REPORTS

A Canadian Workshop on Diabetes

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In 1967 Canada became 100 years old. Since insulin was one of the gifts of Canadian medicine to the world, it was felt by many, that a workshop on current issues of diabetes should be the most appropriate medical celebration of Canada's Centennial year. Under the honorary chairmanship of Professor CHARLES H. BEST, 23 research workers in the field of diabetes from all Canada gathered for 2 days at the exclusive Seignior Club, at Montebello, Quebec, on April 24 and 25, 1967. The meeting was entirely sponsored by Hoechst Pharmaceuticals, a Division of Canadian Hoechst Ltd. The organizing committee consisted of Dr. H. G. GIESE, Vice-President, Hoechst Pharmaceuticals, Dr. M. BLAKE, Director of Medical Services, Hoechst Pharmaceuticals, and Drs. O. V. SIREK and C. K. GORMAN, of the University of Toronto. Unfortunately, Dr. Best, who was recovering from surgery at the time of the meeting, was unable to be present. Dr. H. G. GIESE opened the meeting and read a message of welcome from Dr. C. H. BEST.

The morning session of April 24 was chaired by Dr. O. V. SIREK, Associate Professor of Physiology of the University of Toronto.

The first paper was presented by the guest speaker from the United States, Dr. E. R. ARQUILLA, Associate Professor of Pathology, University of California, Los Angeles. He spoke on "*Studies on the Surface Conformation, Biological Activity and Immunologic Properties of Insulin*". Insulin antibodies produced by inbred strain 2 guinea pigs combined with portions of insulin, with which antibodies from strain 13 cannot combine. By reacting insulin antiserum from strain 2, strain 13, and mongrel guinea pig, with each of six insulin derivatives containing known structural alterations, it was possible to distinguish between the parts of the insulin molecule with which strain 2 antibodies combined, from those with which strain 13 antibodies combined. Strain 2 insulin antibodies combined with antigenic determinants closely related to the N-terminal A chain, N-terminal B chain, and lysine, at position 30 in the B chain. Strain 13 antibodies combined with antigenic determinants related to the aromatic amino acids in the C-terminal portions of A and B chains.

It appears that the C-terminal A and the C-terminal B chains, in close proximity to each other, constitute a centre rich in aromatic amino acids. This centre is directly concerned with the conformation of antigenic determinants with which strain 13 antibodies combine and, in addition, secondarily concerned with the conformation of distant antigenic determinants with which strain 2 and mongrel insulin antibodies bind. Alterations which distort the conformation of immunologic determinants at any of several sites reduce the biological activity of insulin. Therefore, integrity of the total surface conformation of insulin is important to biological activity.

The next paper was presented by Dr. S. WILSON, Research Associate, Connaught Medical Research Laboratories, University of Toronto. Dr. Wilson described studies on passive cutaneous anaphylaxis (PCA) induced by various synthetic insulin peptides in normal guinea pigs previously injected intradermally with antiserum to intact bovine insulin, as well as antisera against isolated bovine A and B chain. The results indicated that the immunization of guinea pigs with bovine insulin elicits production of antibodies mainly against the A₁₀₋₂₁ and B₁₋₈ regions of the insulin molecule, and to a lesser extent, against determinants within the sequences A₁₋₉ and B₂₄₋₃₀.

A number of sera from insulin-resistant diabetic patients gave strong PCA reactions with 0.3 units or less of bovine insulin, and could also neutralize various insulins in the mouse diaphragm assay. In both tests there was a greater reaction with the bovine hormone than with human, chicken, or sulphated bovine insulin.

The antibody levels found in peptic digests of human insulin-resistant sera using the mouse diaphragm assay correlated well with the total hormonal activity in acid-alcohol treated sera, and both estimates agreed with the insulin requirements of the patients. Addition of increasing amounts of peptic-digested sera to a constant amount of ¹³¹I-insulin in Herbert's charcoal immuno-assay yielded much higher levels of ¹³¹I-insulin-binding antibodies than in native serum, but the values obtained were still lower than those by the diaphragm assay. However, there was good correlation between the two assays when the immuno-assay was carried out using increasing amounts of unlabelled insulin, while keeping the levels of native human serum and ¹³¹I-insulin constant. These findings suggested that the sera of insulin-resistant diabetic patients contain relatively large amounts of free, non-avid antibodies, as well as antibodies combined with some of the therapeutically administered insulin. The inability of peptic-digested serum to provoke a PCA reaction indicated that the treatment had split the anaphylactic antibodies into their F_{ab} and F_c fragments (the latter being responsible for binding of antibodies to tissue). In contrast, the high reactivity of the peptic digests in the immuno-assay and diaphragm assay suggested that certain antibody F_{ab} fragments could still bind to, and neutralize, insulin.

