Cardiol

THE CONFUSING SYNDROMES OF CARDIOVASCULAR AUTONOMIC IMBALANCE: CARDIOVASCULAR DYSAUTONOMIAS

Medical Grand Rounds

University of Texas
Health Science Center at Dallas

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I. INTRODUCTION

1. Mitchell, J.H., A.P. Shapiro: The relationship of adrenalin and T-wave changes in the anxiety state. Am. Heart J. 48:323, 1954.

In the long hot summer of 1953, Dr. Alvin Shapiro (Attending Physician), Dr. Richard Hunter (Medical Resident), Dr. Norman Carter (Medical Intern), and myself (MS III) admitted a 21 year old female to one of the medical wards at old Parkland Hospital. Her symptoms at that time suggested an acute myocardial infarction. She complained of palpitations, precordial pain, shortness of breath, and weakness. Physical examination was normal, and the white cell count and sedimentation rate were not elevated. In those olden times cardiac enzymes, PYP scans, MUGA imaging, and exercise tolerance tests were not available. However, the electrocardiogram had been invented, and the patient's admission tracing is shown in Figure 1.

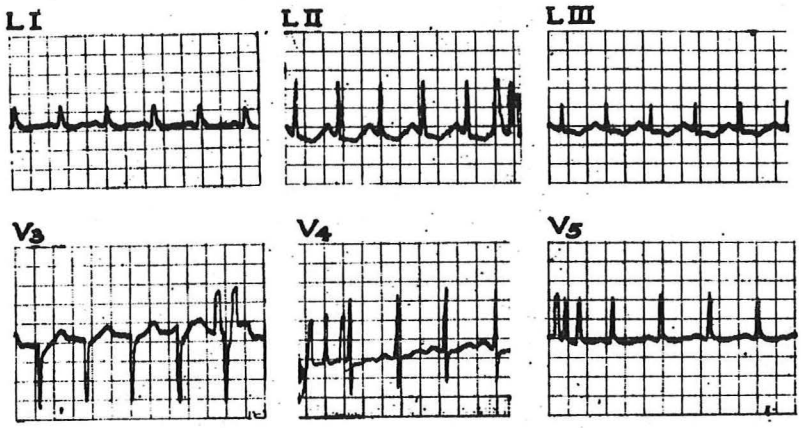

Fig. 1

Her admission electrocardiogram revealed ST segment depression and T-wave inversion in limb leads II and III and in precordial leads V_4 and V_5.

Shortly after admission with only sedation and reassurance, the patient's electrocardiogram was noted to have reverted to normal, and this is shown in Figure 2.

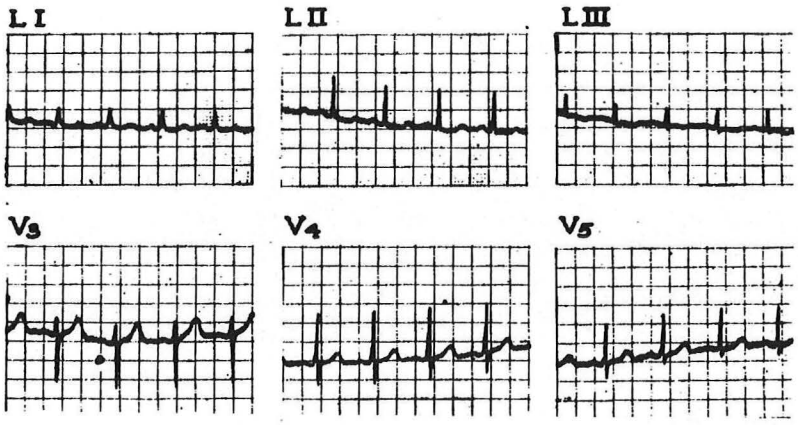

Fig. 2

The ST segment depression is no longer present and the inverted T waves are now upright in the precordial leads V_4 and V_5.

With the new Chairman of Medicine recently installed at the University of Texas, Southwestern Medical School, both the faculty and medical students were being strongly urged to perform research studies. Therefore, this patient was studied and the results later published.

In the study on this patient continuous electrocardiograms were taken while various situations were discussed and experimental protocols were carried out. The effects of discussing an impending venipuncture on lead II of the electrocardiogram are shown in Figure 3.

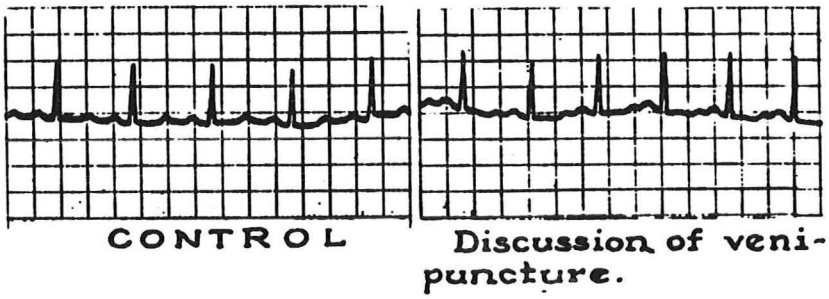

Fig. 3

The control tracing is shown on the left and that during discussion of a venipuncture performed on the right. Again the electrocardiogram revealed ST segment depression and T-wave inversion. The discussion with the patient of the possibility that she had heart disease caused similar findings.

Next, a series of experiments was performed utilizing repeated injections of normal saline or of different amounts of adrenaline. For these studies an infusion was set up so that the injection could be introduced into the tubing either with or without the knowledge of the patient. The results of some of these studies are shown in Figure 4.

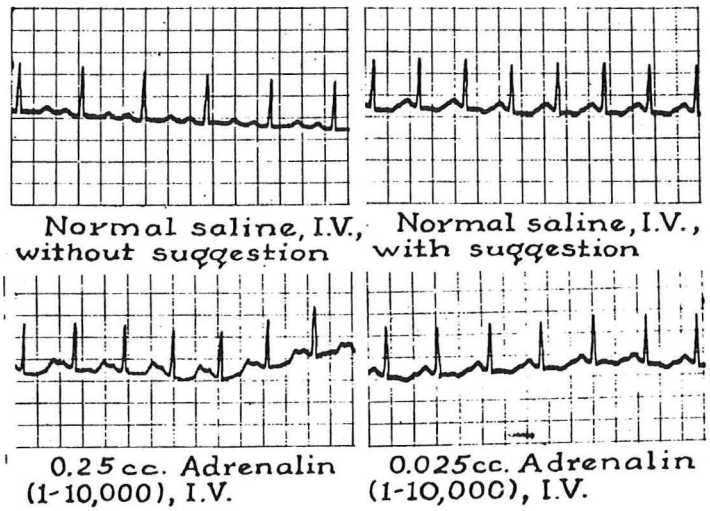

Fig. 4

The injection of normal saline into the infusion tubing without the patient's knowledge caused no change in the electrocardiogram (upper left panel). The injection of 0.25 cc of a 1:10,000 solution of adrenaline produced marked ST segment depression and T-wave inversion simultaneously with the development of the same subjective symptoms (palpitations, precordial distress, shortness of breath, and weakness) that the patient had on her admission (lower left panel). Following this procedure the injection of normal saline with the patient being told that adrenaline was being given again caused the same symptoms and ECG changes (upper right panel). Finally the injection of a smaller amount of adrenaline (0.025 cc of a 1:10,000 solution of adrenaline) without the knowledge of the patient caused ST segment depression and T-wave inversion with no symptoms of palpitation or precordial distress (lower right panel).

In 1953 we felt that this patient had an anxiety neurosis with no organic heart disease. It seemed reasonable to assume that in certain neurotic individuals the myocardium is particularly sensitive to the effects of adrenaline and that these effects can be evoked by anxiety-producing stimuli. At that time the important role of the autonomic nervous system, including its action on alpha and beta-adrenergic receptors, in the precise regulation of the cardiovascular system had not been introduced into clinical medicine.

Today this same patient would be diagnosed as fitting into a poorly defined and understood group of diseases which may be termed "The Confusing Syndromes of Cardiovascular Autonomic Imbalance: Cardiovascular Dysautonomias", which is the subject of this Grand Rounds.

II. CONCEPTUAL EVOLUTION OF CARDIOVASCULAR DYSAUTONOMIAS

Patients with symptoms of palpitation, precordial chest pain, shortness of breath, weakness, sometimes dizziness and even syncope, who are found to have no organic heart disease, have plagued clinicians and have interested cardiovascular physiologists for many years. Today, patients with this symptom-complex are diagnosed as having one of the types of cardiovascular dysautonomias.

The conceptual evolution of the cardiovascular dysautonomias is shown in Figure 5.

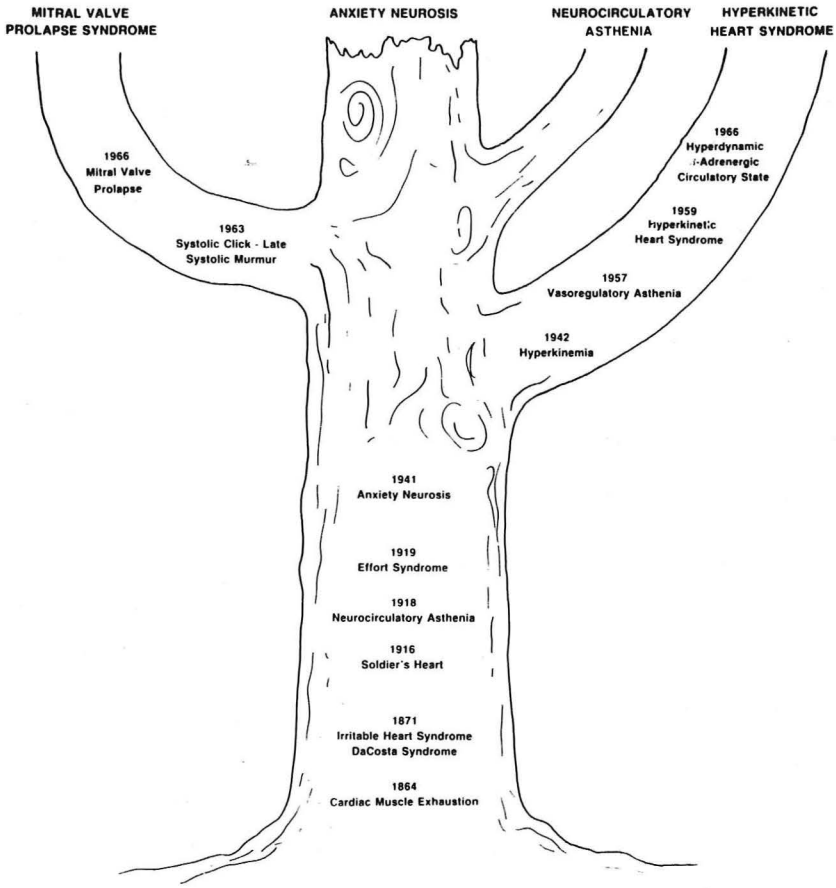

Fig. 5

2. Hartshorne, H.: On heart disease in the Army. Am. J. Med. Sci. 48:89, 1864.
3. DaCosta, J.M.: On irritable heart; A clinical study of a form of functional cardiac disorder and its consequences. Am. J. Med. Sci. 61:2, 1871.

In 1864, Dr. Hartshorne published a paper describing a group of soldiers during the Civil War who had symptoms related to the cardiovascular system and who had no evidence by physical examination of organic heart disease. He labeled this symptom-complex "Cardiac Muscular Exhaustion". In 1871 a more extensive account of soldiers studied during the Civil War with this malady were reported by Dr. Jacob DaCosta. He termed this condition the "Irritable Heart Syndrome", but it was later referred to, by others, as "DaCosta's Syndrome". DaCosta's

study is a particularly important one in the history of cardiovascular disease since it is one of the first to describe a functional disease in a time when medicine was dominated by the search for structural abnormalities.

