrocardiographic data:

Est. QRS Vector age 42 = 0.803 (QRS vect., age 24) +0.257 (ht./wt., age 42) - 0.162 (ht./wt., age 24) +0.038 (T vect., age 24 + 0.032 (dias. BP, age 24) +0.053 (sys. BP, age 42) -0.026 (ht.) -0.032 (dias. BP, age 42).

The QRS vector at age 24 explained 67 per cent of the variance at age 42, and addition of all of the remaining items only explained an additional 3 per cent of variance. Without earlier electrocardiographic data, less than 10 per cent of variance was explained by weight, body habitus (somatotype), and blood pressure. Expressions for prediction of T vector, ΣQRS, and ΣT were also dependent on the earlier values, and addition of other factors did not significantly improve the prediction.

Table V

Influence of Interval Weight Changes on Selected Electrocardiographic Items

Change in Weight Age 24 to 42 (pounds)	QRS Vector Age 42 (degrees)	Change QRS Vector Age 24 to 42 (degrees)	Change Initial 0.04 Age 24 to 42 (degrees)	Change Term. 0.04 Age 24 to 42 (degrees)	Change T Vector Age 24 to 42 (degrees)	QRS-T Angle Age 42 (degrees)	Change ΣQRS Age 24 to 42 (mm)	Change ΣT Age 24 to 42 (mm)
Gain > 25 lbs. N = 228	35.9	-27.3	-16.0	-9.6	-12.4	25.8	-5.0	-2.3
Gain 11-25 lbs. N = 292	40.7	-19.2	- 9.5	-9.4	- 2.7	23.1	-5.2	-2.2
Within 10 lbs. original weight N = 198	48.6	-12.4	- 1.5	-8.9	- 0.2	23.4	-5.0	-2.0

PREDICTIVE VALUE OF ELECTROCARDIOGRAMS

The relationship between electrocardiographic items observed from age 24 to age 42 and the development of heart disease after age 42 was investigated in two ways. Relationships were developed with the observed values (Table VI), and an attempt was made to sharpen the predictive ability of the electrocardiogram by using the expressions described above to remove the influence of physiological variables. There were 19 subjects in whom "definite" cardiac disease developed, and 17 subjects were categorized as having "probable" disease. The two categories were combined for comparison with the "healthy" group as there was no difference in the electrocardiographic items between the two disease categories.

The mean ΣQRS was significantly greater at ages 24 and 36 in the individuals in whom coronary heart disease developed subsequent to age 42, although the mean ΣQRS at age 42 was not significantly different in the same group (Table VI). No significant differences in ΣT or the interval change in ΣT were noted between the two groups. The predictive expressions for ΣQRS and ΣT did not increase the discrimination between the normal and coronary groups.

Although the QRS vector tended to move leftward more in the subjects in whom heart disease subsequently developed than in the "normal" subjects, the difference was not statistically significant. Also, no significant differences were found in QRS vectors at the three ages, and there were no significant differences in T vector orientation or interval change in T vector. To eliminate other factors that might affect vector orientation and obscure pathological alterations, the predicted QRS vector orientation at age 42 was calculated for each individual and compared to the observed values at this age. The differences between observed and predicted values were not significantly different in the group in whom disease subsequently developed.

The striking variability of T waves in leads 1 and 2 and their serial decrease in amplitude are described above. The serial changes of T_1 and T_2 in the subjects in whom cardiac disease developed did not differ from changes noted in the remainder of the group. The variability was comparable, with approximately half having an increase or decrease in amplitude during the second interval opposite in direction to that noted during the first interval. There were no significant differences in eletrocardiographic intervals.