During a lively discussion, the question of iodine-labelled insulin preparations was brought up in connection with immuno-assays. Dr. ARQUILLA pointed out that ¹²⁵I-insulin preparations, labelled at less than 1 atom/mole, were found to have no demonstrable biological activity in rat adipose tissue when separated from non-labelled insulin. It appears that some antibodies are present in most insulin antisera which do not react with ¹²⁵I-insulin. Insulin antisera from strain 2 guinea pigs contain relatively more antibodies which react with ¹²⁵I than antisera from strain 13. While these factors, in his opinion, do not affect the specificity, they influence the precision and sensitivity of the radio-immuno-assays for insulin.

The next paper was presented by Dr. A. BENCOSME, Professor of Pathology, Queen's University, Kingston, Ontario. He reviewed the morphology of the five currently recognized cell types found in pancreatic islets, with special reference to alpha cells. Dogs, surgically deprived of alpha cells by partial pancreatectomy, the uncinata process (supposedly free of alpha cells) being retained on a pedicle, showed no change in blood sugar, but pancreatectomized chickens went into hypoglycemia that could be alleviated by glucagon administration. In a series of experiments designed to study morphological alterations of alpha cells of the dog, neither proliferative changes nor transformation of d and f cells into alpha cells were observed. The author was not able to establish any clear causal relationship between the alpha and delta cells, and diabetes.

Dr. J. M. MARTIN, Assistant Scientist of the Research Institute, Hospital for Sick Children, Toronto, spoke about insulin secretion *in vitro*, using slices of rat pancreas. Glucose in the medium stimulated insulin release, but

this was prevented by glucosamine or 2-deoxy-glucose. This blocking of insulin release could be overcome by addition of citrate to the incubation medium. The stimulatory effects of both citrate and glucose were blocked by the addition of DNP; this suggested that phosphorylation of either substrate provided the trigger signal for the release of insulin. Addition of ATP to the medium strongly stimulated insulin release, and DNP was able to counteract this effect.

Octanoate and tolbutamide stimulated insulin secretion as effectively as glucose. Leucine had no effect on insulin release from rat pancreas. Growth hormone did not exert a direct effect on the secretory process, but it apparently influenced the sensitivity of the islet cells in terms of insulin release to a given glucose load. Epinephrine, vasopressin and 3'5'-cyclic AMP blocked glucose-induced insulin release. This suggested that the effect of vasopressin and epinephrine was probably mediated by cyclic AMP.

Dr. MARTIN concluded that his results supported the concept that the release of insulin is an energy-dependent process, and that at least part of the energy is supplied by oxidation of glucose.

Dr. J. DUPRÉ, Assistant Professor of Medicine and Director of the Fraser Laboratory for Research in Diabetes, Royal Victoria Hospital, Montreal, spoke on the "*Regulation of Endocrine Function of the Pancreas by Gastro-Intestinal Hormones*". Glucose administered to man by way of the gastro-intestinal tract was more rapidly utilized than glucose administered intravenously. Studies in patients with liver disease with and without portocaval anastomoses, in some of whom the portal vein was cannulated under local anaesthesia, indicated that this difference did not depend on portal perfusion of the liver. The response to ingested glucose was characterized by increments in concentrations of immuno-reactive insulin in portal and peripheral serum, which were consistently greater than those associated with infusions of glucose into peripheral or portal veins. Ingestion of glucose was associated less consistently with increments in serum glucagon-like immuno-reactivity. The latter was determined in Dr. R.H. UNGER's laboratory in Dallas. These findings suggested that an intestinal activity modulated the response of the endocrine pancreas to a rise in blood glucose concentration. Studies with secretin and pancreozymin indicated that these hormones may mediate this activity. In fasting subjects, injections of secretin or pancreozymin caused large increments in portal serum insulin concentration, associated with small increments in peripheral serum insulin concentration. Secretin had no effect on serum glucagon concentration. Pancreozymin, which causes marked increments in the glucagon concentration of the pancreaticoduodenal vein in dogs, had inconsistent effects on circulating glucagon in man. Intravenous infusions of secretin together with glucose were associated with enhanced blood levels of insulin and enhanced glucose tolerance. In similar experiments with pancreozymin, enhanced insulin levels were observed, with lesser effects on glucose tolerance. These findings suggest that hormones originating in the intestine may play a physiological rôle in regulating the sensitivity of the endocrine pancreas to circulating nutrients.

