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REVIEW ARTICLE

Late Complications of Diabetes. A Continuing Challenge

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It is appropriate that an Elliott P. Joslin Memorial Lecture be given at a meeting of the European Association because throughout his long life, Dr. Joslin kept in close touch with European medicine by personal contact and by faithful reading of the literature, which fortunately he was able to do in the original, at least in German and French. In all, he made seventeen trips to Europe, the first in 1888 at the age of 19, and the last in 1961 when, at the age of 92, he participated in the Fourth Congress of the International Diabetes Federation in Geneva. It was on one of his early visits to Europe, while on holiday in the Austrian Alps, that he met a remarkable young woman from Boston, Miss Elizabeth Denny, who later became his wife. Dr. Joslin treasured the friendship of his colleagues on this side of the Atlantic and, indeed, throughout the world. In the first edition of his book, "The Treatment of Diabetes Mellitus", published in 1916, he wrote that "Professors Naunyn, Von Noorden, Friedrich von Müller, Magnus-Levy, and Falta all have helped me with my cases". He was a great admirer of Bernard Naunyn and it was to Naunyn, then in Strasbourg, that he took his mother for advice in the treatment of her diabetic condition.

It is instructive to examine the first edition of his book to see what complications of the disease presented the greatest challenge to clinicians six decades ago. Understandably, in that period before the discovery of insulin, the greatest threat was death from diabetic coma. In Joslin's series, from 1894 to 1915, diabetic coma accounted for 273, or 64% of the 426 deaths among 945 patients of all ages [1]. Of 81 patients with onset of diabetes at or under the age of 20 years, only 6 were alive after 4 years of diabetes, and of these young patients, the overwhelming majority died in coma. Next in importance, often leading to ketoacidosis and coma, was infection. The skin was frequently the target, being a prey for slowly-healing wounds, furuncles, and the dreaded carbuncles which carried a mortality of about 50%. Infections of the skin often led to gangrene of a toe or foot. As far as total deaths from infection were concerned, pneumonia and influenza headed the list. On the bright side, even before the advent of insulin, was the experience with tuberculosis, which in Europe prior to the turn of the century accounted for approximately 40% to 50% of the deaths among diabetic patients [2]. As shown in Table 1, even by 1915 this was responsible for only 16, or 3.8% of 426 deaths in Joslin's series.

I have described the situation as it prevailed in one private practice in Boston in 1916 in order to emphasize the contrast with that which confronts us today, namely the problem of long-term complications affecting the vascular and nervous systems. To be sure, such complications were present in the pre-insulin era, but they did not loom large because of the relatively short duration of life after onset of diabetes. Regarding the deaths up until 1916, Dr. Joslin had this to say: "Cardiorenal and vascular changes, uncomplicated by coma, caused the death of 62 cases. Of these, 28 died of heart disease, in 4 instances suddenly with angina pectoris; 14 died of chronic nephritis; 14 from cerebral hemorrhage; 6 of general arteriosclerosis. The average age at death of these patients was sixty-four years." Obviously the patients in this group were those in whom the diagnosis of diabetes had not been made until late in life since the average duration in the entire series was only 4.9 years. As for neuritis, this too at times presented a problem although not to the extent seen today and apparently the diverse manifestations of neuropathy were either not seen or not appreciated. Joslin states that "The type of neuritis almost invariably encountered has occurred in the lower extremities" and he refers to it as "sciatica". He mentions "diminished sensation, pain and tender-

Table 1. Causes of 426 deaths in diabetic patients 1894–1915. Adapted from Joslin [1]

		Number	Percent
Diabetic coma		273	64.0
Cardio-renal vascular		62	14.6
Cardiac	28		
Renal	14		
Cerebral	14		
Other	6		
Infections (non-Tbc)		36	8.5
Pneumonia and influenza	18		
Infection or gangrene, feet	9		
Other	9		
Cancer		17	4.0
Tuberculosis		16	3.8
Miscellaneous		22	5.1
Total		426	100.0

