her illness was becoming the center of attention and obtaining everybody's sympathy yet being a burden to her parents and husband caused her to feel guilty. The unexplained diabetic comas seemed to be her way of expressing regression or running away from everything by needing hospitalization.

The first goal of psychiatric treatment was to help the patient understand the patterns discussed in the history and their detrimental effect on her physical health. However, it was apparent she needed help to take the next step of making some vital adjustments in regard to her home life and environment. The psychiatrist told the parents that they could help their daughter recover from the episodes of coma by moving into an apartment of their own, even though such a move might involve a risk to the patient inasmuch as no one would be at home to look after her all the time. The immediate reaction of the parents was anger and refusal, and they left the psychiatrist's office.

Within a week the patient returned to the hospital for the fifth time in diabetic coma. The internist then emphasized the same point that the psychiatrist had previously made to the parents, namely that the daughter was ensnared in her emotions between parents and husband, and that alleviation of her anxiety situation could not be accomplished unless the parents moved out of her house. The parents finally agreed to seek an apartment of their own and shortly thereafter, on good terms with their daughter, moved from her house.

Fifteen months have elapsed since her last discharge, with no further episodes of coma or acidosis, and she has returned to work. Her weight has increased to 149 lbs. and the diabetes is well controlled with a mixture of 56 units of Lente and 16 units of Regular Insulin. Several episodes of emotional stress have arisen during this period, but now the patient has had the insight to correct them before there is an adverse effect upon her diabetes.

REPORTS TO THE EDITOR

Symposium on Microangiopathy

Rachmiel Levine, M.D., New York

A symposium reviewing current investigation in the pathogenesis of diabetic microangiopathy was held on October 24 and 25, 1963, at the Cherry Hill Inn, Cherry Hill, New Jersey. It was sponsored by the American Diabetes Association, through its Committee on Symposia under the Chairmanship of Alexander Marble, M.D., as the second of its series of Research Symposia.

The sessions began with a review by *Johannes A. G. Rhodin, M.D. (New York University School of Medicine)* of the "Origin of the Capillaries." Of great importance for the general subject was the description of the "pericyte," a cell derived from mesenchyme which possibly may be the producer of the basement membrane material. This cell has also been called the "mural" cell or the "third" cell (Farhquar). Dr. Rhodin illustrated, by means of electron microphotographs, the development of the renal glomerulus from a simple capillary by internal branching.

Don W. Fawcett, M.D. (Harvard University Medical School) emphasized the varying construction of the capillaries of diverse organs, from the tight capillaries of muscle through the fenestrated capillaries of the kidney glomerulus and of the mucous membranes and the more open vessels of the liver. He stated that endothelial cell bodies probably are important vehicles of transport of materials across barriers. The differences in capillary structure must have their counterpart in difference in function and in reaction to pathologic stimuli. The liver, for example, which seems to offer no barrier to the transfer of many materials, has discontinuous capillaries, similar to the spleen. The glomerulus of the kidney and the secretory organs have fenestrated capillaries perhaps to permit readier exit of molecular substances greater in volume than mineral materials or small nonelectrolytes; while muscle and other such tight organs permit only a slower exchange of small molecules and metabolites.

Robert G. Spiro, M.D. (Harvard University Medical School) followed with a clear exposition of glycoproteins. He reviewed the chemistry of glycoproteins and mucopolysaccharides. He suggested that the specific structure of the carbohydrate moieties (in which sialic acid is succeeded by hexosamine, galactose, etc. in a definite sequence) may extend the genetic concept. Perhaps this sequence is not just due to a series of specific enzymes, but does involve a template, which permits such a sequential synthesis. The present genetic hypotheses do not allow the patterning of compounds other than the peptides. If only peptides are genetically determined, then all other specifically arranged materials must get there by the long arm of coincidence. Spiro suggested that intermediary metabolism of carbohydrate portions of the glycoproteins may have a relation to the basis of vascular disease (thickening of the basement membrane). The metabolic fault may be on the level of participating enzymes or on the basis of a disturbance within the "pericyte" cell, which presumably produces the glycoproteins of the basement membrane.