Dr. P. CROCKFORD, Assistant Professor of Medicine, University of Alberta, Edmonton, spoke on "*Glucagon and Insulin*". Intravenous glucagon (5 µg/min) and glucose (650 mg/min) infused for one hour into healthy male subjects (serving as their own controls) produced comparable arterial hyperglycemia. The serum immuno-reactive insulin was consistently greater in the former than in the latter. Free fatty acids (FFA) decreased with i.v. glucose, but increased in two of five subjects given glucagon. In two brothers with von Gierke's disease, the insulin concentration increased after glucagon, but blood glucose and FFA were unchanged.

Glucagon (0.5 mg/hour) infused for 3.5 hours caused a rapid, unsustained and non-synchronous rise in arterial blood glucose and insulin. A further rapid injection of glucagon (1 mg) resulted in a further rise in the concentration of insulin, but not glucose. Glucagon thus affects plasma insulin and glucose independently. FFA levels declined during the infusion. Insulin contamination of the glucagon was not responsible for the increase in insulin levels.

The increase in insulin concentration due to intravenous glucagon was greatest in obese non-diabetics. It was comparable in non-obese normal subjects, and non-diabetic adult probands of bilaterally diabetic parents. The increase was least pronounced in sulphonylurea-treated diabetics.

A double antibody radio-immuno-assay for glucagon was developed. Trasylol (FBA-Pharmaceuticals), a kallikrein inhibitor, was added to prevent activation of proteolytic enzymes in the antisera. This preserved glucagon from degradation by these enzymes. Other kallikrein inhibitors proved to be unsatisfactory. Buffers were kept frozen until just before use, to prevent the formation of bacterial and yeast enzymes. With this assay, neither a glucose load, nor tolbutamide, caused an increase in immuno-reactive glucagon.

The afternoon session was chaired by Dr. G.D. BROWN, Consultant in Diabetes, Division of Endocrinology, Department of Medicine, University of Alberta, Edmonton.

Dr. R.M. EHRLICH, of the Hospital for Sick Children, Toronto, presented his own results on "*Synalbumin*", and gave a very extensive and critical review of the work of Vallance-Owen. In siblings and parents of diabetic children, high synalbumin activity was found in 26 out of 48 siblings of diabetic children, and in one of each pair of parents. There was no correlation between blood sugar and insulin levels on one hand, and synalbumin activity on the other. In some untreated diabetic children, synalbumin antagonism was negligible. The author concluded that: a) synalbumin does exist, b) is probably not diabetogenic, and c) if present, it maintains its activity at a steady level. Follow-up studies are necessary and are in progress.

Dr. N. SIMPSON, Queen Elizabeth II. Scientist, and Assistant Professor of Biology and Paediatrics, Queen's University, Kingston, Ontario, spoke about the "*Family Tree Research Programme*" of the Canadian Diabetic Association. The data contain information on the diabetic status of first-degree relatives of about 6600 diabetics. The data were first classified into six classes by the proband or index case; male with three ages at onset (0-19 years, 20-39 years, and 40 years and over), and female with the same three ages at onset. For the above six groups, the numbers of first-degree relatives (parents, sibs and children) were classified by sex, relationship, decade of birth, living or dead, and diabetic or non-diabetic.

The living population of Prince Edward Island was used as a control, since there exist complete records of diabetics in the province, and the population could be classified by sex, decade of birth, and presence or absence of diabetes. From these control data, an expected value for the proportion of diabetics in relatives of diabetics could be calculated by multiplying the proportion of diabetics in the control by the number of relatives in the appropriate decades for each sex. The sum of observed / sum of expected was designated as K or relative frequency (Table 1). The ten- to twenty-fold increase in familial frequencies for relatives of juvenile diabetics over that in the population was in sharp contrast to that for adult diabetics, which is about twice the population frequency.

The data were interpreted in favour of multifactorial inheritance and excluded any single-gene hypothesis.