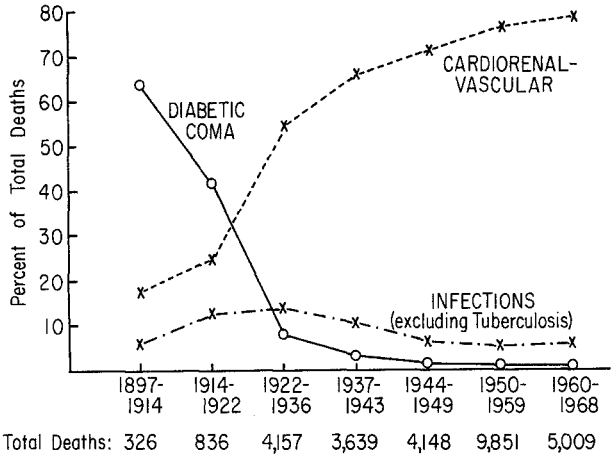

Fig. 1. Causes of death in diabetic patients expressed as percentages of 27,966 total deaths (1897–1968). From Marble [4]

ness" and remarks that it yielded only obstinately to treatment.

Although the epochal work of Banting and Best was done in the summer of 1921 and the first injection of insulin was given to a human diabetic patient on January 11, 1922, it was not until 1923 that it became generally available. In the 50-odd years since that time we have witnessed an ever-changing panorama of events in diabetes. In an attempt to take a broad view of these developments, I have divided arbitrarily the last 54 years into four periods, as shown in Table 2.

I. 1922–36. Triumph over Coma and Infection. Prolongation of Life

In opening an article published after the discovery of insulin, Joslin enthusiastically exclaimed "Insulin is here!", thereby expressing the emotional fervor of clinicians who up until then had witnessed patient after patient succumb to ketoacidotic coma only weeks, months, or at most a few years after the onset of diabetes. Only those with the most stable, least aggressive form of the disease were able to survive for long periods and even then, only by means of rigorous dietary restriction, with resulting undernutrition. Now, with daily injections of insulin, a more liberal food intake became possible and patients lived on and on in apparent health. It seemed as if the diabetes problem had been solved. Indeed, diabetic coma as a cause of death fell from 41.5% of total deaths in 1914–22 to 8.3% in 1922–36. Its place as the leading cause of death was taken by cardiorenal-vascular disease, which in the period of 1922–36 accounted for 54.4% of total deaths, more than double that of 24.6% in 1914–22 and more than treble that of 17.5% prior to 1914 [3]. See Table 3 and Figure 1.

II. 1937–49. Emergence of Long-Term Complications as a Critical Problem

In this second period a greater length of life was favored by the development of insulins with prolonged action and their widespread use beginning in 1937. Deaths from diabetic coma fell still further to 2.7% in 1937–47. In the same period, however, deaths from cardiorenal-vascular disease climbed to 69%.

Although this shift in causes of death is obvious retrospectively, it was actually not until the late 1930's and early 1940's that its impact was fully recognized. A simple fact then became clear, namely that, since ketoacidosis could be prevented and treated successfully with insulin and since infections could be avoided and overcome with insulin and the aid of chemotherapeutic agents and antibiotics just introduced, for the first time in history it was possible for diabetes over a long period of years to demonstrate its deleterious effect upon the body. Diabetes was, as it were, unmasked and forced to show its true colors by virtue of having been granted a longer period of years to exert its effect. Indeed, among Joslin Clinic patients the average length of life after onset of diabetes had grown to 18.7 years for all deceased patients and for those with onset under 20 years and the curve was still pointed upward.

It was not until 1936 that Kimmelstiel and Wilson [5] described the almost unique intercapillary glomerulosclerosis in a now classical paper. Prior to that time, diabetic patients had of course suffered from serious kidney disease, and for a century such had been described by clinicians and pathologists. However, no one had emphasized the characteristic inter-

capillary deposits of glycoprotein which constitute the characteristic nodular, and the less specific diffuse, lesions. No one had correlated these histological findings with the clinical syndrome of proteinuria, edema, renal insufficiency, and hypertension.

