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PRENATAL TREATMENT OF CONGENITAL ADRENAL HYPERPLASIA. P. Speiser, A.B. Mercado, and M.I. New, Dept. of Pediatrics, The New York Hospital-Cornell Medical Center, New York, NY 10021, USA

Prenatal treatment was given to 67 fetuses at risk for classical steroid 21-hydroxylase deficiency (21OHD) congenital adrenal hyperplasia (CAH). The mothers were given dexamethasone (DEX) 1 - 1.5 mg/d po, computed at 20 μg/kg(pre-pregnancy weight)/day, in three divided doses. Treatment began as early as 4 weeks, continuing until birth for affected female fetuses. The diagnosis of 21OHD was established or excluded by DNA analysis using HLA-linked markers or 21OHD gene probes on the tissue provided by chorionic villus sampling (CVS). When amniocentesis was performed the diagnosis was based on the concentration of 17OHP in the supernatant and occasionally DNA was analyzed from amniotic cells. Seventeen fetuses were predicted to be affected, 10 of which were females. In every case the virilization of the genitalia of the unborn prenatally-treated females was significantly less than in the index case. No complications were observed in those fetus treated briefly and who were predicted to be unaffected. Maternal complications were observed in 6 pregnancies out of 67. These included increased appetite, weight gain, mood swings, pedal edema, and mild hypertension. None were permanent. One fetus was spontaneously aborted at 33 wks. It appears unlikely that dexamethasone was causative of the abortion since treatment with dexamethasone occurred from 10-19 weeks.

In conclusion, prenatal treatment of fetuses at risk for CAH is effective and safe.

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ROLE OF GLUCOSE IN DIABETIC COMPLICATIONS. A. Cerami. The Picower Institute for Medical Research, 350 Community Drive, Manhasset, NY 11030

Over time, and despite therapy with insulin or oral hypoglycemics, diabetics frequently develop a number of serious complications such as retinopathy, nephropathy, and atherosclerosis that severely restrict the quality and length of life. For the past 20 years, we have evaluated the hypothesis that the pathogenesis of such long-term complications is attributable to the progressive covalent modification of tissue proteins by non-enzymatic reactions with reducing sugars, such as glucose. Sugar-derived addition products accumulate as a function of elevated glucose levels and protein half-life, and are both chemically and biologically active. The first clue to this glycation process was the discovery that glycohemoglobin (HbA_{1c}) results from the modification of hemoglobin by glucose to form an Amadori product; thus the amount of HbA_{1c} reflects a clinically useful temporal integration of recent blood glucose control. Initial Amadori products can undergo further rearrangement and addition reactions over time to form advanced glycosylation endproducts (or AGEs) which are, as a group, yellow-brown fluorescent pigments that can crosslink proteins. Long-lived proteins such as lens crystallins and basement membrane components accumulate AGEs linearly over a period of years, and many of the physical changes in collagen that occur with chronological aging can be attributed to AGE-crosslinking. Several years ago, we discovered a specific inhibitor of AGE formation, aminoguanidine (AG), which inhibits AGE formation and protein-protein crosslinking in experimental animals. Aminoguanidine can prevent pathological changes seen in experimental diabetes including cataract development, kidney basement membrane thickening, proteinuria and retinal changes. In clinical studies, administration of AG for 28 days can inhibit the formation of AGEs on hemoglobin. Further studies will determine whether AG can halt the progression of diabetic complications.

IDDM: Pharmacologic and Transplant Approaches to Therapy

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DESIGN AND USE OF CELLULAR IMPLANTS FOR TREATMENT OF DIABETES (IDDM). D.W. Scharp, Department of Surgery, Washington University, St. Louis, MO 63110, USA

The primary objective of islet transplantation is to transplant sufficient quantities of normal, functional islet tissue into Type 1, IDDM patients to achieve normal metabolic function without insulin therapy sufficiently early in their disease to prevent their complications while avoiding the use of long-term immunosuppression and autoimmune recurrence. A total of 14 patients with kidney transplants have reached insulin independence after islet transplantation using immunosuppression with the longest at 30 months. Many others have had partial islet function in clinical trials. Immunoalteration studies in which islets are altered in vitro prior to transplantation to eliminate donor immune cells that cause rejection have succeeded in rodent studies. Immunoisolation studies in which islets are encapsulated with specific biocompatible membranes and transplanted without immunosuppression are also showing promise in animals and beginning in human studies. These kinds of approaches will be necessary to make this potential therapy a practical approach for the patient with diabetes.

