Workshop Reports

Highlights from the International Symposium: Diabetes and its Late Complications: New Prospects

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An International Symposium on 'Diabetes and Its Late Complications: New Prospects' was held in Taormina on 28–31 October, 1981. It was of great interest not only because of its subject matter but also because of its uniqueness, in that it assembled specialists from many medical disciplines and many areas of the world to discuss this important subject in an informal and friendly atmosphere.

The Symposium was organized by Professor G. Squadrito of the University of Messina in collaboration with Dr. A. G. Cudworth and Professors H. Keen and D. Andreani and under the patronage of the EASD, the Italian National Research Council and the Italian Society of Diabetology.

During the Symposium, all the main chronic complications of diabetes were discussed with the purpose of highlighting the pathogenic factors which they have in common and emphasizing the ways in which they differ.

There is increasing evidence that the primary common pathogenic factor in the development of late diabetic complications is a chronically elevated blood glucose concentration. Glucose is able to bind to proteins and other biochemical substances by a non-enzymatic mechanism, thereby changing their biophysical properties and leading to metabolic and functional abnormalities.

This non-enzymatic glycosylation is an ubiquitous phenomenon in diabetes and all proteins are affected, glycosylated haemoglobin being the first and the best characterized example (Svendsen).

However, hyperglycaemia per se cannot be considered as the only pathogenic factor in the development of late diabetic complications. Some contributions in the Symposium underlined this aspect. It seems that 20%–40% of patients with diabetes of long duration do not develop significant complications despite poor metabolic control. It seems likely, however, that stable hyperglycaemia has a more damaging effect than fluctuating hyperglycaemia (Pirart). This is suggested by the clinical observation that brittle diabetic patients appear less prone to severe microvascular disease.

Another interesting aspect which was widely debated concerned local influences on thickening of the basement membrane and on microangiopathy in general (Timpl, Williamson). For example, vascular basement membranes of the lower limbs are thicker than in more cephalic regions of the body. Furthermore, dichotomy between retinopathy and nephropathy appears more often than previously recognized and such cases should be investigated more carefully in the future in order to elucidate possible pathogenic heterogeneity.

As far as morphological consequences are concerned, it should be accepted that non-specific factors may aggravate the initiating lesions. Retinal haemorrhage and capillary proliferation as a consequence of hypoxia and/or ischaemia are of major importance in causing physical injury to the retina and disturbing its function. Similarly, inflammatory

changes, capsular drop lesions and other non-specific phenomena, may accompany nodule formation in the glomerulus and aggravate the encroachment upon Bowman's space.

At present, the influence of genetic factors in the development of microangiopathy is obscure. Contributions on this topic seem to exclude any strong association between a particular HLA phenotype and the predisposition to complications in Type 1 diabetes (Bodansky). However, we must remember that HLA is only a small part of the total genome. Many other factors, at the moment unknown, may well play a role. For example, some genetic relationship between the chlorpropamide alcohol flush phenomenon and the impact of late complications in Type 2 diabetes was proposed (Leslie, Pyke). The results encourage further studies including the elucidation of the chlorpropamide alcohol flushing itself, which remains contentious. Clear conclusions remain to be drawn on the possible protective role of this phenomenon with respect to retinopathy and microangiopathy in general.

Great interest was generated by studies on blood viscosity and vascular permeability. Hyperviscosity, which is associated with modifications in plasma proteins, and the reduced deformability of red cells are two prominent abnormalities which are associated with the development of microangiopathy (McMillan, Terranova).

In the initiation and development of diabetic angiopathy, both plasma factors and abnormalities of the vessel walls are concerned; which of these abnormalities is predominant remains unclear.

Immunological factors were widely discussed as possible pathogenic determinants. The occurrence of circulating immune complexes in patients with microangiopathy has been confirmed by several workers (Di Mario, Iavicoli, Triolo). Immune complex levels tend to be very high in those diabetic patients who develop so called 'malignant microangiopathy'. From a histological point of view, it has been well established that immunoglobulins are deposited in the basement membrane of the diabetic kidney and this finding is in accord with the presence of immune complexes in the circulation. In the future, the composition of immune complexes should be identified. This could help to clarify whether immune complexes, containing or not containing insulin, are directly involved in the pathogenesis of microangiopathy or whether they are simply a consequence of it, being a non-specific phenomenon only indirectly related to vascular disease.

