Editorial

Diabetic Cardiopathy

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Recently the terms diabetic cardiopathy and diabetic cardiomyopathy have appeared in medical literature. These terms imply the existence of a specific diabetic heart disease, a new nosological entity that has been growing out of several studies performed the last few years by research workers in diabetes, in heart disease or in both.

The reason for the present upsurge of cardiac research in diabetes is partly the realization that all too little serious work has been done in this important field in the past, and partly the introduction of new techniques and methods which can be applied to the problem of diabetes and the heart.

The fact that there is a heart problem in diabetes has been known for many years. *Epidemiological studies* published 20 years ago showed that the incidence of myocardial infarction was 2–3 times higher among diabetics than among non-diabetics. The acute as well as the long-term mortality of myocardial infarction was also 2–3 times higher in the diabetic population. Recent analyses of the ongoing Framingham study focussing on blood lipids and blood pressure suggest “that diabetes promotes coronary disease in some unique fashion outside the usual atherogenic mechanisms of hyperlipemia and hypertension” [1].

Until recently there have been only few exact studies of cardiac function or cardiac disease in diabetes mellitus. This was due inter alia to the old widespread belief that the heart disease of diabetic patients was “simply coronary atherosclerosis”, just as other macrovascular disease, common in diabetics, was “just atherosclerosis”. The high incidence in diabetics was explained (away) by phrases such as “diabetes enhances the development of atherosclerosis”. In the last few years important information about the state of the heart in diabetes mellitus has been provided by clinical studies with non-inva-

sive techniques, by histological studies of hearts from old and young subjects, by various types of study of the large vessels in general, by observations and experiments in animal models, and also by investigations elucidating the role of the autonomic nervous system in controlling the function of the heart.

The new *non-invasive techniques* for studying left ventricular function in patients without valvular disease have been used to study the diabetic heart. Most of the results available are obtained with the systolic time interval technique (STI), carefully discussed in a recent critical review by Lewis et al. [2]. Regan and co-workers have described a characteristic pattern occurring in many diabetic patients, consisting in a shortening of the left ventricular ejection time and a prolongation of the pre-ejection period, resulting in a pronounced increase in the ratio between these two time intervals [3]. Some patients with this STI pattern had symptoms suggesting coronary disease, but normal coronary arteriograms. In studies by the same group of workers, using cardiac catheterisation, results were obtained which supported the interpretation of the STI studies, namely that the heart muscle is abnormally stiff in diabetic patients [4]. These authors previously reported similar results in studies of alloxan diabetic dogs [5].

Quite recently Sanderson et al. [6], using echocardiography, reported abnormalities in 17 of 23 young diabetics most of them with retinopathy. The last point focusses on the well-known correlation between the duration of diabetes and diabetic vascular disease in general. Such a correlation has not yet been demonstrated with these cardiovascular techniques, but it is hard to imagine that it should not obtain in the heart. This is particularly true with respect to the beautiful studies of the exercise electrocardiogram, performed several years ago by Karlefors [7] which showed this relationship in young

patients with differing duration of diabetes. Sufficiently large and well defined groups of patients of various ages, with various durations of diabetes and with various constellations of other micro- and macrovascular disease will now have to be studied with the new simple and non-invasive techniques.

The *histology of cardiac structures* in diabetes has been reevaluated, employing quantitative and semi-quantitative methods. In old diabetics Ledet found more fat and calcium in the extramural coronary arteries, especially in the most peripheral part, than in a non-diabetic control group. There was also more PAS positive material, but the amount of collagen was normal [8].

A study by the same author of the hearts from young diabetic patients, dying at an average age of 38 years, after an average of 22 years of diabetes, showed stronger PAS-positive staining with a normal area of PAS-positive material in the small intramural arteries than in the control series. The number of media cells was increased. Surprisingly, there were no changes in the capillaries. Three types of connective tissue accumulation were described: interstitial, perivascular and focal scarlike accumulations. All three types seem to occur more commonly and more extensively in the heart from young diabetic patients [9]. Similar types of changes had been observed by Regan et al. in twelve hearts from diabetic patients [10].

Crall and Roberts [11] reported on quantitative studies of 9 hearts from long-term juvenile diabetic patients and 9 comparable control hearts. A more than 50 per cent narrowing of the extramural coronary arteries was found to occur over 47 per cent of the entire length of the four coronary arteries from the diabetics as against only 1 per cent of the non-diabetics. Strong PAS-positive staining was seen more often in the smaller coronary branches of diabetics than of non-diabetics, as in Ledet's study [9].