4. MacKenzie, J.: The soldier's heart. Br. Med. J. I:117, 1916.
5. Lewis, T.: The Soldier's Heart and the Effort Syndrome. New York: Paul B. Hoeber, 1919.
6. Lewis, T.: Diseases of the Heart. New York: MacMillan, 1933.

In 1916 Sir James MacKenzie studied British soldiers during World War I who had the same symptoms as those described by DaCosta. MacKenzie is mainly responsible for labeling this condition "The Soldier's Heart", but he well recognized that the disease was also very prevalent in the civilian population. Also during World War I, Sir Thomas Lewis published a book entitled The Soldier's Heart and the Effort Syndrome, and in 1933 he described this condition in his textbook entitled Diseases of the Heart. He felt that this syndrome might have different etiologies, but felt that it was certainly a medical and not a psychiatric problem.

7. Wood, P.: DaCosta's syndrome (or effort syndrome). Br. Med. J. I:767, 1941.
8. Wood, P.: DaCosta's syndrome (or effort syndrome). The mechanism of the somatic manifestations. Br. Med. J. I:805, 1941.
9. Wood, P.: Aetiology of DaCosta's syndrome. Br. Med. J. I:845, 1941.
10. Wood, P.: Cardiovascular disturbances associated with psychiatric states (Ch. 23). In: Diseases of the Heart and Circulation. London: Eyre & Spottiswoode, 1956.
11. Wood, P.: Diseases of the Heart and Circulation. New York: J.B. Lippincott, p. 1074, 1968.

Between World War I and World War II few studies were published on functional diseases of the cardiovascular system. However, in 1941, Dr. Paul Wood, a noted British cardiologist, evaluated soldiers with this condition and concluded that it was an emotional condition which was peculiar to patients with psychopathic personalities and with various forms of psychoneuroses. Dr. Wood rejected all the previous names used to describe this symptom complex and did not suggest a new one for his studies of patients with this condition, because he stated

> ... "I believe that the recognition of this syndrome, as such, will die. Further if it is at times convenient to speak of this group of physical signs and symptoms there can be no better name than DaCosta's Syndrome. This not only avoids reference to the heart, to the circulation, to effort or to false or unproved mechanisms; but it has the unrivaled merit of making DaCosta responsible for its recognition as a distinct clinical entity, and is especially fitting if the syndrome is to become of historical interest only" ...!

In 1968 in the third edition of his textbook, Diseases of the Heart and Circulation, he placed DaCosta's Syndrome in the chapter on cardiovascular disorders associated with psychiatric states. He thus placed such patients into the care of psychiatrists and thought the problem could not be helped by the cardiologist.

12. White, P.D.: The soldier's irritable heart. JAMA 118:270, 1942.
13. Cohen, M.E., P.D. White, R.E. Johnson: Neurocirculatory asthenia, anxiety neurosis, or the effort syndrome. Arch. Int. Med. 81:260, 1948.
14. Cohen, M.E., P.D. White: Life situations, emotions, and neurocirculatory asthenia (anxiety neurosis, neuroasthenia, effort syndrome. Psychosom. Med. 13:335, 1951.
15. Cohen, M.E., P.D. White: Neurocirculatory asthenia: 1972 concept. Milit. Med. 137:142, 1972.

About this same time in the United States, Dr. Paul White also became interested in similar patients. He also felt that this was largely an emotional illness. With the two most famous cardiologists of their time, Dr. White in the United States and Dr. Wood in Britain, stating that this was not a problem for the cardiologist but one for the psychiatrist, DaCosta's Syndrome was on the way out as a diagnosis to be made by a respectable cardiologist.

16. Starr, I.: Abnormalities of the amount of the circulation (Hyper- and Hypokinemia) and their relation to neurocirculatory asthenia and kindred diagnoses. Am. J. Med. Sci. 204:573, 1942.
17. Holmgren, A., B. Jonsson, M. Levander, H. Linderholm, T. Sjöstrand, G. Ström: Low physical working capacity in suspected heart cases due to inadequate adjustment of peripheral blood flow (vasoregulatory asthenia). Acta Med. Scand. 158:413, 1957.
18. Gorlin, R., N. Brachfeld, J.D. Turner, J.V. Messer, E. Salazar: The idiopathic high cardiac output state. J. Clin. Invest. 38: 2144, 1959.
19. Frohlich, E.D., H.P. Dustan, I.H. Page: Hyperdynamic beta-adrenergic circulatory state. Arch. Int. Med. 117:614, 1966.
20. Vaisrub, S.: DaCosta syndrome revisited. J.A.M.A. 232:164, 1975.

Some patients with the symptom complex described by DaCosta have been found to have a supranormal circulatory state. One of the first physicians to describe this condition was Dr. Isaac Starr. In 1942, he reported on a group of patients who had an "increased amount of circulation" which he termed "Hyperkinemia". Similar patients have been termed "Vasoregulatory Asthenia" by Holmgren in 1957, "Hyperkinetic Heart Syndrome" by Gorlin in 1959, and "Hyperdynamic beta-Adrenergic Circulatory State" by Frohlich in 1966. The general term that is now used to describe patients with this condition is the Hyperkinetic Heart Syndrome.

21. Wooley, C.F.: Where are the diseases of yesteryear? DaCosta's syndrome, soldiers heart, the effort syndrome, neurocirculatory asthenia -- and the mitral valve prolapse syndrome. Circulation 53:749, 1976.
22. Wooley, C.F.: Jacob Mendez DaCosta: Medical teacher, clinician, and clinical investigator. Am. J. Cardiol. 50:1145, 1982.
23. Wooley, C.F.: From irritable heart to mitral valve prolapse: The Osler connection. Am. J. Cardiol. 53:870, 1984.
24. Wooley, C.F.: From irritable heart to mitral valve prolapse: British Army Medical Reports, 1860 to 1870. Am. J. Cardiol. 55:1107, 1985.
25. Wooley, C.F.: From irritable heart to mitral valve prolapse: World War I, the British experience and James Mackenzie. Am. J. Cardiol. 57:463, 1986.

26. Wooley, C.F.: From irritable heart to mitral valve prolapse -- World War I, the British experience and Thomas Lewis. Am. J. Cardiol. 58:844, 1986.
27. Wooley, C.F.: From irritable heart to mitral valve prolapse -- World War I, the British experience and Clifford Allbutt. Am. J. Cardiol., in press, 1986.

In a very provocative Editorial, Dr. Charles Wooley asked the question of "Where are the Diseases of Yesteryear?". He states that the patients in the past who carried various clinical diagnoses such as DaCosta Syndrome, Irritable Heart Syndrome, Soldier's Heart, etc., were probably suffering from the mitral valve prolapse syndrome. In a series of papers that have and that will continue to appear in the Historical Studies section of the American Journal of Cardiology, Dr. Wooley is establishing the lineage of this syndrome to previous studies of patients with so-called functional heart disease.

27. Barlow, J.B., W.A. Pocock, P. Marchand, M. Denny: The significance of late systolic murmurs. Am. Heart J. 66:443, 1963.
28. Hancock, E.W., K. Cohn: The syndrome associated with midsystolic click and late systolic murmur. Am. J. Med. 41:183, 1966.
29. Criley, J.M., K.B. Lewis, J.O. Humphries, R.S. Ross: Prolapse of the mitral valve: Clinical and cine-angiocardiographic findings. Br. Heart J. 28:488, 1966.

In 1963, Barlow showed that patients with a systolic click-late systolic murmur had mitral insufficiency due to prolapse of the mitral valve. Later, it was noted that a significant number of patients with this anatomic abnormality complain of palpitations, chest pain, shortness of breath, fatigue, and have a neurotic behavior. Mitral valve prolapse patients with these problems are said to have the mitral valve prolapse syndrome.

30. Gaffney, F.A., E.S. Karlsson, W. Campbell, J.E. Schutte, J.V. Nixon, J.T. Willerson, C.G. Blomqvist: Autonomic dysfunction in women with mitral valve prolapse syndrome. Circulation 59:894, 1979.
31. Coghlan, H.C., P. Phares, M. Cowley, D. Copley, T.N. James: Dysautonomia in mitral valve prolapse. Am. J. Med. 67:236, 1979.
32. DeCarvalho, J.G.R., F.H. Messerli, E.D. Frohlich: Mitral valve prolapse and borderline hypertension. Hypertension 1:518, 1979.
33. Boudoulas, H., J.C. Reynolds, E. Mazzaferri, C.F. Wooley: Metabolic studies in mitral valve prolapse syndrome. A neuroendocrine-cardiovascular process. Circulation 61:1200, 1980.
34. Gaffney, F.A.: Mitral Valve Prolapse. Medical Grand Rounds, UTHSCD, January 24, 1980.

Six years ago Dr. Drew Gaffney presented a Grand Rounds entitled "Mitral Valve Prolapse" which was a scholarly treatment of this subject. At that time, he and Dr. Blomqvist and several other workers in this field had published convincing data that patients with the mitral valve prolapse syndrome had cardiovascular autonomic imbalance. Since that time, several interesting studies have been published on this subject.

35. Leor R., W. Markiewicz: Neurocirculatory asthenia and mitral valve prolapse--two unrelated entities? Isr. J. Med. Sci. 17:1137, 1981.
36. Uretsky, B.F.: Does mitral valve prolapse cause nonspecific symptoms? Int. J. Cardiol. 1:435, 1982.
37. Hickey, A.J., G. Andrews, D.E.L. Wilcken: Independence of mitral valve prolapse and neurosis. Br. Heart J. 50:333, 1983.
38. Boudoulas, H., B.D. King, C.F. Wooley: Mitral valve prolapse: A marker for anxiety or overlapping phenomenon? Psychopathology 17 (Suppl. 1):98, 1984.
39. Chesler, E., E.K. Weir, G.A. Braatz, G.S. Francis: Normal catecholamine and hemodynamic responses to orthostatic tilt in subjects with mitral valve prolapse: Correlation with psychologic testing. Am. J. Med. 78:754, 1985.
40. Venkatesh, A., D.L. Pauls, R. Crowe, R. Noyes, C.V. Valkenburg, J.B. Martins, R.E. Kerber: Mitral valve prolapse in anxiety neurosis (panic disorder). Am. Heart J. 100:302, 1980.
41. Nesse, R.M., O.G. Cameron, G.C. Curtis, D.S. McCann, M.J. Huber-Smith: Adrenergic function in patients with panic anxiety. Arch. Gen. Psychiatry 41:771, 1984.
42. Gorman, J.M., M.K. Shear, R.B. Devereux, D.L. King, D.F. Klein: Prevalence of mitral valve prolapse in panic disorder: Effect of echocardiographic criteria. Psychosom. Med. 48:167, 1986.

There is still controversy concerning the relationship between mitral valve prolapse and the symptom-complex of cardiovascular autonomic imbalance. Many patients have symptoms with little or no demonstrable prolapse and many patients with marked prolapse have no symptoms. Also there is controversy concerning the incidence of mitral valve prolapse in patients being treated for anxiety neurosis and panic disorders by psychiatrists. Therefore, until more is known about the pathophysiology of this symptom-complex, it is important to leave a category called neurocirculatory asthenia and another called anxiety neurosis.

43. James, T.N.: Sir Thomas Lewis redivivus: from pebbles in a quiet pond to autonomic storms. Br. Heart J. 52:1, 1984.
44. Blomqvist, C.G.: Orthostatic hypotension. Hypertension 8:722, 1986.

For conditions apparently as dissimilar as hyperkinetic heart syndrome, mitral valve prolapse syndrome, neurocirculatory asthenia, and anxiety neurosis, it now appears that a common feature is an imbalance of cardiovascular autonomic activity. It also should be noted that this is an arbitrary classification for patients with a long described symptom-complex with no organic cardiovascular disease. Some patients may well represent an overlap between these separate syndromes which are being proposed in this Grand Rounds.