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ANTIGEN DIRECTED THERAPIES TO PREVENT INSULIN DEPENDENT DIABETES
N Maclaren, D Schatz, Y Song and A Muir, Departments of Pathology and Laboratory Medicine and Pediatrics, University of Florida College of Medicine, Gainesville FL 32610 USA

A number of beta cell antigens have been identified as important targets for the pancreatic islet directed autoimmunity underlying insulin dependent diabetes (IDD), through their reactivities to autoantibodies or peripheral blood T cells in patients prior to and/or at diagnosis. Three of the more important appear to be the 65KDa isoform of glutamic acid decarboxylase (GAD_{65}), a 38KDa beta cell specific protein of undetermined origin and insulin. In non-obese diabetic (NOD) mice, prophylactic daily, subcutaneously insulin therapy both prevents diabetes and attentuates the degree of insulitis seen. The mechanism may involve "beta cell nest" and possibly tolerance induced by insulin immunization. These data have led to the initiation of a randomized human trial in non-diabetic relatives with a positive islet cell antibody (ICA) of >720 JDF who also have impaired first phase insulin release (FPIR) to IV glucose. Diabetes in NOD mice can also be delayed by the introduction of oral feedings of porcine insulin or human GAD_{65} presumably through a mechanism of tolerance induction, and human trials are planned among relatives with strongly positive ICA but normal FPIR. Immunization of NOD mice with insulin in incomplete Freunds adjuvant also specifically delays diabetes, an effect not seen by immunization with BSA, the BSA (ABBOS) peptide, nor human insulin A chain. These findings indicate progress towards the prevention of IDD and provide the rationale for the institution of clinical trials.

Insulin-Like Growth Factors

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IN VIVO METABOLIC ACTIONS OF IGF I
J. Zapf, M. Hussain, and E.R. Froesch, Dept. of Medicine, University Hospital, 8091 Zürich, Switzerland

The availability of IGF I produced by recombinant gene technology has opened the possibility to explore the therapeutic potential of this hormone by studying its metabolic effects in normal subjects and in various diseases in which a pathogenetic role of IGF I may be suspected. The first in vivo studies in healthy men carried out by Guler et al. in 1986 had shown that IGF I did not only act like insulin, but also in an analogous as well as opposite way to growth hormone (GH), the main stimulator of endogenous IGF I production, and that it affected glucose, fat and protein metabolism. Iv bolus injections of recombinant human (rh) IGF I (100 μg/kg) induced sustained hypoglycemia. The hypoglycemic effect was blunted during long-term sc administration by specific IGF serum binding proteins (BPs) which cause sequestration of IGF I into a metabolically inactive large mol. mass (150 kd) complex. Effects of IGF I on fat and protein metabolism were reflected by a decrease of serum triglycerides (TG) and cholesterol and of serum urea. In addition, it stimulated glomerular filtration in the kidney and it suppressed insulin and GH secretion.

Recent studies in normal subjects showed that sc IGF I (7-14 μg/kgxh) as compared to saline treatment 1) lowered fasting blood glucose levels despite suppression of basal insulin secretion; 2) suppressed glucose-stimulated insulin levels without impairing glucose tolerance; 3) increased oxidative and non-oxidative glucose disposal and inhibited hepatic glucose production during a euglycemic, hyperinsulinemic clamp suggesting increased insulin sensitivity; 4) enhanced lipolysis, lipid oxidation and basal metabolic rate (BMR), but reduced protein oxidation (as measured by indirect calorimetry).

In GH-deficient adults, sc infusion of rhIGF I (10 μg/kgxh) for 7 d 1) had no significant influence on fasting glucose levels or basal glucose oxidation, but suppressed serum insulin levels, whereas GH treatment (2 IU/m^2xd) raised fasting blood sugar despite concomitantly elevated serum insulin levels; 2) like GH raised BMR and lipid oxidation and reduced protein oxidation; 3) did not enhance insulin sensitivity during euglycemic, hyperinsulinemic clamping. Thus, IGF I like GH acts as an anabolic agent. However, in the absence of GH, when insulin sensitivity is already increased, IGF I does not further enhance insulin sensitivity. It therefore appears that suppression of GH observed during IGF I treatment of normal subjects is mainly responsible for enhanced insulin sensitivity.

In type 2 diabetics, rhIGF I treatment reduced elevated serum insulin levels, lowered serum TG and improved glucose tolerance. In patients with type A insulin resistance, iv bolus injections of rhIGF I lowered serum insulin and normalized blood sugar levels.

All of these findings suggest that IGF I may become therapeutically interesting for the treatment of catabolic (heavy injuries, burns) and insulin resistant states (type 2 diabetes, syndrome X).