SIGNIFICANCE OF "ABNORMAL" ELECTROCARDIOGRAMS ON THE ORIGINAL EXAMINATION

A significant number of abnormalities were present in the electrocardiographic records of the group at age 24. These included: Wolff-Parkinson-White syndrome (two individuals), left bundle branch block (one), right bundle branch block (two), left axis deviation (eight), first degree heart block (eleven), generalized lowering of T waves (two), and many borderline or suspicious changes. In none of the individuals with these gross ECG abnormalities has clinically apparent heart disease subsequently developed.

Table VI

Relationships between Serial Changes in Selected Electrocardiographic Parameters and Subsequent Development of Coronary Heart Disease

Diagnosis	ΣQRS Age 24 (mm)	ΣQRS Age 36 (mm)	ΣQRS Age 42 (mm)	ΔΣQRS Age 24-42 (mm)	ΣT Age 24 (mm)	ΣT Age 42 (mm)	ΔΣT Age 24-42 (mm)	ΔQRS Vector Age 24-36 (degrees)	ΔQRS Age 24-42 (degrees)
Coronary Heart Disease N = 36	32.1	26.1	24.3	-7.7	6.6	4.4	-2.3	-16.8	-24.4
Healthy N = 391	28.2	23.4	23.0	-5.3	7.2	5.0	-2.2	-12.3	-18.3
Significant	$p < .01$	$p < .05$	N.S.*	$p < .05$	N.S.*	N.S.*	N.S.*	N.S.*	N.S.*

*N.S. -- Difference between means not statistically significant

DISCUSSION

The frequent recording of electrocardiograms in individuals without clinically discernible heart disease and the reliance on the electrocardiogram for objective evidence of coronary artery disease emphasize the importance of determining the reliability and predictive value of the resting electrocardiogram. If the normal characteristics and longitudinal changes can be defined, computer techniques make it practical to analyze quantitatively large numbers of electrocardiograms and assign a probability of the presence of disease. Normal ranges for electrocardiographic items at various ages are available from the extensive cross-sectional studies of Simonson (1), and comparable values from our longitudinal evaluation are strikingly similar, suggesting the validity of his cross-sectional surveys and the electrocardiographic similarity of these two groups of healthy men. Although both studies provide standards for gross discrimination between normal and abnormal, only longitudinal studies can afford information about the reliability of a single electrocardiogram and the prognostic implications of interval changes in the electrocardiograms of individual patients.

The electrocardiogram is generally conceded to be a reliable measurement and, with some exceptions, the results of this study confirm that impression. The pattern of QRS deflections--the presence of Q, R, and S waves in any lead--changed very little during the first 18 years of follow-up, although there were changes in the amplitudes of these deflections. The development of Q and S waves of significant and measurable magnitude was infrequent in leads 1 and 2. However, the appearance of significant Q waves in lead 3 and significant increases in the amplitude of small Q waves already present were considerably more frequent as the group became older. These Q waves in lead 3 were not associated with significant Q waves in leads 2 or aVF. The development of Q_3 deflections appeared to be related to the recording of transitional electrical forces in this lead, as frequently occurs if the frontal QRS vector is approximately 30°. In the electrocardiograms of individuals at age 24, there was occasionally a small, often indistinct Q_3 or a large S wave preceded by a small r deflection. As the electrical forces moved leftward and away from lead 3 with increasing age and weight, the amplitude of the Q_3 or S_3 increased and the amplitude of the R deflection decreased. The result was the development of an apparent QS complex in lead 3, as illustrated in Figure 4. In keeping with the previously stated generalization that the pattern of deflections does not undergo substantial change with aging alone, we found that it was unusual for a Q_3 or QS deflection to develop de novo in an individual who did not have a small Q deflection or an rS pattern present on an earlier electrocardiogram. Therefore, the presence of these patterns on previous electrocardiograms may be combined with the quantitative criteria suggested by Weisbart and Simonson (12) to distinguish between the innocous Q_3 often encountered in older individuals and that associated with myocardial infarction. The development of new S waves was also unusual except in lead 3. The S_1 S_2 S_3 pattern, present in 7 per cent of the subjects, did not change appreciably during the 24 years of study and developed or disappeared in less than 1 per cent of the entire group. There was no apparent relationship between this electrocardiographic finding and the development of cardiac pulmonary disease.