III. CONTROL OF THE HEART AND BLOOD VESSELS BY THE AUTONOMIC NERVOUS SYSTEM

45. Harris, M.D., J.H. Mitchell: Neural regulation of the heart. In: Clinical Cardiology, ed. by J.T. Willerson, C.A. Sanders. New York: Grune & Stratton, p. 518, 1977.
46. Shepherd, J.T., P.M. Vanhoutte: Neurohumoral regulation (Ch. 5). In: The Human Cardiovascular System, Facts and Concepts, ed. by J.T. Shepherd, P.M. Vanhoutte. New York: Raven Press, p. 107, 1979.
47. Stull, J.T., S.E. Mayer: Biochemical mechanisms of adrenergic and cholinergic regulation of myocardial contractility (Ch. 21). In: Handbook of Physiology: The Cardiovascular System,, ed. by R.M. Berne. Bethesda: American Physiological Society, p. 741, 1979.

Marked changes in the oxygen requirement of tissues and organs demand that the heart and blood vessels adjust almost instantaneously over a wide range of activity. For this to be accomplished, the cardiovascular control centers must be provided with moment-to-moment circulatory information and must have access to powerful effector mechanisms which act on the heart and blood vessels. A diagram of the system which accomplishes this task is shown in Figure 6.

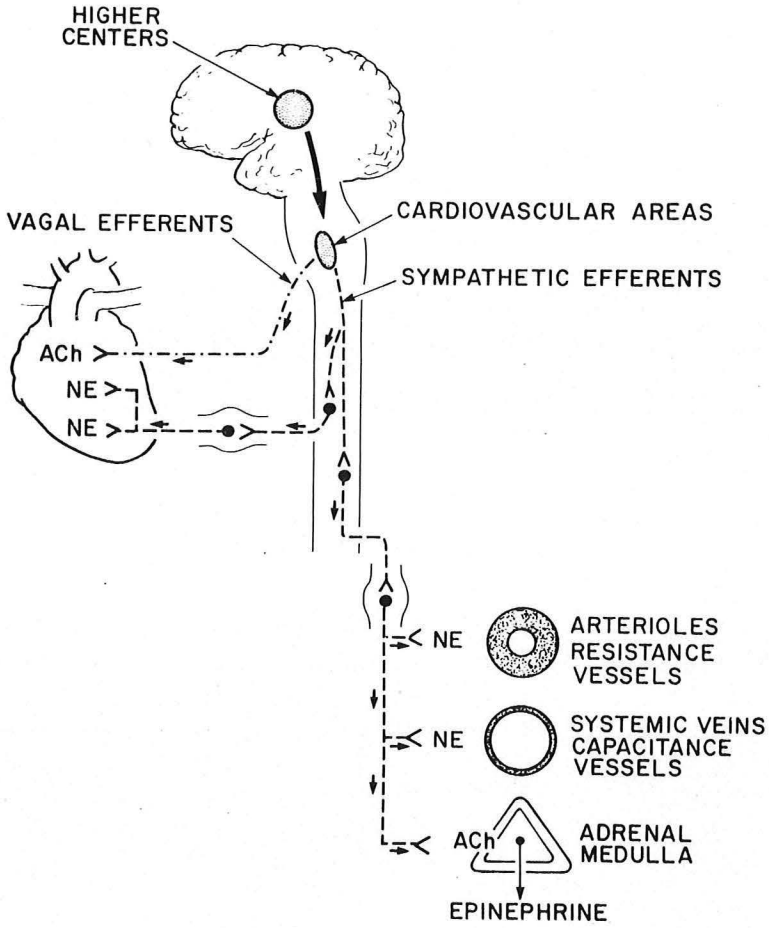

Fig. 6

The cardiovascular control areas reside in the hypothalamus and medulla. These areas receive afferent input from receptors located within and outside of the circulation and from higher centers in the brain. They send efferent output to

the heart and blood vessels. The effector mechanism consists of the sympathetic and parasympathetic autonomic nervous system. Changes in cardiac rate and contractility and in the tone of the smooth muscle surrounding the resistance and capacitance vessels are responsible for meeting the wide range of demands made on the circulation. The sympathetic nervous system activates adrenergic nerves whose endings release norepinephrine to act on receptors located on the heart and blood vessels, and the parasympathetic nervous system activates cholinergic nerves which release acetylcholine to act on receptors which are located in these same areas.

48. Moran, N.C.: Adrenergic receptors, drugs, and the cardiovascular system (I). Mod. Conc. Cardiovasc. Dis. 35:93, 1966.
49. Moran, N.C.: Adrenergic receptors, drugs, and the cardiovascular system (II). Mod. Conc. Cardiovasc. Dis. 35:99, 1966.
50. Weiner, N., P. Taylor: Neurohumoral transmission: The autonomic and somatic motor nervous systems (Ch. 4). In: Goodman and Gilman's The Pharmacological Basis of Therapeutics, 7th ed., ed. by A.G. Gilman, L.S. Goodman, T.W. Rall, F. Murad. New York: MacMillan Publishing Co., p. 66, 1985.

The cardiovascular responses to autonomic nerve impulses releasing norepinephrine by adrenergic nerves and acetylcholine by cholinergic nerves are shown in Figure 7.

	Adrenergic Impulses		Cholinergic Impulses
Effector Organs	Receptor Type	Responses	Responses
Heart			
Atria	β_1	Increase in heart rate, conduction velocity and contractility	Decrease in heart rate and contractility
Ventricles	β_1	Increase in conduction velocity and contractility	Slight decrease in contractility
Arterioles			
Heart	$\alpha;\beta_2$	Constriction +; dilatation ++	Dilatation ±
Skeletal Muscles	$\alpha;\beta_2$	Constriction ++; dilatation ++	Dilatation +
Brain	α	Constriction (slight)	Dilatation
Abdominal Organs	$\alpha;\beta_2$	Constriction +++; dilatation +	----
Veins (Systemic)	α	Constriction ++	----

Fig. 7

Adrenergic impulses to the heart release norepinephrine which acts on beta$_1$-adrenergic receptors causing an increase in heart rate, conduction velocity, and contractility. On arterioles, adrenergic impulses act on alpha-adrenergic receptors to cause constriction and act on beta$_2$-adrenergic receptors to cause dilatation. Adrenergic impulses to the systemic veins act on alpha-adrenergic receptors to cause vasoconstriction.

Cholinergic impulses to the heart release acetylcholine which acts on cholinergic receptors located primarily in the atria causing a decrease in heart rate, conduction velocity, and contractility. On arterioles, cholinergic impulses cause dilatation. Systemic veins are not innervated by the parasympathetic system.

The neural control of the heart and blood vessels usually operates as a highly integrated, smoothly functioning controller which is capable of producing quick changes of large and small variations in sympathetic and parasympathetic output. However, some disease states are caused by an abnormal functioning of these neural control mechanisms. The syndromes of cardiovascular autonomic imbalance: the cardiovascular dysautonomias are due to such abnormal function.

51. Ewing, D.J.: Cardiovascular reflexes and autonomic neuropathy. Clin. Sci. Molec. Med. 55:321, 1978.
52. Bannister, R.: Testing autonomic reflexes (Ch. 4). In: Autonomic Failure, ed. by R. Bannister. New York: Oxford Univ. Press, p. 52, 1984.

The integrity and function of the autonomic control of the cardiovascular system can be tested, but the details of these procedures will not be described in this Grand Rounds. However, studies of the cardiovascular responses to standing (orthostatic stress), lower body negative pressure, dynamic exercise, and static exercise and of the effects of administering adrenergic agonists and antagonists to patients with cardiovascular dysautonomias will be presented.

IV. TYPES OF CARDIOVASCULAR DYSAUTONOMIAS

In the past, at least three types of cardiovascular dysautonomias have been defined and these are: (1) hyperkinetic heart syndrome, (2) mitral valve prolapse syndrome, and (3) neurocirculatory asthenia. Patients with anxiety neurosis whose symptoms are referable to the cardiovascular system may also have an imbalance of autonomic control of the heart and blood vessels. Our patient in 1953 could have been suffering from any one of these conditions.

A. Hyperkinetic Heart Syndrome

1. Description

16. Loc. cit.
17. Loc. cit.
18. Loc. cit.
19. Loc. cit.
53. Starr, I.: Ballistocardiographic studies of draftees rejected for neurocirculatory asthenia. War Med. (Chicago) 5:155, 1944.
54. Gorlin, R.: The hyperkinetic heart syndrome. J.A.M.A. 182:823, 1962.
55. Frohlich, E.D., R.C. Tarazi, H.P. Dustan: Hyperdynamic β-adrenergic circulatory state: Increased β-receptor responsiveness. Arch. Int. Med. 123:1, 1969.
56. Gabor, G.: Cardiovascular hyperkinetic syndrome. Acta Med. Acad. Sci. Hung. 17:181, 1961.
57. Gottsegen, G., G. Okos, T. Romoda: Essential circulatory hyperkinesis. Am. J. Cardiol. 10:785, 1962.
58. Matos, L., E. Torok: Essential circulatory hyperkinesis: Epicritical studies. Acta Med. Acad. Sci. Hung. 26:207, 1969.

Some patients with symptoms of palpitations, chest pain, dyspnea, and weakness who are found to have no organic heart disease have been shown to have a "supranormal" circulation at rest and during exercise. Many studies both in this country and abroad have been performed on patients with hemodynamic findings which are now generally termed the hyperkinetic heart syndrome. As will be seen, our patient in 1953 could have had this syndrome.

59. Guazzi, M., A. Polese, F. Magrini, C. Fiorentini, M.T. Olivari: Long-term treatment of the hyperkinetic heart syndrome with propranolol. Am. J. Med. Sci. 270:465, 1975.
60. Guazzi, M., C. Fiorentini, A. Polese, F. Magrini, M.T. Olivari: Stress-induced and sympathetically-mediated electrocardiographic and circulatory variations in the primary hyperkinetic heart syndrome. Cardiovasc. Res. 9:342, 1975.

Studies of the electrocardiogram of these patients have revealed abnormalities similar to those described in our patient in 1953. Guązzi and his group were able to evoke abnormalities by stressful situations. One stress that was used was to have the patient count backward as rapidly as possible. This seems more humane than threatening to perform a venipuncture. During such "arithmetic" stress, there was deep inversion of the T waves in the precordial leads. After

the stressful calculations were stopped, the T waves promptly returned to normal. These investigators also found that infusion of a pure beta-adrenergic receptor agonist, isoproterenol, caused similar inversion of the T waves. This is also reminiscent of our findings with the infusion of adrenaline.

In addition to the electrographic studies which were similar to those performed in our patient, Guazzi and his group evaluated the effect of a beta-adrenergic receptor antagonist, propranolol, on the electrocardiographic changes found in these patients. An example of this is shown in Figure 8.

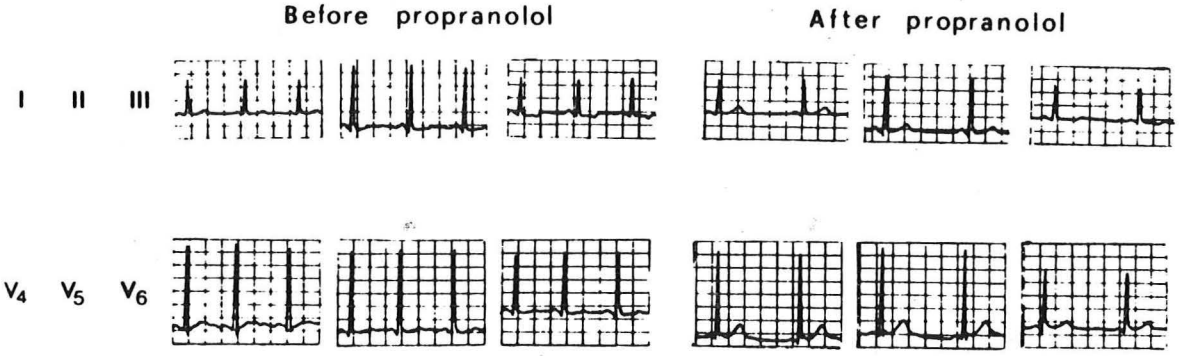

Fig. 8

In the control tracings (before propranolol), the T waves are flat and in some leads biphasic. After the administration of propranolol (after propranolol), the T waves are normal. These studies by Guazzi et al. clearly show that the electrocardiographic changes seen in patients with the hyperkinetic heart syndrome are due to an abnormal adrenergic activity.

