EDITORIALS

The Charles H. Best Institute

The dedication of The Charles H. Best Institute at the University of Toronto in September was an event of major importance in the scientific world. It is natural for the readers of this Journal to be especially interested because of the discovery of insulin in this location, because of the research concerning diabetes and related problems which have been carried on since then under the leadership of one of the partners in this epoch-making discovery and because of the promise of progress in this field which can be expected in the future with the facilities which are now available in the new Institute. The members of the American Diabetes Association also have a strong personal interest in honors bestowed on the former president of the Association whose name appears on the building. For this reason, it is gratifying to present in the Journal a record of the proceedings as well as the speeches made at the meetings held at the time of the opening of The Institute.

The program began in the afternoon of September 15, with a special convocation at which the University of Toronto conferred honorary degrees on five scientists and physicians of world-wide reputation. Addresses were delivered by two distinguished guests, Sir Lionel Whitby and Sir Henry Dale. The official opening of The Institute then took place. At this time Professor Best was presented with a portrait of himself which now hangs in the hall of the building.

In the evening, members of the faculty and their many guests were entertained by the University at a Banquet in the Great Hall of Hart House. Among the guests who had come from various parts of Canada, the United States, Europe and South America were three winners of the Nobel Prize, (Dale, Houssay and Adrian) and three holders of the Order of Merit, (Dale, Adrian and Penfield), the highest distinction held by a total of 24 in the British Empire.

On the second day, the first scientific program was presented at The Institute. Papers were read by Prof. Joseph P. Hoet, Louvain, Belgium and R. D. Lawrence, London, England. Professor Best submitted to distinguished scientists who were present the following question: Which of your scientific investigations has given you the most satisfaction and pleasure? Replies were given by Prof. E. D. Adrian, President of the Royal Society of London, Sir Henry Dale, past President of the Royal Society, Dr. Bernardo A. Houssay, Nobel Prize winner in medicine, Buenos Aires; Dr. Elliott P. Joslin, Boston, Honorary President, American Diabetes Association; Dr. Wilder Graves Penfield, Director of the Neurological Institute, McGill University, Montreal and Sir Lionel Whitby, Vice-Chancellor, University of Cambridge. The information contained in the replies gives an indication of the variety of methods by which scientific progress may be achieved.

The Charles H. Best Institute will be the home of teaching and research in physiology at the University of Toronto. It will provide increased accommodations and facilities for both the Department of Physiology and the Banting and Best Department of Medical Research. Its influence will be felt far beyond the limits of the University and the city. Students trained as undergraduates and graduates by Professor Best and his associates will be enriched by the scientific viewpoint derived from this experience as they leave to carry on their careers in the practice of medicine, in teaching and in laboratory investigation throughout Canada and other parts of the world.

THE DEGENERATIVE COMPLICATIONS OF DIABETES

CURRENT CONCEPTS OF PATHOGENESIS

The specific lesions of the retina and the renal glomerulus mark diabetic vascular disease as something apart from all other varieties. In searching for its cause, we must look further than investigators who are trying to discover why so many middle-aged Americans without diabetes die every year of coronary disease. The diabetic too is subject to coronary atherosclerosis, and perhaps for the same reasons, but it seems more likely that the key to his vascular problem lies in finding the cause of the capillary lesions of the eye and kidney to which he is almost uniquely susceptible.

One of the major questions is whether such disorders of the blood vessels are the result of hereditary or constitutional influences, transmitted along with the tendency toward diabetes, or whether they are the result of diabetes itself. The great majority of vascular abnormalities appear only after 10 to 20 years of diabetes. Therefore, the occasional finding of retinopathy at the time, or shortly after, glycosuria is first discovered suggests that some factor beside or in addition to diabetes was responsible. The observation loses some significance when it is realized how difficult it is to place precisely the actual onset of diabetes in such cases. The fact is that the question of genetic and allied factors is one on which we have no direct evidence.

