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Preface

WE ARE GRATEFUL to the Editor of *Metabolism* for the opportunity to publish the presentations of the symposium in this journal. The guest editorial board had full responsibility for the scientific arrangement and editing of the present supplement. It was sponsored by Novo Nordisk Pharma GmbH in Mainz and attended by 240 participants from 17 countries. Dr Thomas Lander and his staff in Mainz were responsible for the excellent organization of the meeting.

The symposium was intended to present in-depth reviews and previously unpublished update results. We are biased but hope that also in the reader's opinion the overall goal was reached. The presented research centered primarily on the role and actions of insulin-like growth factor-I (IGF-I), its receptors and binding proteins, and those of its parent hormone, growth hormone (GH). The important roles of insulin, "stress hormones," and growth factors other than IGF-I in glucose metabolism and late diabetic manifestations were also included, in keeping with the heading of the symposium.

The growth factor era is comparatively young. Nonetheless, four decades have passed since the first determinations of "sulfation activity" and "nonsuppressible insulin-like activity," using, respectively, rat costal cartilage and epididymal fat, designed originally to estimate bioactivity of GH and insulin, respectively. Both of these bioactivities were later shown to be exerted by two peptides of the insulin family, termed IGF-I and -II. Already early studies indicated that some of the material was protein-associated and that some was dialyzable—a first suggestion that a fraction was "free"—and possibly better available for biological action.

These early bioassays were inherently associated with a considerable inaccuracy, and were abandoned by most when immunoassays became available for determinations of the original analysis targets: GH and insulin. A few notable researchers persisted with their studies, because they had recognized that this bioactivity had merits of its own. It is to these pioneers that we owe the identification of IGF-I and -II and a major part of the ongoing unraveling of the complex system of binding proteins, their proteolytic enzymes, the receptors, and the in vitro and in vivo actions.

Although determination of immunoreactive total serum (extractable) IGF-I is a valuable tool in the clinical assessment of GH-deficient and acromegalic patients, as well as in experimental research, it is often inadequate as a measure of the bioactive fraction. Lately, new bioassays and refined old ones have reappeared, none of them yet solving the riddle. The relative biological contributions of circulating versus locally produced IGF-I and its binding proteins remain to be determined. Free IGF-I in serum can now be measured and has been shown to exhibit large variations opposite to those of IGF-binding protein-1. However, it is still unknown if this minute free fraction may have biological importance.

The role of GH hyperproduction in late diabetic manifestations is still unproven, whereas its importance for the metabolic aberrations of diabetes is well documented. A role of IGF-I in the development of late diabetic lesions has not been established, although there is good evidence that local changes in both IGF-I and its binding protein concentrations take place in relatively early stages of experimental diabetes. This should be viewed in the perspective that it is more than 25 years since opposite changes were demonstrated in serum GH and IGF-I levels that appeared to be related to the degree of metabolic derangement in diabetic man.

Exciting data are currently accumulating from experimental and clinical studies of IGF-I administration in diabetic and catabolic states, as well as in GH-insensitive dwarfs. It appears that IGF-I therapy is associated with no or minor adverse effects, provided that dosage and dosage intervals are cautiously monitored.

As for the intracellular mechanisms of action of growth factors, they were best represented by a black box until a few years ago. However, with the advent of molecular biology and the cloning of multiple receptors and intracellular signaling molecules, an explosion of knowledge on the signaling pathways has resulted in recent years. These mechanisms are dealt with in several articles, with special emphasis on insulin and IGF-I and their effects on glucose transport.

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