18. Loc. cit.
19. Loc. cit.

Gorlin and his group have studied resting hemodynamics in patients with the hyperdynamic heart syndrome. They found that all of the patients had an increased rate of left ventricular ejection as compared to normal subject. However, only 2/3 of these patients had an elevated cardiac index. Patients with an elevated cardiac output at rest were classified as Group A and those with a normal value as Group B. The mean resting hemodynamic data in these two groups of patients and in normal control subjects is shown in Figure 9.

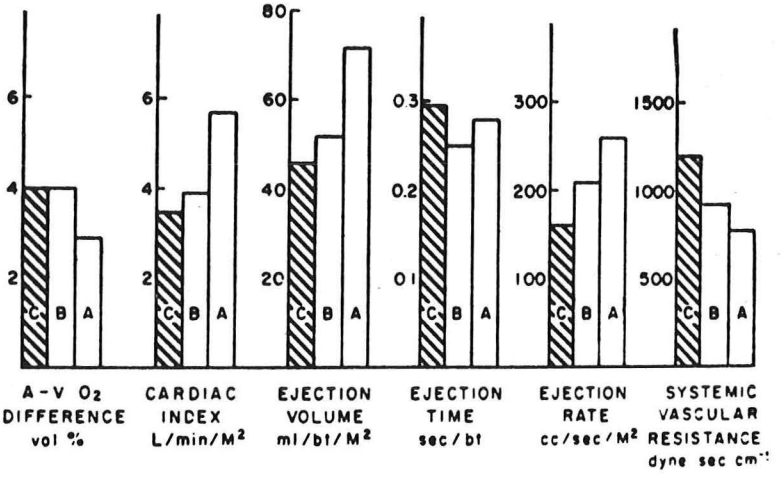

Fig. 9

The normal subjects are represented by cross-hatched bars, and the patients by the solid bars. In group A the arteriovenous oxygen difference and the systemic vascular resistance are low, and the cardiac index, ejection volume, and ejection rate are all high. In group B the left ventricular ejection rate is high and the systemic vascular resistance is low; however, the cardiac index, ejection volume, and arteriovenous oxygen difference are normal.

17. Loc. cit.

Holmgren et al. in Stockholm have also studied a group of patients with symptoms of palpitations, chest pain, shortness of breath, and a low physical work capacity. They were found to have a high cardiac output at rest and during progressive exercise loads. He described these patients as having "Vasoregulatory Asthenia" and their arteriovenous oxygen difference at rest and during increasing workloads as compared to normal subjects is shown in Figure 10.

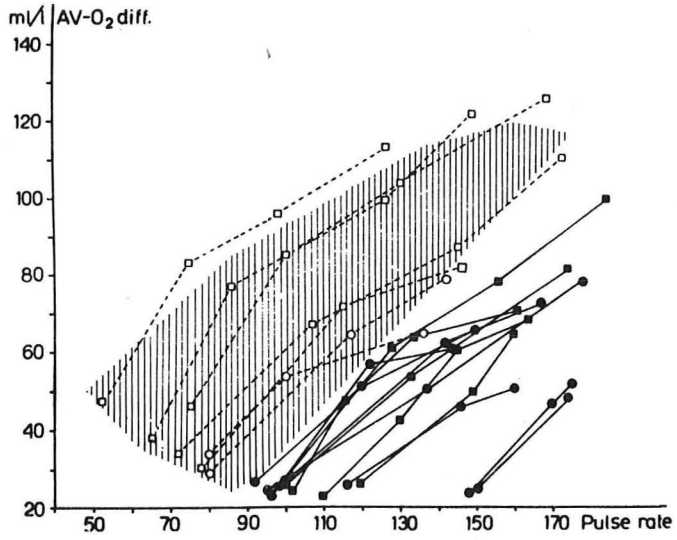

Fig. 10

In this figure arteriovenous oxygen difference (AV-O_2 diff) in ml of oxygen per liter of blood is plotted against pulse rate at rest and during progressive exercise loads. Normal males (□) and normal females (○) lie within the cross-hatched area of normal values. Males (■) and females (●) with vasoregulatory asthenia have wider values at rest and during progressive workloads. They stated that these patients appeared to have a disorder of arteriolar regulation with a relative vasodilatation and a higher than normal blood flow. During work there appears to be an inability to shunt blood away from inactive areas to the working muscles.

19. Loc. cit.
55. Loc. cit.

Frohlich also described a group of patients with similar symptoms and hemodynamic findings of elevated left ventricular ejection rate and cardiac index and termed the condition "Hyperdynamic beta-Adrenergic Circulatory State". He found that patients with this syndrome had a greater increase in heart rate to an infusion of isoproterenol (a pure beta-receptor agonist). The results of his studies are shown in Figure 11.

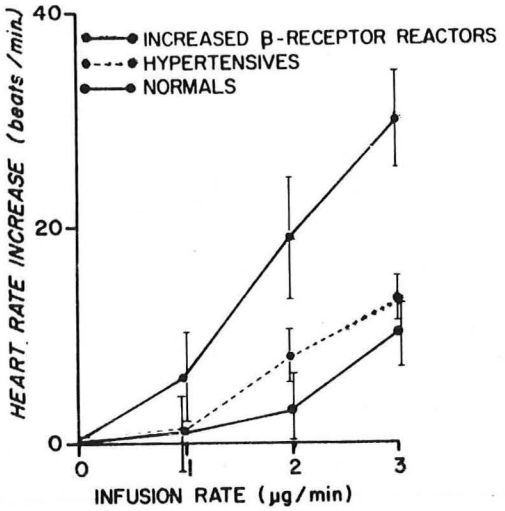

Fig. 11

Patients with hyperdynamic beta-adrenergic circulatory state had a much greater increase in heart rate at the two upper levels of the infusion rate. Further in nine of the 14 hyperdynamic patients isoproterenol evoked a hysterical outburst which was promptly reversed with the administration of propranolol. These studies suggested that the syndrome was due to increased beta-adrenergic receptor sensitivity. In these same patients, he found that the responses to upright tilt, the Valsalva maneuver, and carotid sinus stimulation were all normal. These latter studies demonstrated normal parasympathetic responses in these patients.

61. Hörtnagl, H., D. Magometschnigg, J. Prager: Hyperkinetic heart syndrome: the role of the sympathetic nervous system. Cardiology 69:74, 1982.

62. Dominiak, P., H. Grobecker: Elevated plasma catecholamines in young hypertensive and hyperkinetic patients: Effect of pindolol. Br. J. Clin. Pharmac. 13:381S, 1982.

Whether the level of resting plasma catecholamines or the levels with various stresses is normal or elevated is not clear. Hörtnagl et al. found normal levels in patients with the hyperkinetic heart syndrome as compared to normal control subjects at rest, during head up tilt to 90°, and during exercise. However, Dominiak and Grobecker found elevated plasma catecholamines at rest, during marked stress and during dynamic exercise. It is apparent that more definitive studies are needed in this area.

59. Loc. cit.

The administration of a beta-adrenergic receptor antagonist not only has profound effects on the electrocardiogram of patients with the hyperkinetic heart syndrome, but also on the function of the heart. The hemodynamic feature common to all patients with the hyperkinetic heart syndrome is an increased rate of left ventricular ejection. The values for this measurement and the effects of propranolol in normal subjects and in the patients studied by Guazzi et al. is shown in Figure 12.

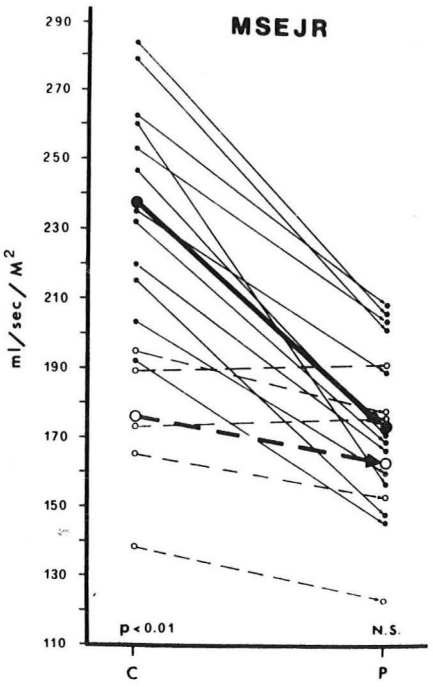

Fig. 12

In the control state the mean rate of left ventricular ejection was about 230 ml/sec/m² in the patients and 170 ml/sec/m² in the normal subjects which was a significant difference. After the administration of propranolol there was a marked drop in this value for the patients and little change in the normal subjects. The difference between the patients and normal subjects was not significant after treatment with propranolol. As mentioned previously, some patients with the hyperkinetic heart syndrome have a high cardiac output. Guazzi et al. have also shown that the high cardiac output can be normalized by the administration of propranolol.

In summary, patients with the hyperkinetic heart syndrome have an excessive activity of beta-adrenergic receptors in the heart and blood vessels. This autonomic abnormality is responsible for their hemodynamic findings and may account for their cardiovascular symptoms.

2. Treatment

59. Loc. cit.
63. Bollinger, A., M. Gander, P.O. Pylkkänen, G. Forster: Treatment of the hyperkinetic heart syndrome with propranolol. Cardiologia 49 (Suppl. II):68, 1966.
64. Rosenblum, R., A.J. Delman: Propranolol in the treatment of hyperkinetic heart syndrome, idiopathic hypertrophic subaortic stenosis, and systemic hypertension. Am. Heart J. 79:134, 1970.
65. Frohlich, E.D.: Beta adrenergic blockade in the circulatory regulation of hyperkinetic states. Am. J. Cardiol. 27:195, 1971.

The Italian group has also studied the more sustained effects of the administration of propranolol in the patients and these results are shown in Figure 13.

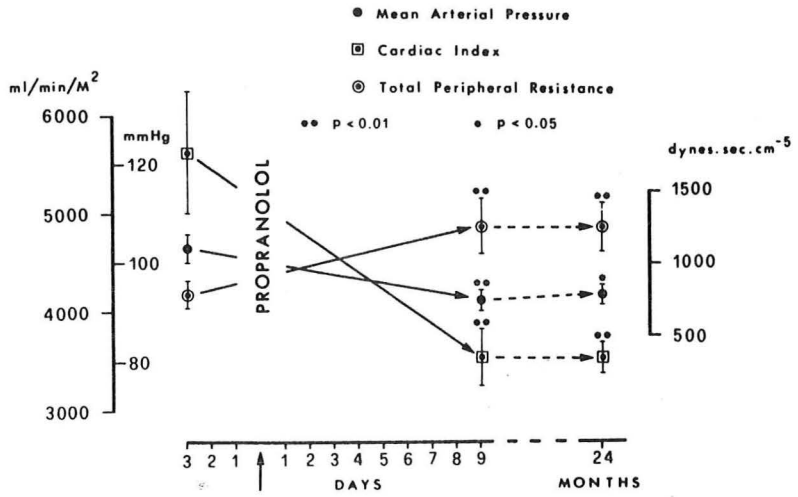

Fig. 13

After 9 days of treatment there was a significant drop in cardiac index and in mean arterial pressure and an increase in peripheral vascular resistance. After 24 months of therapy these effects were still present.