In the early 1940's clinicians generally came to realize the importance of diabetic retinopathy. It is true that as far back as 1856, a few years after the introduction of the ophthalmoscope, Jaeger of Vienna recognized the possibly specific character of the abnormal findings. In 1876 Manz, and in 1888 Nettleship described proliferative retinopathy. The characteristic capillary microaneurysms were described by MacKenzie in 1877 and by Nettleship in 1888, but were almost forgotten until their rediscovery by Ballantyne and Loewenstein in 1944 [6, 7]. However, despite these earlier observations, retinopathy was not regarded as a major problem until large numbers of patients after 10, 15 or more years of diabetes began to experience visual impairment.

III. 1950–65. Efforts to Develop Treatment for Angiopathy and Nephropathy

By 1950 the problem of long-term complications of diabetes had become painfully evident. All too frequent were cases of severe retinopathy with visual impairment, nephropathy leading eventually to death, and neuropathy which was at times unresponsive to treatment. Consequently, efforts were made to deal with the complications on a practical basis even though the basic mechanism of their origin remained poorly understood. Many advances have been made in the treatment of complications after they have become evident. I will discuss some of these developments briefly, citing mainly the experience of the Joslin Clinic.

1. Proliferative Retinopathy

In the 1940's and particularly in the 1950's, we were faced with an ever-growing number of patients with proliferative retinopathy which often advanced to the stage of greatly impaired vision or even blindness. This number was to grow so that at present diabetic retinopathy is the second leading cause of new blindness in the United States. In the five years from 1961 to 1966 we, as well as others, tested pituitary ablation as a means of arresting the advancing retinopathy [8]. During this period, 87 Joslin Clinic patients were subjected to surgery, either pituitary stalk section or removal of as much of the hypophysis as could be done. In an additional 55 patients, irradiation of the pituitary was carried out with the Harvard cyclotron. The entire experience may be summarized by stating that in 65 to 70 per cent of patients treated, the visual status was improved or stabilized as noted in short-term follow-up, but this success rate fell to 50 per cent or less in succeeding years. Hence the results were moderately encouraging, but not enough to persuade us to continue such treatment during the past 10 years except for an occasional patient. None has undergone pituitary ablation since 1971. Additional and important considerations have been the multiple endocrine deficiencies produced, the constant need for hormone replacement therapy to preserve health and life, increased sensitivity to insulin, and in many patients, by virtue of long-duration diabetes, death within five years from acute myocardial infarction or other vascular event. A brief survey of the 87 surgically treated patients was carried out in April, 1975. Over an average follow-up period of 12 years, 42 or 75% of 56 males and 17 or 59% of 29 females were dead. The status of two males and two females was not ascertained. As stated by Field [9] who has done pioneer work in this regard and by Fraser and associates of the Hammersmith Hospital group in London [10], there may well be a place for pituitary ablation, but I agree that its use should be restricted to carefully selected patients with special problems.

Toward the end of our pituitary ablation effort, we at the Joslin Clinic began to refer patients with ad-

Table 2. Noteworthy periods in the insulin era

I.	1922–36	Triumph over coma and infection
II.	1937–49	Emergence of long-term complications as a critical problem
III.	1950–65	Efforts to develop treatment for angiopathy and neuropathy
IV.	1966–	Hope for prevention of late complications through restoration of physiologic state

Table 3. Causes of death in 27,966 diabetic patients (experience of Joslin Clinic [3])

Period	Total Deaths	Deaths due to–	
		Diabetic coma %	Cardio-renal vascular disease %
1897–1914	326*	63.8	17.5
1914–22	836	41.5	24.6
1922–36	4157	8.3	54.4
1937–49	7787	2.2	69.0
1950–65	13948	1.0	76.9
1966–68	912	1.0	74.2

* The number of 326 differs from that in Table 1 because of difference in time intervals and further analysis of data

Table 4. Rationale for effect of pan-retinal photocoagulation (from Aiello [11])