On the other hand, it has been established in both man and animals that premature vascular disease occurs in the presence of diabetes alone under conditions which almost certainly exclude inherited or constitutional influences. Lawrence[1] refers to such lesions in patients with diabetes produced by disease, such as hemochromatosis and chronic relapsing pancreatitis. Degeneration of the aorta[2] and coronary arteries[3] has been observed in the experimental diabetes of dogs, and lesions resembling intercapillary glomerulosclerosis have been reported in pituitary diabetic dogs[4,5] and in partially pancreatectomized[6] as well as alloxanized[7] diabetic rats. The implication of these observations is reinforced by the fact that the incidence of degenerative disorders is more closely related to the duration of diabetes than to any other element of the disease, suggesting, again, that there is something about diabetes itself which, acting over a long period of time, leads to damage of the blood vessels.

SIGNIFICANCE OF SERUM LIPIDS

What this something is has not been determined. It is currently the fashion to regard the serum lipids as the number one enemy of the arteries. In both diabetics and nondiabetics it has been shown repeatedly that there is some overall *association* between high levels of cholesterol and the presence of atherosclerosis. There are, however, several points to be borne in mind. First, there are many cases in which there is no such correlation. Second, association is not synonymous with cause. Third, hypercholesterolemia in the *treated* diabetic is neither so common nor so marked as many have supposed. Fourth, despite the production of atherosclerosis in five species of animals by methods involving cholesterol feeding, no one has reported retinal lesions. Perhaps they have not been sufficiently looked for. I can only say that I have searched for them in vain, in cholesterolized rabbits which later showed severe atherosclerosis at autopsy, and in a number of Dr. Forest Kendall's atherosclerotic dogs with serum cholesterol levels maintained for many months in the neighborhood of 1000 mg. per cent by cholesterol and thiouracil feeding.[8] It should not require emphasis that, until someone succeeds in producing retinal and glomerular lesions as well as atherosclerosis in experimental animals, the complete picture of diabetic vascular disease cannot be said to have been duplicated.

LIPOPROTEINS

Studies of the lipoproteins have closely resembled those of cholesterol in showing a general but decidedly inconstant relationship in both diabetics and nondiabetics between blood levels and the incidence of atherosclerosis. Here, too, it has not been possible to demonstrate that this relationship represents cause and effect. Keiding[9] and his colleagues have reported elevated concentrations of serum lipoproteins in patients with diabetic retinopathy, but it is not stated whether these patients also had intercapillary glomerulosclerosis, and since serum lipids tend to be high in this syndrome as well as in nephritis of other origins, it is difficult to evaluate the significance of their observation.

FATTY ACIDS

The recent investigations of Hirsch, Phibbs and Carbonaro[10] are perhaps the most interesting of any in the field of lipids. Studying especially the esterified fatty acids of the blood in diabetic patients, they have found that these substances, unlike cholesterol and the lipo-

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proteins, increase rather sharply after a fat meal, that such increases are appreciably greater when the blood sugar is high than when it is normal, and that even the fasting levels of the esterified fatty acids, when determined day after day, go up and down in parallel with the blood glucose. For those who believe that atherosclerosis is caused by disturbances in fat metabolism, and that control of the blood sugar is the way to prevent it, here is an experiment that ties both ideas together into a neat and tempting package. The trouble is that no one has proved that hyperlipemia causes atherosclerosis in man. If this is ever established, the work of Hirsch and his colleagues will represent a contribution of major importance, although its relation to the capillary lesions of diabetes remains obscure.