In normal individuals the administration of propranolol decreases maximal oxygen uptake and work capacity. However, Bollinger et al. found that propranolol increased the low work capacity of patients with the hyperkinetic heart syndrome and this is shown in Figure 14.

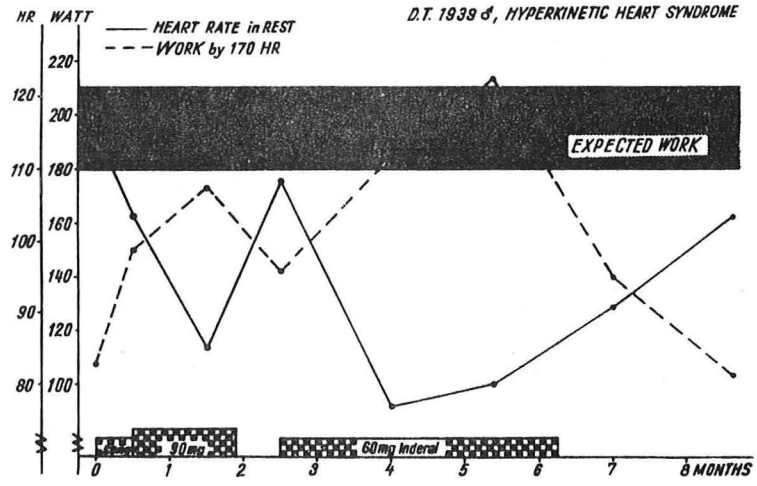

Fig. 14

The patient was a young white male with an expected work capacity (cross hatched area) of between 180 watts (1080 kpm/min) and 210 watts (1260 kpm/min). Before treatment, his resting heart rate was about 118 beats/min and work capacity 108 watts. With the administration of 60 mg/day propranolol for ½ month, his resting heart rate decreased and work capacity increased. Increasing the dosage of propranolol to 90 mg/day for 1½ months further reduced heart rate and increased work capacity. Cessation of propranolol caused an increase in resting heart rate and a decrease in work capacity. Administration of 60 mg/day of propranolol for about 4 months produced a normal resting heart rate and work capacity. Cessation of therapy again resulted in an abnormal resting heart rate and work capacity.

66. Holmgren, A., B. Jonsson, M. Levander, H. Linderholm, F. Mossfeldt, T. Sjöstrand, G. Ström: Physical training of patients with vasoregulatory asthenia. Acta Med. Scand. 158:437, 1957.
67. Holmgren, A., B. Jonsson, M. Levander, H. Linderholm, F. Mossfeldt, T. Sjöstrand, G. Ström: Effect of physical training in vasoregulatory asthenia, in DaCosta's syndrome, and in neurosis without heart symptoms. Acta Med. Scand. 165:89, 1959.

Holmgren and his group have also shown that dynamic exercise training appears to be of benefit in the treatment of patients with the hyperkinetic heart syndrome and decreased work capacity. They trained eight patients and increased the physical work capacity by an average of 85%. More importantly, in the one patient studied, the regulation of peripheral blood flow was normalized, and this data is shown in Figure 15.

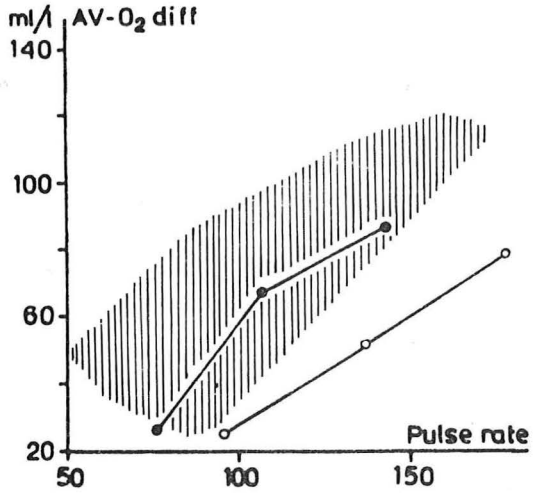

Fig. 15

Again AV-O_2 difference is plotted against the pulse rate at rest and during two levels of exercise. Before training (O) the AV-O_2 difference was wide at rest and during dynamic exercise. After training (●), it fell within the normal range.

3. Prognosis

68. Gillum, R.F., L.E. Teichholz, M.V. Herman, R. Gorlin: The idiopathic hyperkinetic heart syndrome: Clinical course and long-term prognosis. Am. Heart J. 102:728, 1981.
69. Fiorentini, C., M.T. Olivari, P. Moruzzi, M.D. Guazzi: Long-term follow-up of the primary hyperkinetic heart syndrome. An echocardiographic and hemodynamic study. Am. J. Med. 71:221, 1981.
70. The hyperkinetic heart (Editorial). Lancet 2(8253):967, 1981.

In 1981, Gillum et al. reported on the clinical course and long-term prognosis of the patients with hyperkinetic heart syndrome who were studied by Gorlin in 1961. These patients had a rather benign course over this 20-year period. However, there was a slight increased incidence of sustained hypertension.

Also, Guazzi and his group have followed 14 patients with the hyperkinetic heart syndrome for five years and the results are shown in Figure 16.

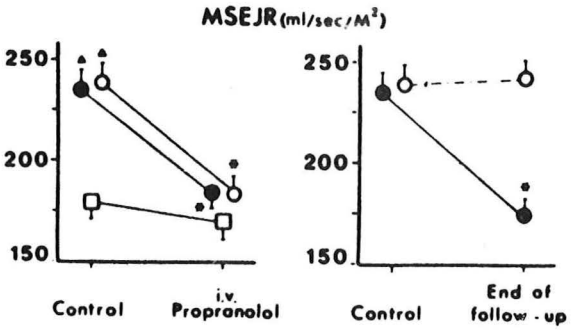

Fig. 16

The left panel demonstrates the effect of the acute administration of propranolol on the mean rate of left ventricular ejection (MSEJR). These are essentially the same data as were shown in Figure 12. The normal controls are indicated by the open squares, the patients to be treated for five years with propranolol by the filled circles, and the patients not to be treated by the open circles. As noted before, the administration of propranolol normalized the mean rate of left ventricular ejection in the patients. Also, there was no difference in the effect of propranolol in the group to be treated for five years and the group to go untreated. The right panel demonstrates the effects after five years. The untreated patients still had an elevated mean rate of left ventricular ejection, and the treated patients remained normal. During this period of time the symptoms were markedly improved in the treated patients and still present in the untreated patients. Also, there were no major clinical problems in either the treated or the untreated group. After five years, however, when a placebo was substituted for the propranolol in the treated patients, palpitations and awareness of the heart reappeared in 2-3 days.

Since it has been suggested that the hyperkinetic heart syndrome may lead to idiopathic hypertrophic subaortic stenosis, echocardiograms were obtained in both the treated and the untreated patients at the beginning of the study and at the end of five years. There was no evidence for left ventricular hypertrophy at the beginning or after five years of follow-up in the treated or in the untreated patients. Thus, they found no evidence that the hyperkinetic heart syndrome progresses into idiopathic hypertrophic subaortic stenosis.

B. Mitral Valve Prolapse Syndrome

1. Description

27. Loc. cit.
28. Loc. cit.
29. Loc. cit.
71. Pocock, W.A., J.B. Barlow: Etiology and electrocardiographic features of the billowing posterior mitral leaflet syndrome. Am. J. Med. 51:731, 1971.

Patients with symptoms of palpitations, chest pain, dyspnea, and weakness who are found to have mitral valve prolapse are diagnosed as having the mitral valve prolapse syndrome. Our patient in 1953 could have had this problem.

72. Barlow, J.B., C.K. Bosman: Aneurysmal protrusion of the posterior leaflet of the mitral valve: An ausculatory-electrocardiographic syndrome. Am. Heart J. 71:166, 1965.
73. Abinader, E.G.: Adrenergic beta blockade and ECG changes in the systolic click murmur syndrome. Am. Heart J. 91:297, 1976.

Several studies have reported that the electrocardiogram of patients with mitral valve prolapse syndrome often have ST segment and T-wave abnormalities. The electrocardiogram of a patient with these findings was published by Barlow and Bosman, and the tracing is shown in Figure 17.

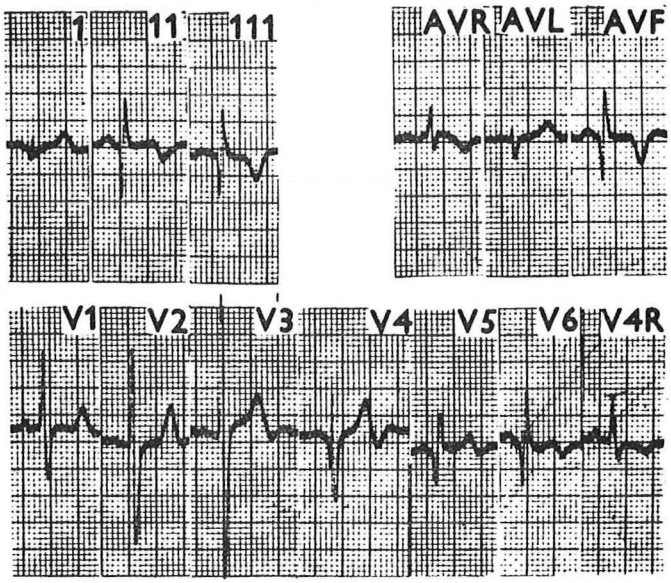

Fig. 17

There are abnormal ST segments and inverted or diphasic T waves in leads II, III, AVF, V_4, V_5, and V_6. An electrocardiogram taken at a later time in this patient revealed a marked improvement in the ST segment changes and the T-wave patterns. The electrocardiogram of some patients with the mitral valve prolapse syndrome are quite similar to the changes seen in the electrocardiogram of the patient we admitted to Parkland Hospital in 1953.

In addition, Abinader has shown that the ST segment and T-wave changes seen in patients with the mitral valve prolapse syndrome can be normalized by beta-adrenergic receptor blockade with propranolol. He suggested that these ECG changes were due to autonomic imbalance in these patients.

30. Loc. cit.
31. Loc. cit.

In addition to changes in the electrocardiograms, other studies of patients with this syndrome suggest that they may have both abnormal parasympathetic and sympathetic responses to imposed tests of cardiovascular autonomic function.

Gaffney et al. used two methods to evaluate cardiac parasympathetic activity in patients with the mitral valve prolapse syndrome. These are to determine the effect on heart rate of: (1) a phenylephrine infusion; and (2) face immersion in cold water. In the first method, an intravenous infusion of phenylephrine was given and blood pressure and heart rate were measured. A plot can then made of

the changes in RR interval (Δ RR interval) in msec against the change in mean arterial pressure (Δ mean blood pressure) in mmHg, and the results are shown in Figure 18.