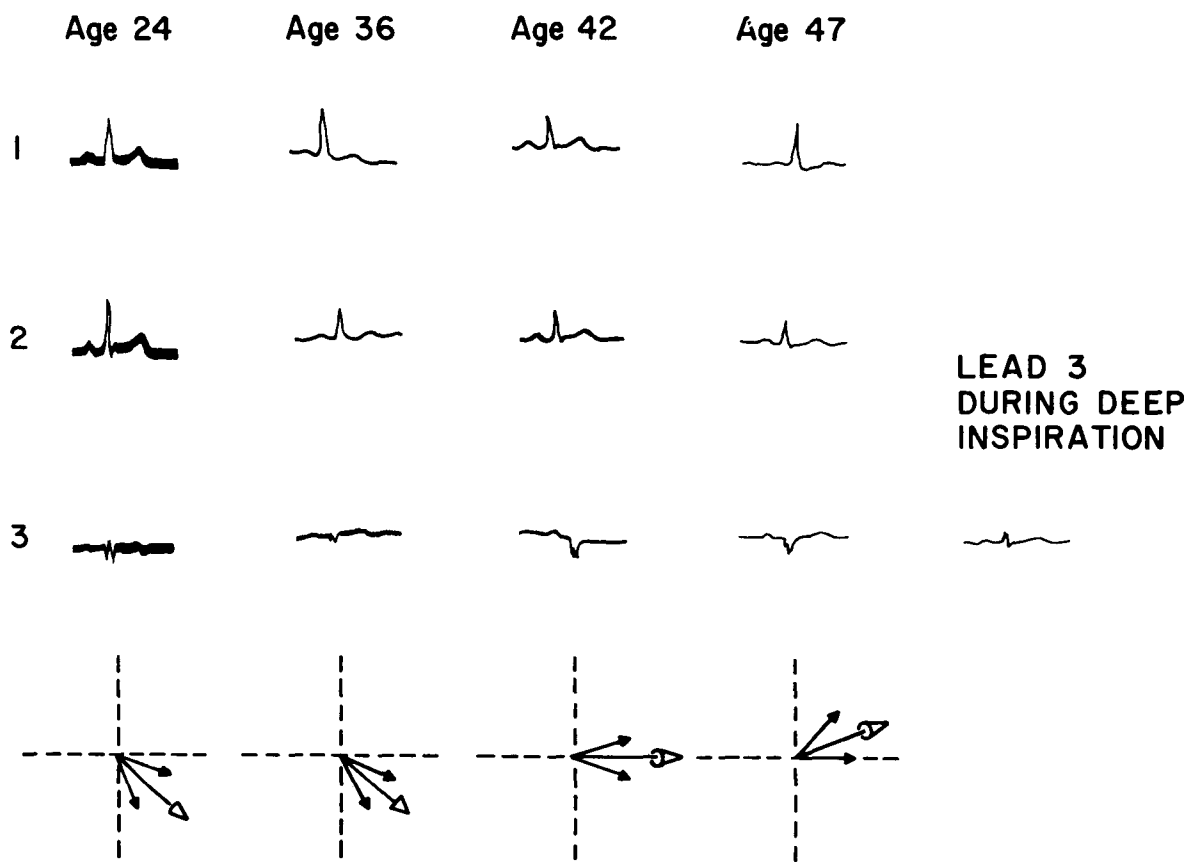

Figure 4

Serial electrocardiograms from the same individual illustrating development of a QS complex in lead 3 with shift of the QRS axis to the left. The mean QRS vector and initial and terminal vectors are presented at the bottom.