F. Peter Woodford, Ph.D. (*National Heart Institute, Bethesda*) reviewed the lipid composition of, and the lipid synthesis in, arterial walls. He implied that arteriosclerosis must begin with some unspecified injury, chemical or otherwise, and that the final lipid composition of the plaque begins to approach the composition (with a few exceptions) of a substance like cholesterol oleate; that is, it takes on the character of the materials found in the plasma. There is thus always a secondary lipid infiltration. There is much less evidence for distinctive synthetic pathways within the arterial wall itself. The possibility exists that the vasa vasora are involved by the specific type of microangiopathy which provides the injury leading to arteriosclerosis. Other elements may also participate. This is consistent with the work of Randerath presented at the second International Diabetes Federation meeting wherein arteriosclerotic lesions in diabetics could be distinguished from those of nondiabetic humans of the same age group, because, in addition to the lipid infiltration, there was intense glycoprotein "staining," beneath the lipid accumulation.

An anatomic-physiologic correlation of the various types of capillaries as they behave in "inflammation" and the reactions of these blood vessels to various chemical materials, was given by *Guido Majno, M.D.* (*Harvard University Medical School*). Whatever may be the origin of the microangiopathic lesion, it is obvious that during the lifetime of the diabetic, as the microangiopathy develops, it is subject to the dehydration that comes from hyperglycemia, to contact with ketones, and other chemical materials of unknown structure. These experiences may influence the extent, location and progress of the lesions.

Paul E. Lacy, Ph.D., M.D. (*Washington University School of Medicine, St. Louis*) and *Bruno W. Volk, M.D.* (*New York State University Downstate Medical Center, Brooklyn*) presented and reviewed islet structure in health and disease. It appeared, especially from the remarks of Dr. Volk, that the islet cell changes may be secondary to lesions in their blood vessels. Many years ago the "pancreatic" etiology of diabetes held sway. The lesions of the islets were thought to lead to a lack of the internal secretion which accounted for the total picture. We have moved from that viewpoint to the endocrine balance theory under the influence of the work of Houssay, Long, and Lukens, Young and others. In recent years the outlook is that of a mixed, "pancreatic" and "extrapancreatic" pathogenesis. Some unknown, "X," genetically transmitted, affects many parts of the body, including the beta cell, and then leads on the one hand to the metabolic deviation, and on the other hand to microangiopathy. The suggestion was made by Dr. Volk that the changes of the blood vessels in the pancreas may precede and be one of the causes, or at least a contributing cause, of a deficiency in the insular apparatus. The measurements of the insulin content of the blood of prediabetics and adult diabetics have led to the present tentative conclusion that the amount of insulin produced is normal, even though it requires a higher blood glucose to elicit its secretion. The subject is far from settled, because the present "normal" concentration of insulin, which has been assayed by the immunological technic, by the fat pad, etc., is a very small amount. It ranges somewhat in the order of 20 to 50 microunits per milliliter. In a recent paper, Haist and Davidson subjected plasma to an acid ethanol extraction procedure, similar to that used to extract insulin from the pancreas. They then assayed the extract by an in vivo mouse convulsion test, and their assay indicates that we have at least ten to one hundred times as much insulin as we can assay by the fat pad method. There were no data from diabetic individuals in that paper. We must tentatively conclude that we are not as yet sure about normal or "diabetic" insulin production and secretion.

J. M. B. Bloodworth, Jr., M.D. (*University of Wisconsin*) discussed microangiopathy found in experimental and nonhereditary diabetes. There are indications that certain lesions resembling the specific diabetic angiopathy may at some time occur in pancreatectomy diabetes, alloxan diabetes, and in the metahypophyseal form of diabetes. The production of this microangiopathy is extremely variable, and its relation to diabetic control unknown. Certain organs in some species may be completely spared. The kidney lesions found in experimental diabetes of the spontaneous variety or those evoked by insulin injections on an immunological basis seem to be of the exudative type rather than of the true nodular glomerulosclerotic variety. Exhaustive, definitive studies with one form of experimental diabetes in one or more species are desperately needed.