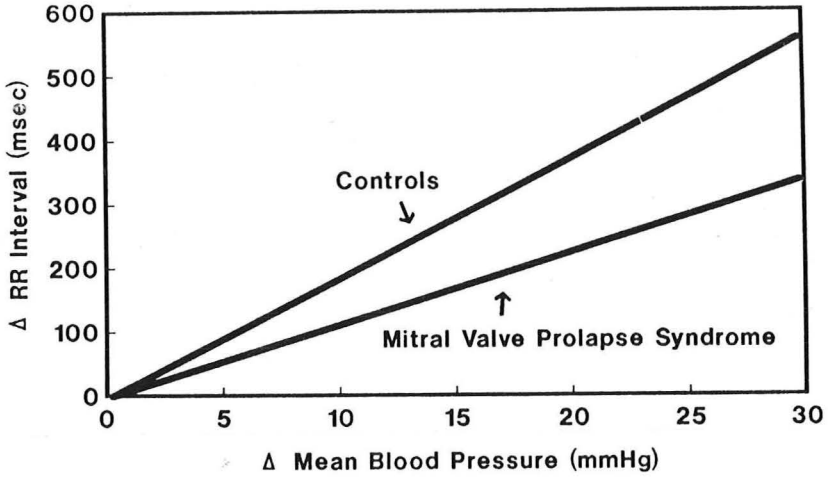

Fig. 18

The slope of this relationship for the patients with mitral valve prolapse syndrome is less steep than that for the normal subjects. Thus, the degree of cardiac slowing for a given change in arterial pressure is less in the mitral valve prolapse syndrome patients than in control subjects. This suggests that patients with the mitral valve prolapse syndrome have decreased cardiac parasympathetic (vagal) responsiveness. Also, the MVPS patients had less heart rate slowing when their faces were immersed in cold water which further indicates diminished parasympathetic responsiveness.

Coghlan et al. have also studied the autonomic neural control in patients with the mitral valve prolapse syndrome. They measured heart rate and blood pressure during a control period in the supine position, for 3 minutes during standing, and for 2 minutes during return to the supine position. The results of this study are shown in Figure 19.

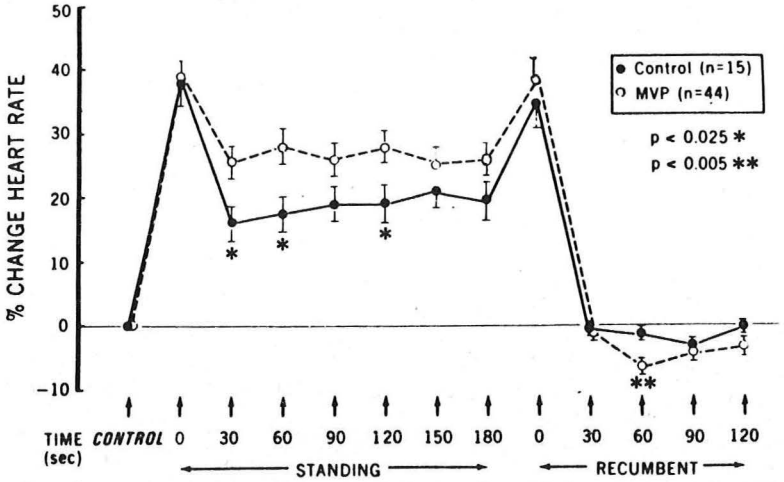

Fig. 19

After standing, the heart rates were higher in the patients than in the control subjects. In both groups, there was an increase in heart rate when returning to the supine position. However, a further reduction in heart rate occurred after 1 minute in the patients with mitral valve prolapse syndrome. Since it has been shown that heart rate changes during this maneuver are principally controlled by parasympathetic activity, the findings suggest an inappropriate adjustment of this part of the autonomic nervous system.

74. Gaffney, F.A., B.C. Bastian, L.B. Lane, W.F. Taylor, J. Horton, J.E. Schutte, R.M. Graham, W. Pettinger, C.G. Blomqvist: Abnormal cardiovascular regulation in the mitral valve prolapse syndrome. Am. J. Cardiol. 52:316, 1983.
75. Boudoulas, H., J.C. Reynolds, E. Mazzaferri, C.F. Wooley: Mitral valve prolapse syndrome: The effect of adrenergic stimulation. J. Am. Col. Cardiol. 2:638, 1983.
76. Gaffney, F.A., C.G. Blomqvist: Pathophysiological role of autonomic dysfunction in symptomatic mitral valve prolapse. Submitted.

Gaffney et al. have studied the effect of lower body negative pressure (LBNP), a maneuver which is a similar pertubation on the cardiovascular system as standing, in normal subjects and in patients with mitral valve prolapse syndrome. The patients were divided into two groups. Patients in Group 1 had a greater frequency of arrhythmias and more severe symptoms than patients in Group 2. The results of LBNP on calf volume, forearm conductance, and mean arterial pressure in these two groups of patients and normal controls are shown in Figure 20.

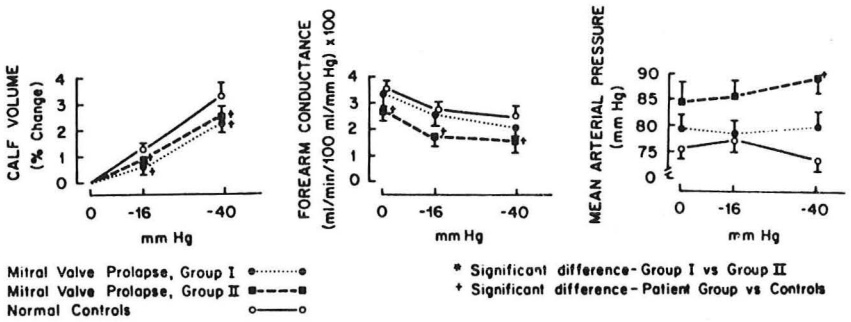

Fig. 20

The changes in calf volume were less pronounced in the patients than in the control subjects, which suggests a decreased venous compliance. Also, at -40mmHg the decrease in forearm conductance (or increase in forearm resistance) was greater in the MVPS patients than in normal subjects. Further, the mean arterial pressure fell in the control subjects, remained the same in Group I patients and increased in the Group 2 patients' at -40mmHg. These findings suggest an increased activity of alpha-adrenergic receptors in the capacitance and resistance vessels.

Wooley and his group have studied the effect of isoproterenol infusion on heart rate in control subjects and in patients with mitral valve prolapse syndrome, and the results are shown in Figure 21.

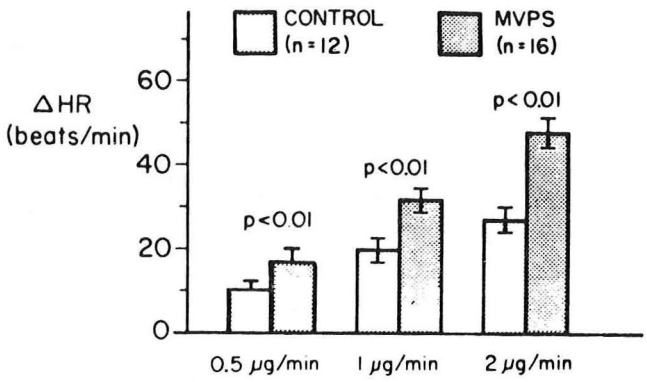

Fig. 21

The increase in heart rate was greater in the patients than in the control subjects. Also, symptoms of palpitations, chest pain, fatigue, and dyspnea were noted in the patients, but only palpitations were noted in the normal subjects. The infusion of normal saline caused no symptoms in either group. These studies would also suggest that the patients have abnormal sympathetic responsiveness.

77. Pasternac, A., J.F. Tubau, P.E. Puddu, R.B. Król, J. deChamplain: Increased plasma catecholamine levels in patients with symptomatic mitral valve prolapse. Am. J. Med. 73:783, 1982.
78. Puddu, P.E., A. Pasternac, J.F. Tubau, R. Król, L. Farley, J. deChamplain: QT interval prolongation and increased plasma catecholamine levels in patients with mitral valve prolapse. Am. Heart J. 105:422, 1983.

Pasternac et al. have measured plasma total catecholamine levels, plasma norepinephrine levels, heart rate, and blood pressure in patients with the mitral valve prolapse syndrome and in normal control subjects in the supine and then in the standing positions. Blood pressure was slightly higher in the patients but there was no difference in the change of pressure with standing. Also, the patients had a slower heart rate in the supine position. However, when assuming the standing position, the patients had a greater increase in heart rate so that the two groups had the same heart rate in the standing position. The plasma norepinephrine levels in these two groups are shown in Figure 22.

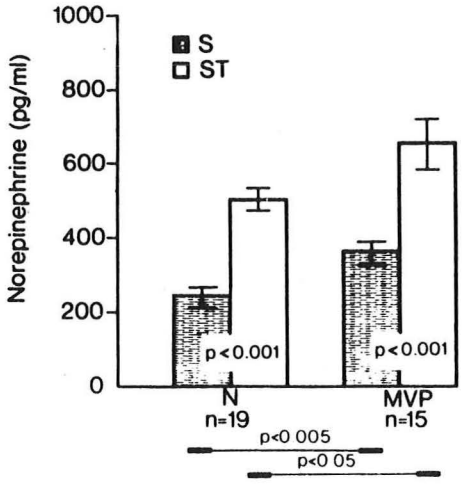

Fig. 22

The plasma norepinephrine levels were higher in the mitral valve prolapse syndrome patients in both the supine and standing positions. Both the control subjects and the patients had a significant increase in plasma norepinephrine in the standing position but the amount of increase was the same in the two groups.

Gaffney et al. have studied the effects of 5 minutes of quiet standing on mean arterial blood pressure, heart rate, cardiac output, and total peripheral resistance in control subjects and in patients with mitral valve prolapse syndrome. In this study, the patients were divided into two groups. Group I had heart rates less than 100 (HR<100) when standing, and Group II had heart rates equal to or greater than 100 when standing (HR$\geq$100). Some of the results of their study are shown in Figure 23.

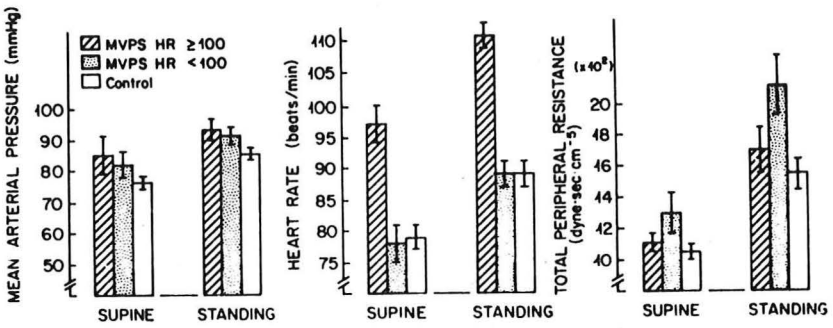

Fig. 23

All three groups had an increase in mean arterial pressure during standing. Patients with orthostatic tachycardia (Group II) had less of a drop in cardiac output than patients in Group I and, therefore, were able to maintain mean arterial blood pressure in the standing position with less of an increase in total peripheral resistance than the patients in Group I. Blood volumes were also measured in this study. Patients in Group I, who had the highest total peripheral resistance, had the lowest blood volumes; and Group II patients had blood volumes lower than normal subjects but higher than the Group I patients.

In summary, patients with the mitral valve prolapse syndrome have an excessive activity of alpha-adrenergic receptors in their blood vessels. Also, they seem to have abnormal parasympathetic activity and, in some cases, a secondary excessive activity of beta-adrenergic receptors.

2. Treatment

79. Winkel, R.A., M.G. Lopes, D.J. Goodman, J.W. Fitzgerald, J.S. Schroeder, D.C. Harrison: Propranolol for patients with mitral valve prolapse. Am. Heart J. 93:422, 1977.
80. Erbel, R., P. Schweizer, W. Merx, S. Effert: Propranolol versus placebo in long-term treatment of patients with mitral valve prolapse. Z. Kardiol. 67:729, 1978.

As was mentioned earlier, beta-adrenergic blockade is very beneficial in patients with hyperkinetic heart syndrome. However, the response in patients with mitral valve prolapse has been less satisfactory. Winkel et al. found that only 37% of patients show any long-term symptomatic improvement. Also, Erbel et al. in an interindividual randomized controlled double-blind study determined the effects of propranolol on the symptom-complex of patients with the mitral valve prolapse syndrome. The results of his study are shown in Figure 24.

