

and that reported in portal vein blood(7,8) and in neurohypophyseal tissue(9) must await isolation of active material in homogeneous form from each of these three sources.

Summary. Fractionation of a crude extract of calf median eminence on carboxymethyl-cellulose columns yields a preparation which induces adrenal ascorbic acid depletion in the median eminence lesioned rat. This partially purified corticotropin releasing factor (CRF) is substantially free from corticotropic and pressor activities.

1. Royce, P. C., Sayers, G., *Endocrinology*, 1958, v63, 794.

2. McCann, S. M., *ibid.*, 1957, v60, 664.
3. Royce, P. C., Sayers, G., *PROC. SOC. EXP. BIOL. AND MED.*, 1958, v98, 677.
4. Peterson, E. A., Sober, H. A., *J. Am. Chem. Soc.*, 1956, v78, 751.
5. Ellis, S., Simpson, M. E., *J. Biol. Chem.*, 1956, v220, 939.
6. Sayers, M. A., Sayers, G., Woodbury, L. A., *Endocrinology*, 1948, v42, 379.
7. Rumsfeld, H. W., Porter, J. C., *ibid.*, 1959, v64, 942.
8. Porter, J. C., Rumsfeld, H. W., *ibid.*, 1959, v64, 948.
9. Schally, A. V., Guillemin, R., *PROC. SOC. EXP. BIOL. AND MED.*, 1959, v100, 138.

Received December 28, 1959. P.S.E.B.M., 1960, v103.

Evaluation of Type and Degree of Change in Postexercise Electrocardiogram in Detecting Coronary Artery Disease. (25554)

GEORGE P. ROBB AND HERBERT H. MARKS (Introduced by E. F. Beach)

Metropolitan Life Insurance Co., N. Y. City

The value of electrocardiographic double standard 2-step exercise test(1) in detection of occult coronary disease has been proved (2,3,4). The criteria for abnormal response to this exercise test indicative of coronary insufficiency, however, have not been adequately tested or defined. Investigation of validity of the original criteria of a positive or abnormal test by a clinical-statistical follow-up study was started in 1952 and completed in 1956 (4). Incidence of coronary occlusion and coronary death subsequent to the test were determined in a large series of military personnel and insurance applicants suspected of having coronary disease who had been given the double exercise test. The results indicated that the only valid evidence of coronary insufficiency in postexercise electrocardiogram was ischemic ST segment depression. The significance of ST junction depression remained undetermined because, through technical fault in the series on military personnel, unrecognized ST segment depression cases were included in ST junction category. Isolated T-wave change after exercise appeared normal. The present report gives new data regarding

significance of (1) various types of ST junction depression after exercise; (2) various types and degrees of ischemic ST segment depression; (3) additional data regarding negative reactors and (4) QS/QT ratio in various types of response to the test(5).

Materials and methods. This is a follow-up study of 922 insurance applicants, most of whom were suspected of having coronary disease and who were given the double standard 2-step exercise test between 1949 and March 1958, and traced to March 1959. Indications for the test, its performance, and electro-cardiographic technique, were described previously(4). The post-exercise electro-cardiograms were analyzed with the P-R segment as the point of reference for measuring ST junction and ST segment depression(1). The term "ischemic" denotes horizontal or sagging depression of the ST segment(6). The changes induced by exercise were classified as in Chart 1: 1. *ST junction depression, any degree.* Types: (a) transitory, during tachycardia; (b) prolonged; (c) "near-ischemic" configuration; i.e., ST segment straight and nearly horizon-

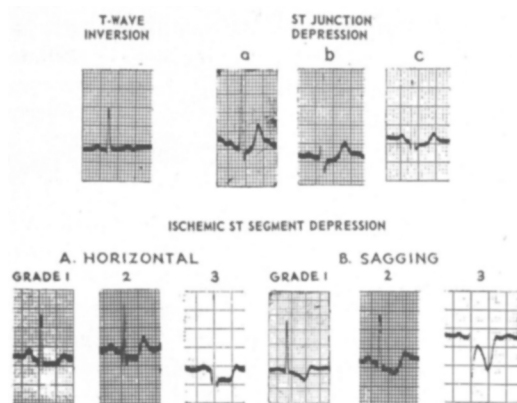


FIG. 1. Types of electrocardiographic response to double two-step exercise test.

tal. 2. *ST segment depression.* Type A: Horizontal segment – without significant T-wave change. Grades: 1– 0.0 to 0.9 mm; 2– 1.0 to 1.9 mm; 3– 2.0 mm or more. Type B: Sagging segment – with diphasic or inverted T-wave. Grades 1, 2, 3, as indicated under “Horizontal segment.” Data on the 922 cases were analyzed according to standard actuarial procedure to obtain mortality rate/1,000 person years of observation from all causes and from coronary disease for each type and degree of response. This statistical basis assures comparability of results in the several classifications.

Results are summarized in Table I. Altogether, there were 29 deaths to date of follow-up. Of these, 13 occurred in the ischemic ST segment depression cases, 12 of them from coronary disease. Only 2 deaths, both from coronary disease, occurred in the more numerous ST junction group; 2 in the T-wave group

(one of them from coronary disease); and 12 in the negative reactors (6 from coronary disease).