1. By direct destruction of retinal tissue, hypoxic areas are converted to anoxic areas, reducing the stimulus for neovascularization
2. The diffusion barrier at the pigment epithelial cell level may be broken, permitting diffusion into the choroidal circulation with reduction of intraretinal edema, thus altering hypoxia and stimulus for neovascularization
3. Hemodynamic changes may be a significant factor in altering direction, rate and volume of blood flow
4. Alteration of specific metabolic factors may prevent the development of vaso-formative factors

vancing retinopathy to ophthalmologists using photocoagulation. The results were sufficiently encouraging that we established an Eye Research and Treatment Unit, named after Dr. William P. Beetham, and in 1967, Dr. Lloyd M. Aiello began the use of the ruby or red laser [11]. He used, and still continues to use in selected patients, a concept of altering the metabolism of the retina by means of multiple (i.e., several hundred) tiny burns around the periphery. This "pan-retinal photocoagulation" is often effective in arresting proliferative retinopathy even in the central part of the fundus to which the laser beam has not been directly applied. (see Table 4).

Experience has shown that in the treated areas, due to the tiny size of the burn points, no blind spots noticeable to the patient are created. Since 1972 Dr. Aiello and his associates have used chiefly the argon or green laser which enables the operator to attack single vessels even if they are close to or even upon the disc. The Eye Unit of the Joslin Clinic is a participant in a national Diabetic Retinopathy Treatment program, involving 15 centers over the United States, designed to answer the question as to whether in the long run laser treatment is truly beneficial. Patients are chosen who have fairly comparable proliferating retinopathy in both eyes. With the patient's consent, one eye is treated and the other left untreated. The study, which uses the xenon arc as well, now in its third year, is supervised by a Fundus Photography Reading Center and a Coordinating Center which directs randomization, tabulates results, and in the end, will analyze the combined findings in the various centers.

2. Diabetic Nephropathy

In the latest tabulation of causes of death, we have reported that among patients of all ages, diabetic nephropathy accounted for 8.9% [4]. However, this does not reveal the true impact of chronic renal disease in diabetic patients. Among those who develop diabetes prior to the age of 15 years, death is ascribed to diabetic nephropathy in 40 to 50 per cent of cases, due in part perhaps to the aggressive and unstable character of diabetes in young people and certainly to the fact that because of their young age at the start, survival to at least 20 years after onset of diabetes usually occurs, thereby allowing ample time for the development of nephropathy. Up until recently, diabetic patients with progressive renal impairment were denied the possible benefit of hemodialysis and/or renal transplant. Indeed, early experience discouraged such trials. In 1969 Chazan et al. [12] reported the results of peritoneal and or hemo- dialysis in 44 Joslin Clinic patients of whom 32 were dialyzed because of refractory anasarca. Only eight survived as long as three months. The outcome was good for those with acute renal failure, but poor with those with pre-existing nephropathy. Ideally, hemodialysis is used as a preparation for a kidney transplant. Up until 1970, only two of our patients had received such, in each case from a cadaver. One patient died in less than two months of a cerebro-vascular accident and the other in a year with diffuse fungus (Aspergillus) infection of the lungs.

With this background, as well as poor results reported by others, it was difficult to make the decision to pursue such treatment further. However, Drs. Goldstein, D'Elia and Bradley of our group have worked actively as members of the "renal team" at the New England Deaconess Hospital. From 1970 to the present 32 patients with chronic, progressive nephropathy have received long-term hemodialysis and about half of these have received kidney transplants. The transplanted organs have been from relatives in 9 instances and from cadavers in 11 cases. Seven of the nine are alive for periods up to 27 months, whereas only 2 of the 11 are alive, with survival of one of them 18 months after transplant.