BLOOD SUGAR

This brings us to the subject of hyperglycemia. That an excess of circulating glucose alone is injurious to blood vessels has not been seriously entertained by most investigators, although it must be admitted that definite proof is lacking. The possibility exists, however, that some substance associated with high glucose levels may be pathogenic. Perhaps the esterified fatty acids are one example. It may be that another is the mucopolysaccharides of the blood. Much interest attaches to these compounds today, for they have been found in both the microaneurysms of the retina [11] and the glomerulus of the Kimmelstiel-Wilson kidney,[12] a fact which, together with certain similarities in structure, more than hints at a common pathogenesis. It has been suggested, indeed, that lesions of the capillaries and smaller arteries may occur in other places where they have been difficult to demonstrate by ordinary technics, and that they may be the primary manifestation of vascular disease. Ditzel,[13] for example, utilizing microscopic examination of the brilliantly illuminated conjunctiva, has reported abnormalities of the capillaries and venules in diabetic patients and even in their children. Megibow and his associates [14] have shown by microplethysmographic methods that there is impairment of circulation in the toes of some diabetics in whom available methods fail to show disease of the more proximal arteries. Vasospastic influences were excluded by the use of tetraethylammonium. Since these studies were carried out in living patients, it was not possible to confirm the integrity of the larger vessels by histologic means.

GLUCOSAMINE

Returning to the mucopolysaccharides, it should be said for purposes of orientation that this term is applied to such substances as chondroitin sulfate (a component of cartilage), mucoin sulfate, hyaluronic acid (the intercellular cement substance) and heparin. Chemically, a mucopolysaccharide is a polysaccharide containing a hexosamine. One of the hexosamines is glucosamine. Glucosamine, which is present in the blood in a protein-bound polysaccharide, can be measured by chemical means, thus providing some estimate of the concentration of serum polysaccharides. It must be stated that the methods for determining this substance are rather tricky and possess a somewhat uncertain degree of specificity although they do yield fairly reproducible results.

In 1948 Jacobs [15] reported that the blood glucosamine levels were higher in diabetic than in nondiabetic individuals, and further that among the diabetics they varied directly with the blood sugar. In 1953 Berkman and associates[16], although failing to confirm this relationship, found elevated levels of protein-bound polysaccharides and glucosamine in the blood of diabetics with degenerative vascular disease compared with diabetics without such complications. The presence of mucopolysaccharides in the specific histologic lesions of the diabetic makes this finding one of unusual interest. Enthusiasm, however, must be tempered, as the authors are careful to point out, by the knowledge that concentrations of blood glucosamine are increased in a number of disorders manifested by tissue destruction and repair—processes which surely take place over many square centimeters of intima in advanced arteriosclerosis. Thus it is possible that hyperglucosaminemia may be a result rather than a cause of vascular disease. At any rate these investigations provide us with a new perspective in the search for the cause of the mysterious capillary lesions of the eye and kidney.

PITUITARY AND ADRENALS

This search has been given fresh impetus by the finding of Becker[17] of capillary aneurysms and Kimmelstiel-Wilson lesions in alloxan diabetic rabbits treated with corticotropin. Attempts to produce the lesions with alloxan alone have been unsuccessful. Rabbits treated with cortisone or Compound F alone showed the glomerular changes but not the retinal. Becker's working hypothesis is that both insulin deficiency and adrenocortical overactivity are factors in the development of these lesions. This hypothesis receives some support from a few clinical observations. Two cases are reported by Lawrence[18] and three by Becker[17] in which retinopathy first appeared or became much worse during

pregnancy and subsided after delivery. Rich[19] refers to the finding at autopsy of lesions of the Kimmelstiel-Wilson type in a nondiabetic patient treated for a prolonged period with corticotropin. Poulsen[20] has described a case of well established diabetic retinopathy from which the patient recovered following the onset of Simmond's disease.

Studies of the retina in patients with acromegaly and diabetes and with Cushing's syndrome and diabetes might be expected to shed some light on this subject. Several years ago, the records of a number of such cases were reviewed with somewhat disappointing results.[21] Of 16 patients with acromegaly, three had diabetes, and of these, two had diabetic retinopathy. Among 10 patients with Cushing's syndrome there were seven with diabetes or impairment of glucose tolerance; of these only one had retinopathy and this was of the hypertensive, not the diabetic, type. A larger number of these important cases must be studied before we can come to any conclusions regarding the relationship of the anterior pituitary and the adrenal cortex to the renal and retinal lesions of diabetic patients.