Among the 226 ST junction cases of all types the death rate from coronary disease was only 2.8 per 1,000 years of observation, essentially the same as the rate of 3.1 in the negative group. Analysis of transitory, prolonged, and “near-ischemic” subgroups showed no significant differences, but the experiences are all small in size. Among the 145 cases with ischemic ST segment depression, death rate from coronary disease was 23.8 or about 8 times the rate for the ST junction and negative series. The experience on horizontal and sagging types of ST depression have been combined to obtain a greater volume of data for statistical analysis according to degree of depression. This analysis showed a progressive and accelerating increase in coronary death rate with increasing ST segment depression. Thus, among the 85 cases of Grade 1 the death rate was 12.9; among the 42 cases of Grade 2, 21.2 or about one-half more than for Grade 1; while for the 18 cases of Grade 3, the coronary death rate was 95.1 or more than 7 times the rate for Grade 1. The T-wave change group was too small for statistical analysis.

The QS/QT ratio showed distinct differences between negative reactors and those with ST segment depression, particularly of the sagging type, but not between negative reactors and those with ST junction depression. Moreover, the ratio does not discriminate well between cases with various degrees of ST

TABLE I. Death Rates/1,000 Person Years of Observation among Insurance Applicants Given Double Standard 2-Step Exercise Test. Negative reactors and those with ST depression, classified by type and degree of change in postexercise ECG. Metropolitan Life Ins. Co., cases tested in 1949-March 1958, traced to March 1959.

Classification	No. of cases	Deaths ———		Death rates ———	
		All causes	Coronary	All causes	Coronary
Negative	519	12	6	6.3	3.1
ST Junction Depression (more than 0.5 mm)	226	2	2	2.8	2.8
a. Transitory, during tachycardia	114	1	1	3.0	3.0
b. Prolonged	100	1	1	2.9	2.9
c. “Near-ischemic” configuration	12	0	0		
Ischemic ST Segment Depression	145	13	12	25.7	23.8
1. .0 to .9 mm	85	4	4	12.9	12.9
2. 1.0 to 1.9 mm	42	3	3	21.2	21.2
3. 2.0 mm or more	18	6	5	114.1	95.1

segment depression. In isolated T-wave inversion the method is not applicable.

Discussion. This follow-up of 226 cases of ST junction depression provides additional evidence that ST junction depression is a normal response to exercise. Even the prolonged and "near ischemic" types ascribed by some investigators to mild coronary insufficiency had a low death rate. In contrast, all grades of ischemic ST segment depression had a high coronary death rate. This type of electrocardiographic response to exercise evidently is due to coronary insufficiency caused by coronary atherosclerosis. The increase in coronary death rate that accompanies the increase in ST segment depression suggests that degree of ischemic depression is directly related to severity of coronary insufficiency induced by the test. It is of interest that the 8 coronary deaths in the Grade 2 and 3 cases showed sagging ST segments and diphasic or inverted T-waves. This type of reaction probably denotes a more severe degree of coronary insufficiency than does the horizontal type. Further analysis according to type and degree will be made when enough material is available. While QS, QT ratios differ for the ex-

tremes—negative reactors and those with ischemic ST segment depression—this technic does not offer any special advantage over inspection of the tracings.

Summary. Ischemic ST segment depression after exercise is due usually to coronary atherosclerosis and insufficiency. Our data suggest that type and degree of ischemic ST segment depression after exercise reflects the severity of the coronary disease. The results of this investigation indicate also that ST junction depression is a normal response to exercise.

1. Master, A. M., Friedman, R., Dack, S., *Am. Heart J.*, 1942, v24, 777.
2. Master, A. M., Pordy, L., Chesky, K., *J.A.M.A.*, 1953, v151, 458.
3. Myers, G. B., Talmers, F. N., *Ann. Int. Med.*, 1955, v43, 361.
4. Robb, G. P., Marks, H. H., Mattingly, T. W., *Tr. A. Life Insur. M. Dir. America*, 1956, v40, 52.
5. Lepeschkin, E., Surawicz, B., *New England J. Med.*, 1958, v258, 511.
6. Wood, P., McGregor, M., Magidson, O., Whitaker, W., *Brit. Heart J.*, 1950, v12, 363.

Received December 4, 1959. P.S.E.B.M., 1960, v103.

Immunocytochemical Demonstration of Intranuclear Localization of 18S Gamma Macroglobulin in Macroglobulinemia of Waldenström (25555)

THOMAS F. DUTCHER AND JOHN L. FAHEY

Pathologic Anatomy, and Metabolism Service, Natl. Cancer Inst., Bethesda, Md.*

We recently reported the presence of intranuclear material within lymphoid plasma cells of 3 patients with macroglobulinemia of Waldenström(1). This material was histochemically identified as a protein with high carbohydrate content. The carbohydrate component was shown not to consist of glycogen since it was periodic acid-Schiff(PAS) positive after digestion with diastase. The isolated serum 18S gamma macroglobulin from each of the 3 patients also had a high carbohydrate content and was strongly PAS positive following electrophoresis on filter paper strips.

The present study, utilizing the fluorescent antibody technic of Coons and Kaplan(2), supports the probable identity of protein material within the nucleus and cytoplasm of lymphoid plasma cells and the circulating serum 18S gamma macroglobulin from a patient with macroglobulinemia of Waldenström.

Methods. Antisera preparation: Purified gamma macroglobulin from serum of patient J.W. was obtained by repeated precipitations of the protein from solution by dialysis against low ionic strength pH 8.0 buffers. The final product was homogeneous by analytic electrophoresis and upon ultracentrifugation consisted of 18S macroglobulin (with small

* Nat. Inst. H., U. S. Dept. H.E.W.