The experience at the University of Minnesota Hospitals is likewise encouraging. In 1972, Kjellstrand et al. [13] at that institution challenged the view that patients with diabetes are poor candidates for renal transplants. At the time of his report, 34 such transplants had been done in 31 recipients aged 23 to 57 years. Twenty were alive after 3 to 6 months and some for more than three years. Of 23 patients who received first kidneys from related donors, 16 were well at the time of the report. Of eight who got first transplants of cadaver origin, six were alive and well, five with first kidneys and the sixth with a second cadaver organ.

3. Myocardial Revascularization

Another area of possible benefit in which diabetic patients usually have not been allowed to share is that of myocardial revascularization. The long-term effec-

tiveness of this procedure is, of course, still being weighed, but there are definite indications that in some patients severe angina may be ameliorated and in other selected subjects with a first myocardial infarction, the outlook may be favorably influenced as regards both symptoms and length of life. Between November, 1970 and August, 1973, 45 diabetic patients, largely from the Joslin Clinic, had aorto-coronary by-pass surgery [14]. Nine of these had additional procedures such as valvular replacement or surgical treatment of an aneurysm, or had only "chemical" diabetes. In the remaining 36 patients who had aorto-coronary by-pass grafts, preoperative angiograms had shown one coronary artery involved in three patients, two vessels in five patients, and three vessels in 28 patients. Of the 36 patients, 32 survived surgery and were followed for an average time of 21 months. Of these, 24 or two-thirds of the entire group had significant relief of angina, in 5 the symptoms remained the same, and in 3 patients were worse. Post-operative complications included myocardial infarction [7], arrhythmias [11], congestive heart failure [4], hemorrhage [4], and other events, chiefly vascular. It is obvious that not enough time has elapsed to permit a definite conclusion as to the long-term value of such a procedure with diabetic patients, but the results to date appear to warrant further application.

4. Peripheral Vascular Surgery

Widely used for many years and of proven benefit is peripheral vascular surgery employing endarterectomy, and by-pass grafts of various types, chiefly femoral and femoro-popliteal. These operations with the present-day trend toward conservatism, such as the transmetatarsal procedure in selected cases, are saving useful feet and legs for many diabetic patients [15].

5. Neuropathy

It would be heartening to report significant advances in the prevention and treatment of diabetic neuropathy, whether this be of the radiculo-, or mono-, poly-, or autonomic type. To be sure, the patient with classical diabetic neuritis usually can be freed from the characteristic pain down the legs, but left behind and often slowly progressing are varying degrees of numbness, insensitivity, diminution of tendon reflexes, etc. The "neuropathic foot" becomes an easy prey for unrecognized trauma of thermal, chemical and mechanical nature, often with disastrous end-results. The pseudo-Charcot joint always presents a challenge. Likewise the treatment of established visceral neuropathy, including neurogenic bladder, diabetic diarrhea, gastroparesis, postural hypotension, and impotence-leaves much to be desired, although in certain of these troublesome complications, a good deal may often be accomplished by meticulous application of measures – diet, surgery, medication, etc., as the case may be – found by experience to be helpful in some patients.

IV. 1966–19–. Hope for Prevention of Angiopathy and Neuropathy

Thus far I have dealt with attempts at treating complications after they have occurred. Such stop-gap procedures are important, they are valuable, and day after day they provide better health and more useful lives for those who are afflicted. Methods for the treatment of complications must be constantly improved because we may well be forced to live with them for a long time in the years ahead. However, we would be remiss indeed if we direct our efforts solely along these lines at the expense of trying to learn more about their pathogenesis. All would agree that prevention would be far better than attempted treatment after the fact.

Is it possible, at least theoretically, to prevent the late complications of diabetes? Accepting as a baseline a prescribed diet which is in every respect nutritionally adequate for the individual concerned, is it possible to avoid angiopathy and neuropathy by careful and consistent chemical control of diabetes? The matter has been discussed for decades, and even now there is no consensus. However, as I survey the scene, I gain the impression that in recent years and particularly in the past decade, more and more workers – investigators and clinicians alike – are swinging to the view that if it were possible to maintain blood glucose and lipid values constantly within the narrow range of normal, the late complications might well be avoided. I hasten to admit that blood glucose and lipids may not be basic to the diabetes problem, but certainly they are easily measured indices of the underlying metabolic defects. There is much evidence to suggest that the basic defect in diabetes resides in the endocrine pancreas, with resulting deficiency of insulin, relative or absolute, with probably an important role played by glucagon. Unger and Orci [16] suggest that, primarily, under-utilization of glucose is due to insulin deficiency and overproduction to relative hypersecretion of glucagon. The exact role of the newly discovered hormone, somatostatin [17], in human metabolism has yet to be elucidated.