They also suggested that more genetic factors are necessary for the early-onset type of diabetes than for the adult type, whereas genetic factors may not be as important in the older groups.

Dr. J. BERGERON, President of the Professional Division of the Diabetes Association of the Province of Quebec, and Consultant in Medicine, St. Foy and St. Augustin Hospitals, Quebec City, presented results of a recent "Diabetes Detection Drive" under the auspices of the Diabetes Association of the Province of Quebec. This was a low-cost study, comprising 16 395 persons who were mostly contacted through Red-Cross Clinics. Screening was done by Clinistix, Dextrostix, and by Clinotron in the early phases of the study. The total cost was \$ 12 000.—, i.e. 73 per person. Dr. Bergeron felt that this was a small sum to pay in view of the realistic hope that early detection and treatment may prevent coma and a premature onset of vascular complications. In the province of Quebec, the cost for patients discharged from hospitals with the diagnosis of diabetes in 1962 was \$ 86 033 510.—. To this cost one must add all persons hospitalized for

Table 1. Mean K^* values for living relatives of diabetics

Proband (Onset years)	Parents	Sibs	Children	Number
0—19	1.52	8.93	18.48	9,442
all relatives				
0—19	3.59	12.62	22.22	9,442
juvenile diabetic relatives				
≥ 20	2.08	2.52	2.24	24,949

* K is familial frequency/frequency in population (explained in text).

complications of diabetes and discharged without any mention of diabetes. Diabetes causes 10% of all cases of blindness in Quebec, and 14% of all home nursing care is given to diabetics. Dr. Bergeron felt that testing for diabetes should be an initial procedure in all persons receiving medical care or check-ups, and stressed the need for a uniform set of standards for evaluating glucose tolerance tests.

Dr. J.B.R. MCKENDRY, Director of the Metabolism Unit, Ottawa Civic Hospital, presented details of his own modification of a technique for continuous *in vivo* sampling for blood glucose, determined by the Technicon AutoAnalyzer. The method employs a concentric double-lumen intravenous cannula, at the tip of which heparin solution mixes with incoming blood in a constant proportion, since the same proportioning-pump is used for both streams. The modification described has been found satisfactory in over 25 experiments, totalling over 100 hours of sampling time. With the exception of the AutoAnalyzer, the apparatus required can be assembled from components found in every hospital, and at the cost of only a few dollars.

Dr. ELEANOR COLLE, of the Montreal Children's Hospital, reported results of a study on preclinical diabetes mellitus in 3 groups of children: a) twin siblings of diabetic children, b) young diabetics of normal weight, and c) obese children. The parameters of study were oral glucose tolerance tests, intravenous tolbutamide tests, immuno-reactive insulin response to a single injection of glucagon; K -values, as well as serum growth hormone levels, were measured occasionally. All parameters were repeatedly normal in siblings of insulin-dependent diabetic children. The only unexplained constant observation was a second peak of the glucose level in the oral glucose tolerance test at 2 hours sampling time. Glucagon produced a secondary rise in serum insulin levels when injected 3 hours after glucose administration.

In the group of young diabetics of normal weight, there was a strong family history of insulin-dependent diabetics. Glucose loading caused an initial rise in serum insulin level, which was not sustained in spite of persistent hyperglycemia. The blood sugar response to tolbutamide and glucagon was within normal limits, except for a time-delay in response after tolbutamide. The maximum rise in serum insulin levels occurred after tolbutamide and glucagon within the first 15 minutes. A hyperinsulinemic phase was not observed in this or the previous group of children.

In the group of 22 obese children, glucose intolerance was present in 12, diabetes was present in 10 out of 12 families, and a history of diabetes of the maturity-onset type was present in 9 out of 10. Fasting blood sugars were normal in all children. The insulin response to glucose and glucagon was exaggerated. No rise in growth hormone levels was observed during carbohydrate deprivation; the hypoglycemic phase following an intravenous tolbutamide test was delayed.

The contents of the papers of the day, and the nature of the discussion, indicated that emphasis is currently placed on regulatory mechanisms that are responsible for the maintenance of a normal blood sugar. Measurements of hormone levels such as insulin, glucagon, and growth hormone, in response to a variety of stimuli, and the effective blockade of response, appear to be in the foreground of interest. Thus, the morning and afternoon sessions seemed to be keyed essentially to the question of the etiology of the disease, and served as an appropriate introduction to the evening session, which was devoted to "Prediabetes".