Symptome der Patienten mit Mitralklappenprolaps. v = vor Therapie, n = nach Therapie, p = Signifikanzniveau, n.s. = nicht signifikant.

		Gruppe C		Gruppe A		Gruppe B	
		v	n	v	n	v	n
1. Dyskardien	ja	15	10	13	6	16	9
	nein	5	10	7	14	4	11
	p	n.s.		<0,05		<0,05	
2. Müdigkeit	ja	10	6	8	7	6	3
	nein	10	14	12	13	14	17
	p	n.s.		n.s.		n.s.	
3. Atemnot	ja	8	2	7	3	8	5
	nein	12	18	13	17	12	15
	p	<0,05		n.s.		n.s.	
4. Herzstolpern	ja	10	4	5	4	7	2
	nein	10	16	15	16	13	18
	p	<0,05		n.s.		n.s.	
5. Herzrasen	ja	7	2	8	3	5	5
	nein	13	18	12	17	15	15
	p	n.s.		n.s.		n.s.	
6. Schwindel	ja	10	2	10	4	9	5
	nein	10	18	10	16	11	15
	p	<0,01		<0,05		n.s.	

Gruppe C = Placebo, Gruppe A = 2 × 40 mg Propranolol täglich, Gruppe B = 2 × 80 mg Propranolol täglich oral.

Fig. 24

Dyskardien (atypical chest pain) was significantly improved after treatment with propranolol. Müdigkeit (fatigue) and herzrasen (tachycardia) were the same before and after treatment. Atenmot (dyspnea) and herzstolpern (palpitations) were better during placebo therapy! Schwindel (dizziness) was improved by placebo and low dose propranolol but not by high dose propranolol. This study shows no significant symptomatic improvement with beta-adrenergic receptor blockade.

81. Gaffney, F.A., L.B. Lane, W. Pettinger, C.G. Blomqvist: Effects of long-term clonidine administration on the hemodynamic and neuroendocrine postural responses of patients with dysautonomia. Chest 83S:436S, 1983.
82. Schmitt, H., H. Schmitt-Jubeau, N.T. Daskalopoulos: Central mechanisms of clonidine. Trends Pharmac. Sci. 1:71, 1979.
83. Haeusler, G.: Cardiovascular regulation by central adrenergic mechanisms and its alteration by hypotensive drugs. Circ. Res. 36/37:I-223, 1975.
84. Williams, C.A.: Effect of clonidine and naloxone on the pressor response during contraction of cat hind-limb muscles. Cardiovasc. Res. 19:474, 1985.

Since beta blockade, which is so effective in the treatment of the hyperkinetic heart syndrome, did not relieve symptoms in patients with the mitral valve prolapse syndrome, Gaffney et al. decided to treat patients who had evidence of increased alpha-adrenergic activity with clonidine. Clonidine, which is a centrally active alpha agonist, decreases efferent sympathetic activity. Williams has studied this effect in an animal model of static exercise. Exercise was induced in anesthetized cats by nerve stimulation before and after the injection of clonidine into the cisterna magna. The results of this study are shown in Figure 25.

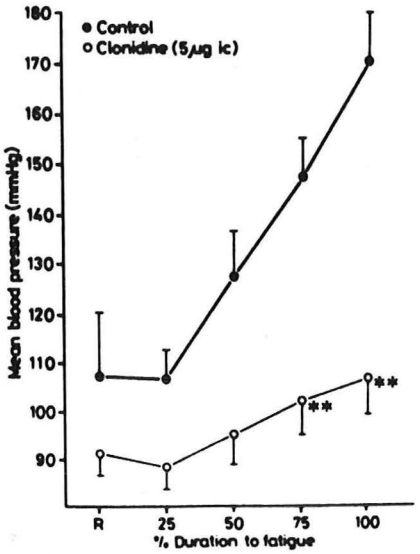

Fig. 25

The values for mean blood pressure are shown at rest and at various percentages of time until an induced isometric contraction demonstrated fatigue. During control conditions, mean arterial pressure was 109mmHg at rest and increased to 170mmHg at the time of fatigue. After the injection of clonidine, the resting mean arterial pressure decreased to 90mmHg at rest and only increased to 106mmHg at fatigue. This clearly demonstrates that the central action of clonidine is to decrease efferent sympathetic activity at rest and during simulated exercise.

All eight of the patients who were given clonidine by Gaffney et al. had orthostatic intolerance but only five had diagnostic echocardiograms of mitral valve prolapse. The results of this study are shown in Figure 26.

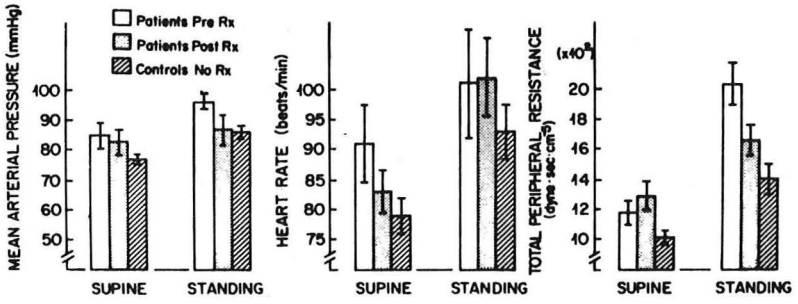

Fig. 26

The increase in mean arterial pressure with standing was less in the patients after treatment with clonidine and was the same as control subjects. Heart rate in the supine position was reduced but increased to the same level upon standing. Total peripheral resistance in the supine position was not changed by clonidine treatment, but the increase upon standing was much less pronounced. Thus, the patients could maintain mean arterial pressure with less systemic arteriolar constriction or less alpha-adrenergic activity. In this same study, the plasma norepinephrine levels were not altered after clonidine in the supine position but were significantly lower after clonidine while standing. Also, in this study, plasma volumes were below normal in the patients before treatment with clonidine and increased significantly to near normal values after treatment.

3. Prognosis

85. Braunwald, E.: Valvular heart disease (Ch. 32). In: Heart Disease, A Textbook of Cardiovascular Medicine, Vol. 2, 2nd Ed., ed. by E. Braunwald. Philadelphia: W.B. Saunders, p. 1089, 1984.
86. Criley, J.M., J. Heger: Mitral valve prolapse (Ch. 11). In: Adult Congenital Heart Disease, ed. by W.C. Roberts. Philadelphia: F.A. Davis, p. 331, 1987.

There is some controversy concerning the clinical course of patients with mitral valve prolapse, but that subject will not be covered in this Grand Rounds. However, there is probably no difference in long-term prognosis between patients with mitral valve prolapse and with the mitral valve prolapse syndrome.

C. Neurocirculatory Asthenia

13. Loc. cit.
14. Loc. cit.
15. Loc. cit.
87. Mäntysaari, M.: Hemodynamic reactions to circulatory stress tests in patients with neurocirculatory dystonia. Scand. J. Clin. Lab. Invest. 44 (Suppl. 170), 1984.

Since the description of the hyperkinetic heart syndrome and the mitral valve prolapse syndrome, it is difficult to know what patients comprise the syndrome called neurocirculatory asthenia. However, there are reports in the literature of patients with the symptom-complex of the cardiovascular dysautonomias who do not have evidence of mitral valve prolapse or of a hyperkinetic circulation.

88. Tzivoni, D., Z. Stern, A. Keren, S. Stern: Electrocardiographic characteristics of neurocirculatory asthenia during everyday activities. Br. Heart J. 44:426, 1980.

Some patients with neurocirculatory asthenia have been reported to have abnormal electrocardiograms. Tzivoni et al. studied the electrocardiographic changes that occur in these patients during daily activity by ambulatory electrocardiographic monitoring. The results from a study on one patient are shown in Figure 27.

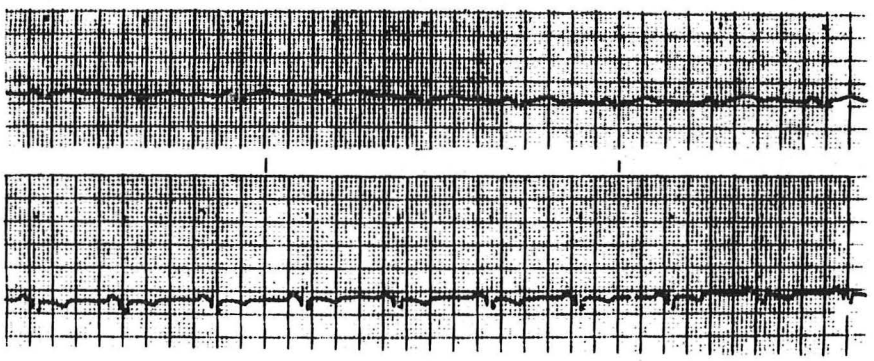

Fig. 27

As seen in the upper panel, the ST segments were normal and the T waves were upright in a lead corresponding to V_4 or V_5 during most of the day. However, as seen in the lower panel, there were occasional occurrences of a depression of the ST segment and inversion of the T waves with very little change in heart rate. These electrocardiographic changes are similar to those seen in our patient in 1953.

87. Loc. cit.

Mäntysaari has recently studied the response of patients with neurocirculatory asthenia, which he termed neurocirculatory dystonia, and normal subjects to the stress of isometric exercise. In this study he measured mean arterial blood pressure, stroke volume (impedance cardiogram), and heart rate and calculated cardiac output and peripheral vascular resistance. The change in mean arterial pressure (Δ MBP), change in cardiac output (Δ CO), and change in peripheral vascular resistance (Δ PVR) are shown in Figure 28.

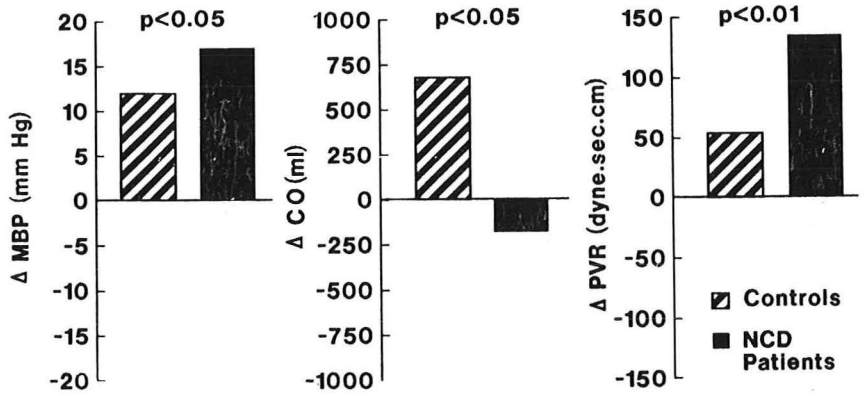

Fig. 28

The increase in mean blood pressure was greater in the patients than in the control subjects. This was accomplished by a much larger increase in peripheral vascular resistance in the patients since cardiac output decreased as compared to the increase in the normal subjects. Thus, the greater increase in blood pressure in the patients was due to a much greater vasoconstriction in the resistance vessels. This would indicate a greater alpha-adrenergic activity which is similar to that seen by Gaffney et al. in patients with the mitral valve prolapse syndrome in response to orthostatic stress. Mäntysaari suggested that this difference was due to an abnormal venous return in the patients.

The cause for the difference in cardiac output during static exercise between the patients and normal subjects is shown in Figure 29.