However, the architecture of the vascular wall, especially the localization of the calcium deposits in the large extramural coronary arteries of diabetic patients, has not yet been studied. It ought to be, for we know that the large arteries in the legs of long-term diabetic patients are characterized by linear calcification, localized in the tunica media, not by the spotty calcification seen in non-diabetics with atherosclerosis [12–15]. Neubauer has shown that there is a positive correlation between the degree of carbohydrate intolerance and the quantitatively estimated amount of linear – not of spotty – calcification in elderly patients with and without manifest diabetes [15].

A paper by Root strongly suggesting that large vessel disease in diabetes mellitus has a specific ele-

ment in it has been available in the literature for many years, but is often overlooked. At the time of that study – 1949 – before distinction was made between spotty and linear calcification, a very close correlation was shown between large vessel calcification of the lower extremities and duration of diabetes [16]. What makes this study really significant is the fact that it was carried out on 83 juvenile diabetics within the narrow age limit of 26–34 years! In the various diabetes duration groups calcification was noted as follows: 0–10 years; 0%; 10–15 years, 33%; 15–20 years, 55%; 20–28 years, 83%; – exactly the same kind of relationship that is known from so many studies of diabetic microangiopathy. New detailed studies of the structure of the coronary artery wall and the topography of the calcium deposits are needed to see if the situation in the large vessels of the heart is similar to that of the large vessels of the extremities.

Recent studies in animal models have dealt with cardiac structures in the heart of long-term diabetic rats, and with myomedial cells from the rabbit aorta. Baandrup et al. [17] found an increase in the amount of connective tissue and of the number of media cells of the cardiac vessel after 9 months of *streptozotocin diabetes in the rats*. These results are similar to those described above, obtained in studies of hearts from young long-term diabetics [9].

Ledet has published a series of studies that show the presence of a growth promoting factor in the serum from diabetic man or rabbit stimulating the in vitro growth of *rabbit aortic myomedial cells* [18–22]. The effective agent in diabetic serum seems to be a large molecule with a molecular weight of between 3000 and 30,000. A similar effect is obtained by addition of small amounts of growth hormone to the growth medium. The growth promoting effect of diabetic serum disappears after addition of growth hormone antibody. This last mentioned fact may be of interest in connection with the hypothesis that growth hormone is in some way implied in the pathogenesis of diabetic angiopathy [23]. This hypothesis has been supported very recently by studies showing an increase of the thickening of glomerular basement membrane in streptozotocin diabetic rats given growth hormone in doses producing body growth but not elevation of blood glucose, in comparison to that of diabetic rats not given growth hormone [24].

Symptomatic *autonomic nervous system disease* occurs in some long-term diabetic patients, and asymptomatic autonomic nervous system abnormalities can be shown in many. Wheeler and Watkins introduced a new and very simple method for studying the function of the autonomic nervous system of the heart, determining the variation of the beat to

beat time by electrocardiography. During deep breathing a marked decrease of the variation was found in patients with signs or symptoms of autonomic neuropathy [25]. Gundersen and Neubauer, using the same technique but without deep breathing periods determined 3 types of variations, all of which decreased gradually with increasing duration of diabetes [26].

The biochemical correlates of these functional abnormalities appear from Christensen and co-workers' studies showing a reduction of the catecholamine content of the blood [27] and of cardiovascular tissue in long-term diabetes [28].

These various results and ideas emanating from clinical studies, histological and biochemical studies as well as from animal experiments during recent years cannot be put together to form a well organized and convincing story about the heart in diabetes mellitus. They do, however, make it reasonable to postulate, as a working hypothesis for future endeavours, the existence of a diabetic heart disease. At the moment it looks like a combination of diabetic microangiopathy, diabetic macroangiopathy and diabetic neuropathy. On top of that there are, of course, atherosclerotic changes in elderly patients.

As to nomenclature it seems to us that the term diabetic cardiopathy is better, because broader, than diabetic cardiomyopathy which may imply the idea of a non-vascular heart disease.