The evening session was chaired by Dr. E. R. ARQUILLA.

Dr. C.K. GORMAN, of the Department of Medicine, University of Toronto, and the Toronto General Hospital, spoke about the advantages of a multicentre-approach to "Prediabetes". Because of the vague nature of the limits of this condition, a more precise definition was necessary. At present, "prediabetics" are defined as people having diabetes in both parents, or in a monozygotic twin, or women with a characteristic obstetrical or perinatal history. The glucose tolerance test, as currently used, leaves much to be desired as a means of distinguishing between "prediabetes" and diabetes. The results can be falsely positive, or negative. The addition of the terms "compensated" and "uncompensated" to the present North American classification was suggested. The compensated "prediabetic" has a very high predisposition to develop diabetes, but must have absolutely no detectable signs, e.g. retinal or renal changes, of diabetes. The cause of the loss of compensation is unknown.

Methods for identifying a diabetic trait are necessary. The identification of "para-diabetic" features (obesity, coronary artery disease, strokes, lipoprotein abnormalities, etc.) in a family study could lead to the recognition of a family diabetic profile. This could identify a trend, but identification of the "prediabetic" would need more refined study.

There is no satisfactory laboratory test for "prediabetes". Consideration of available data suggests that investigation of the following parameters on a serial basis might be rewarding: 1. Oral glucose tolerance tests with simultaneous serum immuno-reactive insulin and growth hormone, and free fatty acid determinations. — 2. Determination of the resistance of the patients' insulin to inactivation with insulinase. — 3. Lipoprotein determinations. — 4. Electron-microscopic study of capillary basement membrane thickness.

The collection of a large amount of data would be necessary. A concerted, coordinated study involving several centres could provide this, and the means of organizing such a study were discussed.

Dr. GORMAN's paper was followed by a lively discussion

which took up the rest of the evening. It was felt that a well-defined programme may result in the much desirable standardization of the GTT and other conventional tests; but it was also felt that any major contribution to our knowledge of diabetes will probably require new parameters of study which, at present, are not available. It was unanimously agreed upon that a meeting of Canadian investigators in diabetes, this one being the first of its kind, was an enrichment of our scientific life; further communications between participants and others could, undoubtedly, lead to amalgamation of forces in certain areas of research.

The second morning's session was chaired by Dr. J. BERGERON, of Quebec City.

The first speaker was Dr. G.D. BROWN, of Edmonton. A study of 170 pregnancies in 132 diabetics was presented. The abortion rate was 5.9%; there were 155 viable infants. The stillbirth rate was 3.2%, the neonatal death rate 3.9%, resulting in a successful outcome of 92.9% of viable pregnancies. Control of diabetes was strict; effective diet therapy was stressed. Insulin was used in 109, tolbutamide in 20 pregnancies, phenformin alone in 10, and in combination with insulin therapy in 15 pregnancies, and diet therapy alone in 30 pregnancies.

Infection, especially pyelonephritis, in the mother, and respiratory-distress syndrome and lethal congenital abnormalities in the infant contributed heavily to infant loss. Thiazide diuretics did not cause an increase in insulin requirements. There was a marked fall in insulin requirements (averaging 28%) after hospital admission before delivery. The caesarean section rate for the whole series was 52%, and for primigravidae 60%. The importance of an early diagnosis of diabetes in pregnancy was stressed.

Dr. O.V. SIREK, of the University of Toronto, spoke on "*Serum Proteins in Newborn Infants of Diabetic Mothers*". Newborn infants of diabetic mothers had elevated serum glycoprotein levels in comparison with newborn infants of normal mothers. Correlation of immuno-electrophoretic patterns revealed the presence of at least two additional carbohydrate-stainable precipitation arcs in sera of infants of diabetic mothers, one in the alpha-one and the other in the beta-one globulin region. The former showed immunological identity with alpha-one lipoprotein, although the arc itself was not stainable for lipid. The arc in the beta-one globulin region was capable of binding heme, and reacting with benzidine, and was identified as the glycoprotein, hemopexin.