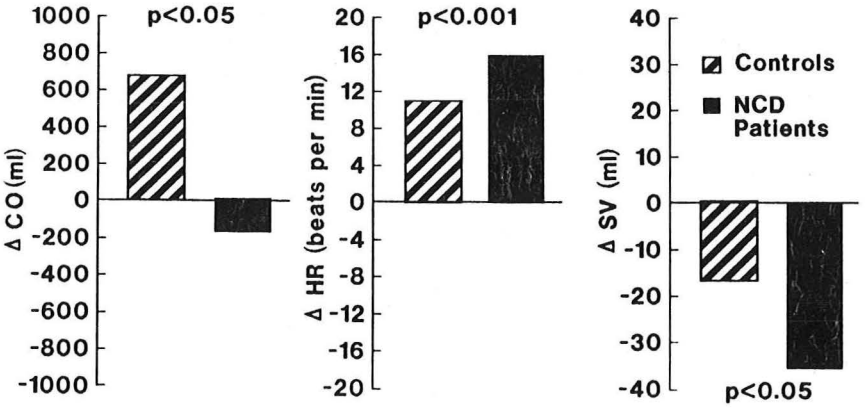

Fig. 29

As shown in the last figure, when the patients with neurocirculatory asthenia performed isometric exercise, there was a slight decrease in cardiac output as compared to an increase in normal subjects. The lack of an increase in cardiac output in the patients was due to a marked decrease in stroke volume, since the increase in heart rate was greater in the patients than in the normal subjects. The decrease in stroke volume is further evidence of an abnormal venous return in the patients.

89. Walker, J.L., F.M. Abboud, A.L. Mark, M.D. Thames: Interaction of cardiopulmonary and somatic reflexes in humans. J. Clin. Invest. 65:1491, 1980.

As already mentioned, the response of Mäntysaari's patients to the stress of isometric exercise is similar to that of the patients studied by Gaffney with orthostatic stress (see Figure 23). Also, Walker et al. were able to obtain a similar response to static exercise in normal subjects if they superimposed lower body negative pressure at the same time. Some of the results of their study are shown in Figure 30.

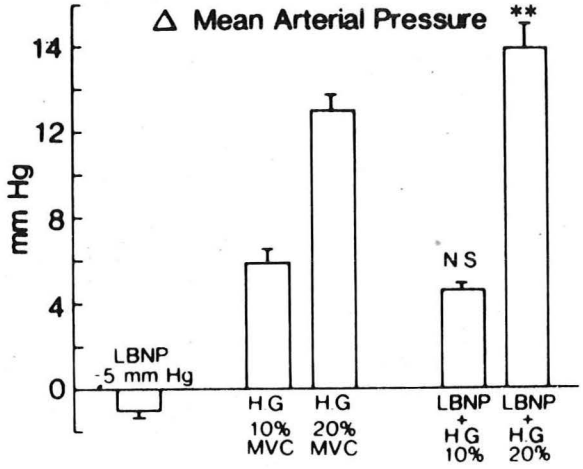

Fig. 30

The changes in mean arterial pressure to several interventions is demonstrated. Lower body negative pressure (LBNP) alone caused a small decrease in arterial pressure. Isometric handgrip at 10% and at 20% of maximal voluntary contraction (MVC) caused significant increases in arterial pressure. However, with the 20% MVC level of handgrip, there was a larger increase in blood pressure when lower body negative pressure was superimposed. Walker et al. also demonstrated a greater increase in forearm vascular resistance in the resting arm with the combined stress. Thus, an induced abnormality in venous return can cause an increased alpha-adrenergic response to static exercise in normal subjects and would strengthen the suggestion of Mäntysaari that an abnormal venous return was present in his patients with neurocirculatory asthenia (neurocirculatory dystonia). It would be of interest to know the blood volume and to study the effect of clonidine in his patients.

In summary, patients with no evidence of mitral valve prolapse or a hyperkinetic circulation who are diagnosed as having neurocirculatory asthenia also appear to have an excessive activity of alpha-adrenergic receptors in their blood vessels. Further studies are needed on this group of patients since many in the past have included patients with mitral valve prolapse and with a hyperkinetic circulation.

D. Anxiety Neurosis

10. Loc. cit.
38. Loc. cit.
39. Loc. cit.
40. Loc. cit.
41. Loc. cit.
42. Loc. cit.

Patients with debilitating cardiovascular symptoms and abnormal electrocardiograms who have been treated by psychiatrists are now being reevaluated as to the etiology of their symptoms. It has been found that many patients who are being treated for panic disorders and various phobias have mitral valve prolapse demonstrated by echocardiography. However, it is not clear whether the incidence of mitral valve prolapse is any higher in this group than in the normal population since the criteria for making the diagnosis are not always the same and since it is a rather common lesion.

90. Gorman, J.M., A.F. Fyer, J. Gliklich, D. King, D.F. Klein: Effect of imipramine on prolapsed mitral valves of patients with panic disorder. Am. J. Psych. 138:977, 1981.
91. Evans, D.L., K. Kalina: Effect of phenelzine on the prolapsed mitral valve in a patient with agoraphobia with panic attacks. J. Clin. Psychopharm. 3:36, 1983.

It is of great interest that psychiatrists are now treating patients with drugs which also affect the cardiovascular control areas in the brain. In patients treated with either imipramine, a tricyclic antidepressant, or phenelzine, a monamine oxidase inhibitor, their symptoms have improved with no effect on the degree of mitral valve prolapse. It is possible that both of these drugs are relieving symptoms by correcting an abnormality of central autonomic control of the cardiovascular system.

V. PATHOPHYSIOLOGY OF THE CARDIOVASCULAR DYSAUTONOMIAS

The functional disorder in the cardiovascular dysautonomias may be due to abnormal afferent input from receptors or input from higher centers, improper central processing in the cardiovascular areas with inappropriate discharge of efferent sympathetic and parasympathetic activity, or abnormal end organ responses to released transmitter substances. At present, it would appear that abnormal processing in the cardiovascular areas is the most likely culprit in these syndromes.

92. Reis, D.J.: Experimental central neurogenic hypertension from brainstem dysfunction: Evidence for a central neural imbalance hypothesis of hypertension. In: Brain, Behavior and Bodily Disease, ed. by H. Weiner, M.A. Hofer, A.J. Stunkard. New York: Raven Press, p. 229, 1981.
93. Reis, D.J., A.R. Granata, T.H. Joh, C.A. Ross, D.A. Ruggiero, D.H. Park: Brain stem catecholamine mechanisms in tonic and reflex control of blood pressure. Hypertension 6 (Suppl. II):II-7, 1984.
94. Shepherd, J.T., G. Mancia: Reflex control of the human cardiovascular system. Rev. Physiol. Biochem. Pharmacol., Vol. 105, in press, 1986.

As has previously been discussed in this Grand Rounds, the central nervous system plays a vital role in regulating the cardiovascular system. For many years, cardiologists and cardiovascular physiologists had considered the important cardiovascular control areas as a "black box" and had not applied new information derived from neurophysiological studies in their understanding of the normal and abnormal function of the heart and blood vessels. Recently, however, Reis and his associates have used neurophysiological techniques in an attempt to unravel the mystery of essential hypertension.

Shepherd and Mancia have recently presented a description of cardiovascular control which is more current and a diagram of these concepts is shown in Figure 31.

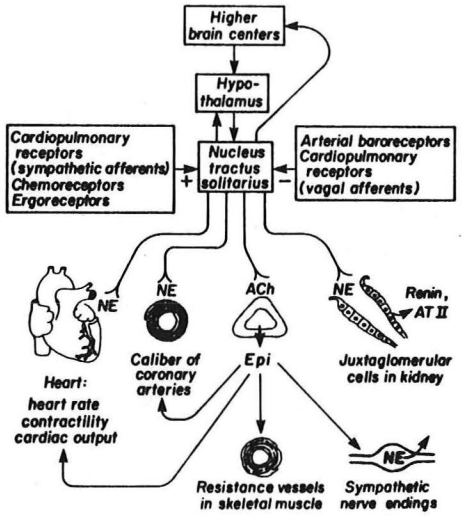

Fig. 31

The nucleus tractus solitarius receives input from cardiopulmonary receptors (sympathetic or spinal afferents), arterial chemoreceptors and skeletal muscle ergoreceptors which are excitatory and cause pressor responses, and from arterial baroreceptors, cardiopulmonary receptors (vagal afferents) which are inhibitory and cause depressor responses. This area also receives information from the hypothalamus and higher brain centers. Efferent nerve fibers from this area project to the hypothalamus, higher brain centers and also to areas which determine the patterns of sympathetic outflow to the heart and blood vessels. Cardiovascular control by the parasympathetic system is not shown in this diagram.

A more detailed description of the control of sympathetic and parasympathetic activity to the heart and blood vessels has been described by Reis. A schematic diagram of his model is shown in Figure 32.

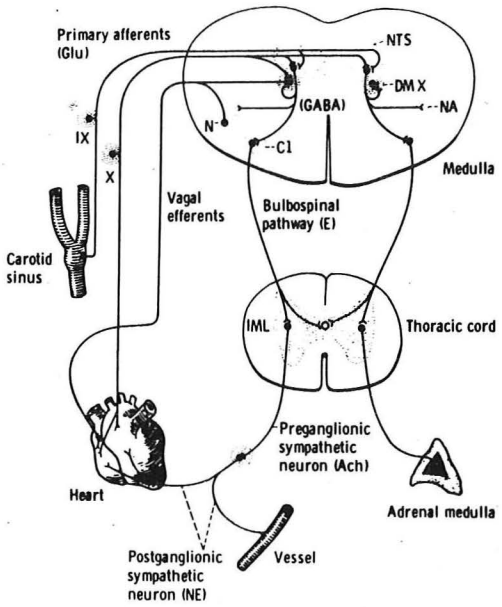

Fig. 32

Primary afferents from the carotid sinus and the aortic baroreceptors terminate in the nucleus tractus solitarius (NTS) of the medulla. As shown in the previous figure, afferents from receptors located in other sites (heart, lungs, and skeletal muscle) also terminate in this same area. Nerve fibers from the nucleus tractus solitarius terminate the dorsal motor nucleus (DM X) which activates the parasympathetic system and communicate with the intermediolateral horn cells (IML) of the thoracic spinal cord (via a bulbospinal pathway) which activates the sympathetic nervous system. An important area of research at the present time is to identify the neurotransmitters which play important roles in these cardiovascular control areas.

Many of the drugs which have improved the symptoms of patients with cardiovascular dysautonomias may act in medullary sites which are important in cardiovascular control. Clonidine, for example, is thought to act on alpha-adrenergic receptors on cells in the region of the ventrolateral medulla. Thus, it may be that the imbalances of sympathetic and parasympathetic activity which have been demonstrated in patients with cardiovascular dysautonomias may be due to improper function of the cardiovascular control areas in the brain.

57. Loc. cit.

In 1944, Starr, after studying patients with neurocirculatory asthenia, stated

> "I am much impressed with the analogy between neurocirculatory asthenia and another and more familiar abnormality of adjustment, the ordinary clumsiness of muscular movements. The person who is clumsy suffers from a true disability.... It is in no sense a disease, for it affects neither health nor duration of life.
>
> All these statements seem equally true for neurocirculatory asthenia, which may be thought of as clumsiness of the circulation."

Clumsiness of the circulation or, more specifically, a lack of precise and proper responses in the autonomic nervous system controlling the heart and blood vessels may well be the primary defect in the confusing syndrome of cardiovascular autonomic imbalance.

VI. CONCLUSIONS

"Where are the Diseases of Yesteryear?" (Wooley, Ref. 21) continues to be a very provocative and interesting question. If our patient of 1953 was admitted today, she would be complaining of the same symptoms, have the same electrocardiographic finding, and have the same basic pathophysiology. However, she would probably be given a different diagnosis and her problem would be somewhat better understood. Her predicted quantity of life would be the same now as then, but hopefully her quality of life would be improved. For example, she would now be considered treatable by an understanding cardiologist and not only treatable by our psychiatry colleagues.

The syndromes of cardiovascular autonomic imbalance may prove to be experimental models provided by nature which will enable clinical cardiovascular investigators to provide us with a better understanding of the precise control and regulation of the heart and blood vessels by the autonomic nervous system.