The T wave, as might be expected, exhibited the greatest variability. Although the amplitude of the T wave decreased with increasing age, considerable intraindividual variability of T amplitude was found on serial evaluations. This variability was probably the result of physiological influences and did not reflect pathological changes in the myocardium. The ingestion of food, particularly carbohydrate, may cause depression of T waves in susceptible individuals, which constitute perhaps 5 per cent of the general population (13). Although meal ingestion was not controlled during two of the four examinations, this phenomenon explains only a small part of the T-wave variability. The higher percentage (50%) in whom variability was noted and the observation that increases as well as decreases were found suggest that many other factors, poorly

delineated and difficult to control, were also responsible for much of the variability. This lack of reliability means that serial T wave changes will have little predictive value in a young group of men, although it is recognized that in older and more selected groups of men, decreases in T amplitude are associated with cardiac disease and are, to a limited extent, predictive of future development of symptomatic disease (14, 15). Undoubtedly some of the T wave changes in our relatively young population also reflected disease, but there is at present no means of separating changes due to underlying pathology from those related to physiological factors.

Despite the relatively constant pattern of QRS deflections, significant and, in some instances, striking changes were observed in the total amplitude of the QRS and T waves (ΣQRS and ΣT) and in the orientation of the QRS vector. The ΣQRS decreased continuously between 24 and 48 years of age and ΣT decreased between ages 24 and 42. These changes were greatest between 24 and 36 years of age. The orientation of electrical depolarization, the QRS axis, moved leftward in the frontal plane, and the greatest movement occurred between 24 and 36 years of age with relatively little subsequent change in the mean values, although considerable individual variability was noted. In contrast to the QRS vector, the T vector did not change significantly during the 24-year period. Because the QRS vector movement was from one side of the unchanging T vector to the other, there was also no significant change in the mean QRS-T angle. Interval changes in the QRS vector correlated with weight changes during corresponding periods ($r = 0.33$, $p < 0.001$) and to lesser degrees with blood pressure. Despite suggestions to the contrary in some cross-sectional surveys, the changes in QRS axis were not related to changes in ΣQRS, the latter measurement being influenced very little by changes in weight or blood pressure within the relatively limited ranges encountered in this study.

The leftward movement of the QRS vector and the decrease in ΣQRS occurred between 24 and 48 years of age when pathological studies (16, 17) indicate that coronary arteriosclerosis is increasing at the greatest pace. Furthermore, left axis deviation (less than -30°) is clearly associated with myocardial fibrosis (18) and with a greater likelihood of subsequent development of symptomatic heart disease (19). These observations and the correlation between vector orientation, ΣQRS, and the presence of coronary heart disease in populations with widely differing prevalence of disease suggest that these changes might be due to clinically silent arteriosclerosis and thus afford a clue to the presence of coronary disease (17, 18). Our experience, although limited by the small number of men in whom overt disease developed, is compatible with this hypothesis. Individuals experiencing the greatest decrease in QRS amplitude (ΣQRS) during the first two periods of study were more likely to have manifest cardiac disease develop during the most recent period of study. There was also a tendency for subjects in whom coronary disease developed to have a greater leftward movement of the QRS vector, but this difference was not statistically significant. However, coronary arteriosclerosis is so ubiquitous in this age group and its clinical expression so variable that another follow-up period and the inclusion of more individuals with coronary disease will be required to completely assess these factors. Interval changes in ΣT were not related to development of disease; this was somewhat surprising because ΣT is less in patients with symptomatic coronary disease (20).

Despite the suggestive evidence that the resting electrocardiogram has some potential in detecting occult cardiac disease in groups, the application of these findings is limited in individual men less than age 50. Even with serial records, including tracings from a time when the men were free of disease, and many other measurements, the electrocardiogram cannot be relied upon for diagnosis of asymptomatic disease in a specific individual, and has limited usefulness in groups of younger men. As these men increase in age and the incidence of coronary heart disease increases, this increased experience may reveal a greater diagnostic value in the older group, but it seems unlikely that the resting electrocardiogram will have diagnostic validity in the individual patient, although its value in epidemiological studies where some diagnostic error is acceptable may be considerable. In the individual patient, the determination of the relative likelihood of disease might be of value in determining which patients should have more definite tests performed.