CONCLUSION

Thus, we must end this discussion, as we have ended all others like it, with the conclusion that, despite encouraging advances, the cause of degenerative vascular disease in diabetes remains unknown. Until it is known, it seems but the part of wisdom to employ against this destroyer of blood vessels the only weapon we possess, imperfect as it is—the careful control of blood sugar.

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REFERENCES

1 Lawrence, R. D.: Types of human diabetes. Brit. M. J. *1*:373, February 24, 1951.

2 Dragstedt, L. R.: The role of the pancreas in arteriosclerosis. Biol. Symposia *11*:118, 1945.

3 Ricketts, H. T.: Unpublished observations.

4 Lukens, F. D. W., and Dohan, F. C.: Experimental pituitary diabetes of five years' duration with glomerulosclerosis. Arch. Path. *41*:19-24, January 1946.

5 Conn, J. W.: Personal communication.

6 Foglia, G. V., Mancini, R. E., and Cardeza, A. F.: Glomerular lesions in the diabetic rat. Arch. Path. 50:75, 1950.

7 Mann, G. V., Goddard, J. W., and Adams, L.: The renal lesions associated with experimental diabetes in the rat. Am. J. Path. *27*:857, 1951.

8 Steiner, A. and Kendall, F. E.: Atherosclerosis and arteriosclerosis in dogs following ingestion of cholesterol and thiouracil. Arch. Path. *42*:433, 1946.

9 Keiding, N. R., Mann, G. V., Root, H. F., Lawry, E. Y., and Marble, A.: Serum lipoproteins and cholesterol levels in normal subjects and in young patients with diabetes in relation to vascular complications. Diabetes *1*:434-440, December 1952.

10 Hirsch, E. F., Phibbs, B. P., and Carbonaro, L.: Parallel relation of hyperglycemia and hyperlipemia (esterified fatty acids) in diabetes. Arch. Int. Med. *91*:106, January 1953.

11 Friedenwald, J. S.: Diabetic retinopathy. Diabetes *2*:237, *May-June 1953.*

12 McManus, J. F. A.: The development of intercapillary glomerulosclerosis. Proc. Am. Diabetes A.: 9:303, 1949.

13 Ditzel, J.: Vascular and hemodynamic changes in the smaller blood vessels of diabetics and prediabetics. Unpublished. Paper read at the Thirteenth Annual Meeting of the American Diabetes Association, New York, May 31, 1953.

14 Megibow, R. S., Megibow, S. J., Pollack, H., Bookman, J. J. and Osserman, K.: The mechanism of accelerated peripheral vascular sclerosis in diabetes mellitus. Am. J. Med. *15*:322, September, 1953.

15 Jacobs, H. R.: The bound glucosamine of serum mucoid in diabetes mellitus: fluctuations observed under the influence of insulin. J. Lab. & Clin. Med. *34*:116, January, 1949.

16 Berkman, J., Rifkin, H. and Ross, G.: The serum polysaccharides in diabetic patients with and without vascular disease. J. Clin. Invest. *32*:415, May, 1953.

17 Becker, B.: Diabetic retinopathy. Ann. Int. Med. *37*:273, August, 1952.

18 Lawrence, R. D.: *Acute retinopathy without hyperiesis* in diabetic pregnancy. Brit. J. Ophth. *32*:461, 1948.

19 Rich, A. R.: Johns Hopkins Hosp. Clin.-Path. Conf., February 1952, Quoted by Friedenwald, J. S.[11]

20 Poulsen, J. E.: Recovery from retinopathy in a case of diabetes with Simmond's disease. Diabetes, *2*:7, January-February, 1953.

21 Ricketts, H. T.: The problem of vascular disease in diabetes. Proc. Am. Diabetes A. *8*:151, 1948.