References

- Kannel, W. B.: Role of diabetes in cardiac disease: conclusions from population studies. In: Diabetes and the heart. Zonerach, S. (Ed.), pp. 97–112. Springfield, Ill.: Charles C. Thomas 1978
- Lewis, R. P., Rittgers, S. E., Forester, W. F., Boudoulas, H.: A critical review of the systolic time intervals. *Circulation* **56**, 146–158 (1977)
- Regan, T. J., Lyons, M. M., Ahmed, S. S., Levinson, G. E., Oldewurtel, H. A., Ahmad, M. R., Haider, B.: Evidence for cardiomyopathy in familial diabetes mellitus. *J. Clin. Invest.* **60**, 885–899 (1977)
- Regan, T. J., Levinson, G. E., Oldewurtel, H. A., Frank, M. J., Weisse, A. B., Moschos, C. B.: Ventricular function in noncardiacs with alcoholic fatty liver: Role of ethanol in the production of cardiomyopathy. *J. Clin. Invest.* **48**, 397–407 (1969)
- Regan, T. J., Ettinger, P. O., Khan, M. I., Jesrani, M. U., Lyons, M. M., Oldewurtel, H. A., Weber, M.: Altered myocardial function and metabolism in chronic diabetes mellitus without ischemia in dogs. *Circ. Res.* **35**, 222–237 (1974)
- Sanderson, J. E., Brown, D. J., Rivellese, A., Kohner, E.: Diabetic cardiomyopathy? An echocardiographic study of young diabetics. *Br. Med. J.* **1978 I**, 404–407
- Karlefors, T.: Exercise tests in male diabetics. I. Electrocardiographic study. *Acta Med. Scand. [Suppl. 449]* **180**, 3–18 (1966)
- Ledet, T.: Histological and histochemical changes in the coronary arteries of old diabetic patients. *Diabetologia* **4**, 268–272 (1968)
- Ledet, T.: Diabetic cardiopathy. Quantitative histological studies of the heart from young juvenile diabetics. *Acta Pathol. Microbiol. Scand. [A]* **84**, 421–428 (1976)
- Regan, T. J., Ahmed, S. S., Levinson, G. E., Oldewurtel, H. A., Ahmad, M. R., Haider, B., Lyons, M. M.: Cardiomyopathy and regional scar in diabetes mellitus. *Trans. Assoc. Am. Physicians* **85**, 217–223 (1975)
- Crall, F. A., Roberts, W. C.: The extramural and intramural coronary arteries in juvenile diabetes mellitus. Analysis of nine necropsy patients aged 19 to 38 years with onset of diabetes before age 15 years. *Am. J. Med.* **64**, 221–230 (1978)
- Ferrier, T. M.: Radiologically demonstrable arterial calcifications in diabetes mellitus. *Aust. Ann. Med.* **13**, 222–228 (1964)
- Ferrier, T. M.: Comparative study of arterial disease in amputated lower limbs from diabetic and non-diabetics. (With special reference to feet arteries). *Med. J. Aust.* **1**, 5–11 (1967)
- Christensen, N. J.: Muscle blood flow, measured by xenon¹³³ and vascular calcifications in diabetics. *Acta Med. Scand.* **183**, 449–454 (1968)
- Neubauer, B.: A quantitative study of peripheral arterial calcification and glucose tolerance in elderly diabetics and non-diabetics. *Diabetologia* **7**, 409–413 (1971)
- Root, H. F.: Diabetes and vascular disease in youth. *Am. J. Med. Sci.* **217**, 545–553 (1949)
- Baandrup, U., Ledet, T., Rasch, R.: Experimental diabetic cardiopathy preventable by insulin treatment. (Submitted for publication)
- Ledet, T., Fischer-Dzoga, K., Wissler, R. W.: Growth of rabbit aortic smooth-muscle cells cultured in media containing diabetic and hyperlipemic serum. *Diabetes* **25**, 207–215 (1976)
- Ledet, T.: Growth hormone stimulating the growth of arterial medial cells in vitro. Absence of effect of insulin. *Diabetes* **25**, 1011–1017 (1976)
- Ledet, T.: Growth of rabbit aortic smooth muscle cells in serum from patients with juvenile diabetes. *Acta Pathol. Microbiol. Scand. [A]* **84**, 508–516 (1976)
- Ledet, T.: Growth hormone antiserum suppresses the growth effect of diabetic serum. Studies on rabbit aortic medial cell cultures. *Diabetes* **26**, 798–803 (1977)
- Ledet, T., Vuust, J.: Studies on the effect of diabetic serum on the synthesis of procollagen type I and type III, and glycoprotein by aortic medial cell culture. *Acta Endocrinol. [Suppl. 219] (Kbh.)* **88**, abstract 52 (1978)
- Lundbæk, K.: Growth hormone's role in diabetic microangiopathy. *Diabetes* **25** [Suppl. 2], 845–849 (1976)
- Østerby, R., Seyer-Hansen, K., Gundersen, H. J. G., Lundbæk, K.: Growth hormone enhances basement membrane thickening in experimental diabetes. A preliminary report. *Diabetologia* **15**, 487–489 (1978)
- Wheeler, T., Watkins, P. J.: Cardiac denervation in diabetes. *Br. Med. J.* **1973 IV**, 584–586
- Gundersen, H. J. G., Neubauer, B.: A long-term diabetic autonomic nervous abnormality. *Diabetologia* **13**, 137–140 (1977)
- Christensen, N. J.: Plasma catecholamines in long-term diabetics with and without neuropathy and in hypophysectomized subjects. *J. Clin. Invest.* **51**, 779–787 (1972)
- Neubauer, B., Christensen, N. J.: Norepinephrine, epinephrine and dopamine content of the cardiovascular system in long-term diabetics. *Diabetes* **25**, 6–10 (1976)

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