Because some of the vectoral and amplitude changes found with aging were related to "physiological" factors, weight and blood pressure, an attempt was made to remove the influence of these variables and thus to delineate better the changes resulting from pathological alterations. However, use of expressions to compensate for these factors did not significantly improve the prediction of subsequent development of disease. These expressions did emphasize the value of earlier electrocardiograms in predicting absolute values for vectors and amplitudes. Previous studies (21, 22) had suggested that the QRS axis might be predicted from weight and anthropometric measurements, but it is apparent from these longitudinal studies that there is considerable individual variability in QRS axis that is unrelated to these variables. Absolute vector orientation cannot be determined accurately from nonelectrocardiographic variables only. Although the comparison of predicted and actual changes in QRS vectors may be more successful in predicting underlying myocardial disease as morbidity experience increases, this approach is dependent upon the availability of baseline electrocardiograms.

Gross electrocardiographic abnormalities in young, asymptomatic individuals with a normal examination were not associated with significant morbidity or mortality. In none of the individuals with conduction defects, bundle branch block, left axis deviation, or abnormal T waves detected at 24 years of age did significant disease develop during the 24 years of follow-up. The more extensive longitudinal evaluation of the Wolff-Parkinson-White syndrome (23) and the total experience with bundle branch block in young naval aviators confirm this concept. This general statement is, of course, limited to individuals below 30 years of age who have no past history of cardiac disease and a normal clinical examination.

Some recommendations can be offered regarding the recording and interpretation of electrocardiograms in young men without clinically apparent heart disease. An electrocardiogram recorded in the basal state in a 20-year old man is a valuable baseline that can be compared reliably with subsequent tracings to determine alterations in the QRS deflections. Little further information is gained by repeated recording of the electrocardiogram below age 40. This initial electrocardiogram would also prevent the later mistaken diagnosis of cardiac disease in the small, but troublesome, number of

individuals with gross electrocardiographic abnormalities apparently unrelated to disease. The predictive value of this original electrocardiogram would be small, but its availability for comparison with electrocardiograms at age 40 or 50 years would be particularly valuable in the diagnosis of acute myocardial changes and, as suggested by this study, in providing a clue to the presence of occult coronary artery disease when compared with subsequent tracings. The predictive value of resting electrocardiograms in middle-aged individuals is certain to be improved by comparison with earlier electrocardiograms. However, the limitations of serial resting electrocardiograms in individual patients should be emphasized. Despite the improved diagnostic discrimination afforded by serial electrocardiograms and their potential value in epidemiological studies, a resting tracing can only suggest the relative probability of disease in an individual, and exact diagnosis will require more precise means.

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13. ABSTRACT

The reliability and prognostic validity of serial electrocardiograms were determined in a group of young men who were followed from 24 to 49 years of age. Electrocardiographic durations, amplitudes, and vectoral orientations at each of the four evaluations were similar to values from cross-sectional surveys of men at the same ages. The pattern of QRS deflections did not change although there were changes in the amplitude of these deflections. A significant decrease in QRS and T amplitude (ΣQRS and ΣT) was found with increasing aging and did not correlate significantly with weight and blood pressure. The QRS axis moved leftward as the group became older and the change in QRS axis was related to interval weight changes and to blood pressure. The T axis and the QRS-T angle did not change during the 24 years of study. The group in whom coronary heart disease subsequently developed had a greater decrease in QRS amplitude and tended to have a greater leftward movement of the QRS vector. The resting electrocardiogram is a reliable measurement despite minor serial changes in amplitude and vectoral orientation, but has limited predictive value in men below the age of 50 years.

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