In proceeding further in the matter of the pathogenesis of late complications, I will make the assumption that they are due to the metabolic defect. I will assume that the tendency to angiopathy is not

inherited as a separate trait, as proposed by Siperstein et al. [18], based on his work with capillary basement membrane, but instead, that the predilection to vascular disease is due directly to basic abnormalities in the islet tissue which are in large part inherited. This latter point of view is strengthened by the work of Kilo, Vogler and Williamson [19] and others in capillary basement membrane studies and by the demonstration that characteristic retinopathy and nephropathy can and do occur in non-hereditary diabetes. I will cite two examples from the area of experimental diabetes. Bloodworth and Engerman [20], in studies extending over many years, have found that dogs maintained for 5 years with poor chemical control of diabetes, developed microaneurysms and other changes of diabetic retinopathy; extensive, diffuse, and often nodular diabetic glomerulosclerosis; and basement membrane thickness greater than expected due to the age of the dogs. On the other hand, dogs maintained under as good control as practicable, after 5 years showed minimal retinal changes, essentially normal glomeruli by light microscopy and minimal changes by electron microscopy. These dogs showed a slight increase in basement membrane thickness which, however, was less than that in the poorly controlled dogs.

Mauer et al. [21], using an inbred strain of rats, found that 6 to 8 months after induction of diabetes with streptozotocin, renal glomeruli showed mesangial thickening. When kidneys were transplanted from diabetic rats into normal recipients, there was disappearance or arrest in formation of the glomerular lesions. Contrariwise, when kidneys were transplanted from normal rats into diabetic animals, mesangial matrix thickening occurred. Finally, transplantation of islet tissue into diabetic rats resulted in restoration of normal blood glucose and insulin levels and regression of glomerular lesions.

If one accepts the evidence just cited, then one must try to devise ways of prevention of angiopathy in an attempt to approach the physiological state. *A priori*, pancreas transplants would seem to be a real possibility, and some good results have been secured in experienced hands [22]. The familiar problems of rejection and infection are formidable ones, although by no means insoluble. Of more practical importance, it seems to me, is the fact that the transplanted pancreases must be of cadaver origin, thus limiting sharply the supply of suitable organs. Attention has been drawn in the last several years to the possibility of transplants of B-cells [23, 24] and the development of a mechanical device which might serve as an "artificial pancreas" [25]. Both of these projects have been underway in the Joslin Research Laboratory for some years. Great technical difficulties remain to be overcome before either of these well-conceived efforts will result in direct application to human patients. One should be careful not to raise unduly the hopes of patients and their families in this regard.

One cannot mark time until these projects in the laboratory come to fruition. A great deal can be accomplished by using to best advantage the tools which we have at hand. These are familiar to all: diet, insulin, oral hypoglycemic agents, exercise, help with emotional problems, and the continuing education of the patient and his family. If these are planned to fill the needs of the individual patient and if he can become sufficiently motivated, good results can almost always be obtained. One recognizes that, since it is not possible to secure *ideal* control of diabetes with the means presently available, late complications will continue to occur even with what is commonly called good control. Nevertheless, there is good evidence to suggest that the development of angiopathy may be delayed and minimized.

When one approaches a more basic problem, that of the prevention of diabetes itself, one is faced by tremendous gaps in knowledge. One starts with the basic premise that it is likely that the tendency to diabetes is usually inherited, but that its onset and course are influenced by a variety of environmental factors. However, we do not know exactly what it is that the diabetic person inherits. We do not know whether the inheritance comes about through a single gene or one or more genes. The former thought was that inheritance was of simple recessive type although some argued for a dominant trait. Present thinking favors a multifactorial origin of the disease, with a major role attributed to environment.