David G. Cogan, M.D. and *Toichiro Kuwabara, M.D.* (*Harvard University Medical School*) presented a novel theory concerning retinal microaneurysms. The authors pointed out that the retinal capillary consists of endothelial tubing and of special cells in the wall of that tubing. These "mural" cells may be concerned with the distribution of the microcirculation and the vasomotion. They are very similar cells to the pericytes of

the mesangium of the kidney. In diabetes the mural cells degenerate. The destruction of these cells causes the tubing to lose its capacity to carry blood adequately, and therefore forces open other capillaries, which permit direct arteriovenous junction. Because of the increased flow and the pressure, aneurysms are formed. Dr. Cogan has not in this way accounted for the other findings that one sees in the eyes of the diabetic. He did account for the microaneurysms, and perhaps for the hemorrhages. But the exudates that one sees are not accounted for on this basis.

Philip M. LeCompte, M.D. (*Harvard University Medical School*) gave a very clear exposition on how to differentiate a nodular lesion from the exudative lesion, which does not seem to be pathognomic of diabetes, and how to relate it to the diffuse lesion. In the view of most electron microscopists the glomerular lesion is one that begins in a diffuse fashion. A widening of the membrane, and accumulation of the same material in the basement-membrane-like branches increases, and finally the basement membrane curls, coils and coalesces to form a nodule. From his presentation it would appear that this may be a naive view; Dr. Le Compte pointed out the formation of nodules without too much thickening of the basement membranes of surrounding capillaries, and placed the nodular lesions more in the stalk.

Arnold Lazarow, Ph.D., M.D. (*University of Minnesota School of Medical Sciences*) reviewed the cytological and biochemical data concerning basement membrane material. It is a collagen-like protein (or a reticulin-like protein) joined to a carbohydrate moiety of undetermined structure. The evidence is convincing that this glycoprotein accumulation is not due to a passive filtration from plasma materials. It may be due to increased synthesis in situ, or to decreased destruction and turnover which leads to an increased storage of the material.

Is the problem related to the activities of the pericyte cell? Are we dealing with an X factor which in some way goads the cell into making more glycoprotein material? Or does the factor inhibit the destruction of this material?

The presentations by *Searle B. Rees, M.D., James B. Caulfield, M.D.,* and *Rafael Camerini-Davalos, D.P.H., M.D.* (*Harvard University Medical School*) form a unit dealing with the phenomena of "prediabetes" or "premellitic" diabetes. We mean thereby the disease as it appears before the glucose tolerance becomes abnormal. In this period, which may vary from one day to seventy years, certain changes have been observed and these were illuminated by the work reported. By carefully observing the state of blood vessels in the conjunctiva, the behavior of the retinal blood flow, the changes in elastic and connective tissue in the accessible portions, like ear and skin, indications are seen that before there is a significant change in glucose tolerance, changes appear in the dimensions of the blood vessels, especially the veins, in some of the supporting structures, in the elastic tissue and in the basement membranes. Such deviations are small and variable, and this is to be expected, since the duration plays such a large part in the development. These are extremely interesting studies which have to continue with adequate controls. The investigators have been very careful to define the "prediabetic" as an individual who has either a uni-ovular twin with overt diabetes or whose parents are both diabetic. One wonders whether the venular distension and the increased venous-arterial ratio, may not be due to a phenomenon similar to that Dr. Cogan described at a more advanced stage—that some of the controlling elements or cells which direct flow in the small blood vessels have already become weakened.