In addition, the relationship between immune complexes and platelet factors should be investigated further in the light of preliminary data suggesting a possible correlation between these two factors in the initiation and progression of microangiopathic lesions.

As mentioned above, functional abnormalities of the microcirculation in diabetes appear to be a result of stable hyperglycaemia (Ditzel) and tend to disappear when normal metabolism is restored.

In hyperglycaemia, disturbances of some fluid phase coagulation

factors, platelet function and prostaglandin metabolism (Squadrito, Colwell, Almer) have been observed. The increase of some coagulation and platelet factors, together with the reduction of fibrinolysis and the decrease of prostacyclin, are interrelated pathogenic factors which could be involved in damage to the vessel wall and result from the diabetic state. Such damage could create a form of local 'vicious circle' inducing further platelet adhesiveness and liberation of substances stimulating proliferation, a mechanism perhaps common to both micro- and macroangiopathy. Carefully coordinated cooperative studies at several centres are necessary and the potential of this was fully discussed particularly in view of possible preventive measures.

Studies of the effects of different oral hypoglycaemic agents on disturbed haemostatic activity suggested that glibenclamide might have advantages over chlorpropamide in these abnormalities. Further studies are necessary to confirm these findings.

Regarding diabetic nephropathy (Ireland, Viberti, Osterby, Steffes), the syndrome of glomerular hypertrophy and hyperfunction, the classical initial phase of diabetic kidney disease, is now well characterized. It can be reversed with appropriate antidiabetic treatment. At this stage, for reasons not completely understood, (there are changes in the electric charge of basement membrane) and an increase in glomerular permeability is found. Soon after the establishment of diabetes, changes are found in the mesangium. Mesangial cells have important physiological activities and their impairment has been recently demonstrated in patients with nephropathy.

A new finding reported was the observation that thickening of the basement membrane depends little on age but has some relation with sex, being more marked in males. In addition, new data were presented on renal tubular abnormalities in diabetes (ischaemia of the interstitial areas, thickening of basement membrane and abnormal reabsorption).

Among the other more frequent diabetic complications, neuropathy seems to be more frequent than anticipated (Pozza, Ewing, Ward, Clements).

The session on large vessel disease in diabetes (Jarrett, Ledet, Mancini, Stout) confirmed that ischaemic coronary disease is more frequent in diabetic subjects and that hypertension and smoking are two high risk factors (Keen, Jarrett).

It has been demonstrated that the proliferation of mesenchymal cells is partly due to some circulating plasma factor, which according to some research, may be growth hormone. The importance of hormones was emphasized in several contributions, and in particular the role of catecholamines in aggravating vascular lesions was considered. The possible role of insulin excess in producing arterial wall damage was also stressed (Stout).

Investigation of the proliferative stimulus of insulin on smooth muscle cells could be a promising area for research into the understanding of the pathogenic mechanism of diabetic vascular disease. Interesting data were presented on the relationship between hypertriglyceridaemia and coagulation factors, again potentially linking micro- and macroangiopathy in a common mechanism.

This account is by no means fully comprehensive of what was discussed during the Symposium, but indicates the main lines of investigation and thought which emerged from the papers and during discussion. The proceedings of the Symposium will be published in book form later this year.

Those present included:

L.O. Almer, D. Andreani, R. Blach, H.J. Bodansky, R. Brancato, U. Butturini, R. Clements, J.A. Colwell, G. Coscas, G. Crepaldi, U. Di Mario, J. Ditzel, D. Ewing, G. Giorgino, A. Gnudi, M. Iavicoli, J. Ireland, J. Jarrett, H. Keen, E.M. Kohner, T. Ledet, D. Leslie, D. McMillan, M. Marcini, L. Motta, R. Navalesi, R. Osterby, J. Pirart, G. Pozza, P. Pozzilla, D. Pyke, C. Scandellari, G. Scuderi, G. Squadrito, M.W. Steffes, R.W. Stout, A. Svendsen, R. Terranova, A. Tiengo, R. Timpl, G.C. Viberti, J. Ward, J. Williamson

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