It is common knowledge that emergence of diabetes from a subclinical state to an overt process may be favored by obesity, infection, pregnancy, certain medications such as steroids, oral contraceptive agents, and thiazides and, of course, diminishing carbohydrate tolerance which accompanies advancing age. Some of these influences, notably obesity, can be prevented and, indeed, careful planning of a diet to avoid or correct obesity forms the basis of treatment of all diabetes.

Currently, an exciting possibility under consideration is that of the origin of diabetes in young people with the insulin-requiring form of the disease. It has been proposed that possibly in certain persons viruses may play a role in the pathogenesis of juvenile-onset diabetes, particularly since diabetes in the young often has an abrupt, and to some extent a seasonal, onset. Some viruses are known to produce specific lesions in the islet tissue of the pancreas of rodents [26]. Added to this is the apparent lack of consistency of appearance of diabetes in the identical twin mate of a diabetic patient [27]. Related to this and to the possible role of

the body's immune response to virus infections is the finding in juvenile-onset diabetics of an increased frequency of the histocompatibility antigen HL-A8 in only concordant twins whereas W_{15} was increased in discordant pairs as well [28].

To date the cumulative evidence regarding a positive viral origin of diabetes in young patients is not great. So far no one has demonstrated the presence of viruses in the blood, pancreatic islets or body wastes. Nevertheless, the idea is intriguing because if viral etiology could be proved, then it might be possible to develop prophylaxis against specific viruses.

It is through continued research that progress in treatment will be made. Knowledge that research is being pursued vigorously brings hope to the diabetic patient. Without such hope for betterment, it will be difficult to inspire patients to follow year after year the best available treatment.

The continuing challenge is therefore two-fold: first, to continue to treat patients in the very best way possible with the excellent means at hand, and second, to foster creative and imaginative thinking leading to research, which although it may not quickly provide prevention or cure, may at least direct us to new and better ways of treatment.