Dr. W.C. NICHOLAS, Assistant Professor of Medicine, Dalhousie University of Halifax, reported on 269 diabetic patients who were evaluated as to degree of control and possible complications. Criteria for "good", "fair", and "poor" control were established. Control was "good" in 39.4%, "fair" in 14.8%, and "poor" in 45.8%. The incidence of complications was highest in the "poor-control" group. The duration of the illness correlated well with the incidence of complications, especially when diabetes developed at about 40 years of age.

Diabetic coma had occurred on one or more occasions in 23, or 8.5%, of patients. Diabetic retinopathy was present in 35, or 16.7%, nephropathy in 19, or 7.6%, neuropathy in 26, or 9.8%, and renal infection in 38, or 14.2%, of patients. At the time of examination, 55.8% of the patients were on oral hypoglycemic agents, 37.1% on insulin, and 7.1% on diet only. The incidence of complications in patients on oral hypoglycemic agents was almost as high as in those patients on insulin therapy. If diabetic coma is excluded, patients on oral agents had a complication rate of 10.1%, and those on insulin 14.8%.

Dr. G.E. JORON, Assistant Professor of Medicine, McGill University, and Montreal General Hospital, presented a paper on "*Factors Associated with Increased Prevalence of Diabetic Retinopathy*". The prevalence of

retinopathy in 324 diabetics, who had their disease for more than 10 years, was reported. Increased prevalence of retinopathy was observed in patients who had frequent glycosuria, hyperglycemia, diastolic hypertension, proteinuria, bacteriuria, elevation of blood urea-nitrogen and acute onset of diabetes. It also increased with the duration of the disease. Severity of retinopathy increased linearly in adult diabetics with increase in the average fasting blood sugar. Obesity, parity, serum cholesterol levels, and different parameters of arteriosclerosis had poor correlation with retinopathy in this group of patients.

Dr. C.S. RENNIE, Attending Staff Physician of the Vancouver General Hospital, and Clinical Instructor, University of British Columbia, reported on "*Recent Studies Related to Diabetes at Vancouver General Hospital*". He mentioned experiments in which glucose tolerance tests, measurements of blood pyruvate, lactate and free fatty acids were performed in conjunction with various degrees of physical exercise in normal and diabetic individuals. He also mentioned the interest of the Ophthalmology Department in diabetic retinopathies. Diabetes, apparently, accounts for nearly 30% of all cases of blindness in British Columbia. Results with photo-coagulation of the retina, and with pituitary stalk sections, are not encouraging. He further reported in length on the work of Dr. C.L. Dolman, who studied histologically the appearance of the brain, spinal cord, and peripheral nerves in diabetic autopsy material. Demyelination and gliosis were persistently observed in the cord, roots, and peripheral nerves. There was little correlation between the severity of anatomical lesions and the degree of incapacitation of the patient. The primary lesions appeared to be in the peripheral nerves and nerve roots, with secondary changes in the spinal cord. Correlation of nervous and vascular changes was not complete in patients with diabetes, and absent in hypertensive persons who served as controls. This suggested that the cause of demyelination was not vascular in origin.

Dr. R. ALARIE, of the Hôpital de Sacre-Coeur, Cartierville, Quebec, and Secretary of the Montreal Chapter of the Diabetes Association of the Province of Quebec, spoke on "*Diabetic Neuro-Arthropathy*". Alterations in nerve function and small vessel structure characteristic of diabetes are often seen before the disease becomes manifest. Neuro-arthropathy, a part of the diabetic syndrome, could arise from any of the forms of diabetic neuropathy that have been described. In a study of 1401 diabetic patients over three years, four patients with neuro-arthropathy were discovered. In these patients, diabetes was of long duration and poorly controlled. There was no pain. The affected foot was short, wide, and plano-valgus. Non-infected plantar ulcers were present. Circulation was good, but proprioceptive sensation and stretch reflexes were depressed. X-ray revealed osteolysis, joint destruction, and new bone formation. Histopathology showed osteoclastic, osteoblastic, and fibroblastic activity, and arterial intimal thickening. The cerebro-spinal fluid protein was increased.

Many diseases cause neuro-arthropathy. Diabetic neuro-arthropathy should not be diagnosed till all other possible causes have been excluded. The cause of diabetic neuropathy has been blamed on vascular and metabolic defects, but is still undecided.

Treatment consists of improved diabetic control, rest, relief of swelling, antibiotics for infection, and protection of the joint against further trauma, if necessary, by immobilization in a plaster walking-cast for three to four months. Diabetic neuro-arthropathy is rare, but may become more common with an aging population.