References

1. Joslin, E. P.: The treatment of diabetes mellitus, p. 54. Philadelphia: Lea and Febiger 1916
2. Root, H. F.: The association of diabetes and tuberculosis. New Engl. J. Med. **210**, 1–13 (1934)
3. Marks, H. H., Krall, L. P.: Onset, course, prognosis, and mortality in diabetes mellitus. In: Joslin's Diabetes Mellitus, 11th Ed. (eds. A. Marble, P. White, R. F. Bradley, L. P. Krall), p. 255. Philadelphia: Lea and Febiger 1971
4. Marble, A.: Insulin-clinical aspects: the first fifty years. Diabetes **21** (Suppl. 2), 632–636 (1972)
5. Kimmelstiel, P., Wilson, C.: Intercapillary lesions in the glomeruli of the kidney. Amer. J. Path. **12**, 83–97 (1936)
6. Bradley, R. F., Ramos, E.: The eyes and diabetes. In: Joslin's Diabetes Mellitus, 11th Ed. (Eds. A., Marble, P. White, R. F. Bradley, L. P. Krall), pp. 479–480. Philadelphia: Lea and Febiger 1971
7. Ballantyne, A. J., Loewenstein, A.: Pathology of diabetic retinopathy. Trans. ophthal. Soc. U. K. **63**, 95–115 (1944)
8. Bradley, R. F., Ramos, E.: The eyes and diabetes. In: Joslin's Diabetes Mellitus, 11th Ed. (Eds. A. Marble, P. White, R. F. Bradley, L. P. Krall), pp. 495–508. Philadelphia: Lea and Febiger 1971
9. Field, R. A.: Pituitary ablation: a review. Paper presented at a symposium on diabetic retinopathy. Annual meeting of the American Diabetes Association, New York, June 15, 1975
10. Fraser, R., Kohner, E. M., Joplin, G. F., Doyle, F. H., Hamilton, A. M., Black, R. K.: The place and the effect of pituitary ablation for diabetic retinopathy. In: Diabetes. Proceedings of the Eighth Congress of the International Diabetes Federation: (Eds. W. J. Malaisse, J. Pirart), pp. 431–438. Amsterdam: Excerpta Medica 1974
11. Aiello, L. M.: Personal communication
12. Chazan, B. I., Rees, S. B., Balodimos, M. C., Younger, D., Ferguson, B. D.: Dialysis in diabetics. A review of 44 patients. J. Amer. med. Ass. **209**, 2026–2030 (1969)
13. Kjellstrand, C. M., Simmons, R. L., Goetz, F. C., Buselmeier, T. J., Shideman, J. R., von Hartizsch, B., Najarian, J. S.: Renal transplantation in patients with insulin-dependent diabetes. Lancet 1973 **II**, 4–8
14. Draskoczy, S. P., Leland, O. S., Bradley, R. F.: Aorto-coronary bypass in the diabetic patient. Kidney Int. (Suppl.) **1**, 37–40 (1974)
15. Wheelock, F. C., Jr., Filtzer, H. S.: Femoral grafts in diabetics. Resulting conservative amputations. Arch. Surg. **99**, 776–780 (1969)
16. Unger, R. H., Orci, L.: The essential role of glucagon in the pathogenesis of diabetes mellitus. Lancet **1975 I**, 14–16
17. Meissner, C., Thum, Ch., Beischer, W., Winkler, G., Schröder, K. E., Pfeiffer, E. F.: Antidiabetic action of somatostatin-assessed by the artificial pancreas. Diabetes **24**, 988–996 (1975)
18. Siperstein, M. D., Unger, R. H., Madison, L. L.: Studies of muscle capillary basement membranes in normal subjects, diabetic and prediabetic patients. J. clin. Invest. **47**, 1973–1999 (1968)
19. Kilo, C., Vogler, N., Williamson, J. R.: Muscle capillary basement membrane changes related to aging and to diabetes mellitus. Diabetes **21**, 881–905 (1972)
20. Bloodworth, J. M. B., Engerman, R. L.: Diabetic microangiopathy in the experimentally diabetic dog and its prevention by careful control with insulin (abstract). Diabetes **22**, 290 (1973)
21. Mauer, S. M., Steffes, M. W., Sutherland, D. E. R., Najarian, J. S., Michael, A. F., Brown, D. M.: Studies of the rate of regression of the glomerular lesions in diabetic rats treated with pancreatic islet transplantation. Diabetes **24**, 280–285 (1975)
22. Goetz, F. C.: Conference on beta cell function, transplantation, and implantable glucose sensors: a summary. Metabolism **23**, 875–884 (1974)
23. Chick, W. L., Like, A. A., Lauris, V.: Beta cell culture on synthetic capillaries: an artificial endocrine pancreas. Science **187**, 847–849 (1975)
24. Chick, W. L., Like, A. A., Lauris, V., Galletti, P. M., Richardson, P. D., Panol, G., Mix, T. W., Colton, C. K.: A hybrid artificial pancreas. Trans. Amer. Soc. artif. intern. Org. **21**, 8–14 (1975)
25. Soeldner, J. S., Chang, K. W., Aisenberg, S., Hiebert, J. M.: Progress towards an implantable glucose sensor and an artificial beta cell. In: Temporal aspects of therapeutics: (Eds. J. Urquhart, F. E. Yates), pp. 181–204. New York: Plenum Press 1973
26. Craighead, J. E., McLane, M. F.: Diabetes mellitus: induction in mice infected with encephalomyocarditis virus. Science **162**, 913–914 (1968)
27. Tattersall, R. B., Pyke, D. A.: Diabetes in identical twins. Lancet **1972 II**, 1120–1125 (1972)
28. Nelson, P. G., Pyke, D. A., Cudworth, A. G., Woodrow, J. C., Batchelor, J. R.: Histocompatibility antigens in diabetic identical twins. Lancet **1975 II**, 193–194

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