The afternoon session was chaired by Dr. J.B.R. MCKENDRY.

The first paper on the programme was given by Dr. N. KALANT, Director of the Lady Davis Institute for

Medical Research, The Jewish Hospital of Montreal, who spoke on the *glycoprotein, mucopolysaccharide (MPS) and cholesterol content of aortic tissue of experimental animals*. When diets high in fat content were fed for 20 weeks to normal and alloxan-diabetic rabbits and rats, cholesterol was deposited into the intima, especially of the rabbit. The higher the cholesterol level in blood, the greater was the influx and deposition of cholesterol in the intima. In both the rat and the rabbit, accumulation of lipids in the intima was associated with an increase in glycoprotein content. Accumulation of lipid in the rat aorta was associated with a fall in the concentration of sulphated MPS. The fatty streaks of the rabbit aorta showed increased amounts of sulphated MPS relative to surrounding tissues. Diabetic and non-diabetic animals responded to atherogenic diets in a comparable fashion. Diet had no effect on hyaluronic acid, but caused a low concentration of sulphated MPS, due to diminished synthesis and increased removal. Diabetes *per se* caused a slow turnover of sulphated MPS, and caused accumulation of hyaluronic acid. The high content of sulphated MPS in the rabbit streaks was a result of an increase in synthesis of sulphated MPS.

These results were interpreted by Dr. KALANT as compatible with the view that increased lipid deposition is intimately associated with accumulation of chondroitin-sulphuric acid (CSA). Subsequently, increased removal of CSA takes place, but some of the CSA-lipid complex remains and accounts for the permanent deposition of cholesterol and CSA.

Dr. J. A. LITTLE, Assistant Professor of Medicine, University of Toronto, and Director of the Clinical Investigation Unit, St. Michael's Hospital, Toronto, presented results of *biochemical studies of a patient with hereditary fructose intolerance*. A 27-year old male with hereditary fructose intolerance was studied, following oral ingestion of 50 g of fructose. Severe abdominal pain occurred after 15 minutes, followed by vomiting, diarrhea, trembling, sweating, depression, semi-coma and cyanosis. Plasma fructose rose (66 mg%), glucose fell (34 mg%), insulin remained low, and there was an excessive rise in FFA (3.4 mEq/l) and in blood lactate (28.4 mg%). The urine contained fructose, but not glucose. Proteinuria and amino-aciduria indicated transient renal damage. Elevation of serum bilirubin (2.3 mg%), SGOT (92 units/100 ml), isocitric dehydrogenase (420 units/ml), and of

amino-acids indicated hepatic injury. Biopsies showed the development of striking cytoplasmic membrane changes in hepatocytes and small intestinal epithelial cells two hours after fructose ingestion.

Evidence from other laboratories suggests that in hereditary fructose intolerance, fructose-1-phosphate aldolase and fructose 1,6-diphosphate aldolase activities (probably the same enzyme) are deficient in liver, kidney and intestine. The resulting interference with the Embden-Meyerhof pathway may partially explain the chronic fatigue in this patient. After fructose ingestion, the accumulated fructose-1-phosphate appears to inhibit fructokinase, glycogenolysis, and gluconeogenesis, which helps to explain the fructosemia, hypoglycemia, and lactic acidosis. The patient also had recurrent thrombotic disease, and a marked tendency for excessive platelet aggregation. This, and the strong family history of diabetes mellitus, had no apparent connection with hereditary fructose intolerance.

At the conclusion, Dr. J. B. R. MCKENDRY, on behalf of all participants of the Workshop, thanked Hoechst Pharmaceuticals for sponsoring this meeting. He expressed hopes for another meeting of this kind, and also mentioned again the discussion of the previous evening. He stressed the fact that there is the general feeling that some medium of communication amongst investigators interested in diabetes ought to be introduced, and moved that a News-Bulletin, appearing once or twice a year, should be established. It would require maintenance of an up-to-date mailing list, and should contain news of general interest. The motion was seconded by Dr. JORON, and was unanimously approved. Drs. O. V. SIREK and C. K. GORMAN accepted the responsibility as editors.

Dr. SIREK then summarized the highlights of the Workshop. He expressed his appreciation of the tireless efforts of Dr. M. BLAKE, who acted as Executive Secretary, and thanked all participants of the meeting on behalf of the Organizing Committee.

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