Herman T. Blumenthal, Ph.D., M.D. (*Veterans Administration Hospital, St. Louis*) gave an exposition of his views that the lesion of diabetic microangiopathy, that of the kidney in particular, may have something to do with an antigen-antibody reaction. Either the body regards its native insulin as foreign, or there may be a subtle change in the insulin produced by diabetics—so that it becomes an antigen rather than a tolerated protein. The demonstration of a combination of insulin to some tissue structure is insufficient for an immunity phenomenon. Insulin has been known to adhere to many molecular structures, even to glass. It combines with many proteins that have SH groups, because of its SS linkages. Blumenthal has done away with some of the objections by showing controls with other proteins, and by data which indicate that the insulin-basement membrane combination occurs in glomerulosclerotics who had not received any exogenous insulin. Many technical problems are involved which have to be clarified before one can accept the thesis of angiopathy as an autoimmune disorder.

Steven C. Mohos, M.D. (*New York Medical College*) (in discussion) could not confirm the inhibition by nonfluorescent insulin, a point of some importance. Blumenthal's hypothesis is extremely intriguing because we have learned that insulin varies from species to species in amino acid composition. Recently two species

of insulin have been isolated from the rat pancreas. It has also been shown that the hypoglycemic activity of insulin may still be retained even when an insulin, differing in nineteen places in amino acid composition, is found, as it is in cod insulin. The insulin biogenetic mechanism inherited by the group called diabetics may be somewhat different.

John A. Colwell, M.D. (Northwestern University Medical School) presented a review of the relation between the severity of vascular disease and the metabolic control of the diabetes. There are indications that, statistically speaking, diabetics who exhibit less ketosis and less hyperglycemia over the years do show less progression of the "vascular complications." The speaker pointed out, however, that these data do not mean that there is any causative relation between the metabolic disturbance in diabetes and the angiopathy; or between insulin as an agent and the lack of progress in the angiopathy. Considering retinopathy, the exudative stage was affected mostly by therapy, while stage one (microaneurysms) was not.

The symposium was intensely interesting, due to the authoritative and critical presentations by the participants and to the able arrangements and leadership of the Chairman, Dr. Alexander Marble.

1964 Award Essays of the New York Diabetes Association

The following abstracts describing original research in the field of diabetes are the prize-winning entries in the first annual prize essay contest for medical students, house officers and fellows sponsored by the Clinical Society of the New York Diabetes Association during 1964. The papers were presented to the Clinical Society at the New York Academy of Medicine May 20, 1964.

Although the Clinical Society had presented work done by young physicians-in-training at its meetings in the past, an entire program of this type describing research at institutions in the New York metropolitan area was possible for the first time in 1963. It was apparent to our members that diabetes is still a field that can provide rich rewards to the young investigator whose time, laboratory space, scientific training, funds and access to high-powered machines are limited. The Society therefore decided to sponsor a contest early this year, open to medical students, house officers and fellows performing original research in the field of diabetes at institutions in the metropolitan area. The prize was set at $100. When the large number of entries was reviewed by a committee led by Dr. Max Ellenberg, as chairman, the excellence of the papers submitted persuaded us to add second and third prizes of $25 each.

The sponsorship of a contest to stimulate research by young people is not unique with the Clinical Society of the New York Diabetes Association. However, such a contest limited to the field of diabetes is, I believe, of unusual interest to the readers of DIABETES. The success of this undertaking may serve to encourage our sister societies which may be considering similar projects.

KERMIT L. PINES, M.D.
Past Chairman, Clinical Society,
The New York Diabetes Association

Inactivation of Insulin by Adipose Tissue

Mario Di Girolamo, Daniel Rudman,
Martin F. Malkin, and
Luis A. Garcia, New York

Adipose tissue reacts to two classes of peptide hormone: "adipokinetic" hypophyseal peptides stimulate conversion of stored triglyceride to free fatty acids (FFA), with resulting increase in rate of discharge of FFA from adipose tissue into the blood; in contrast, insulin stimulates conversion of FFA into triglyceride, thereby curtailing the mobilization of FFA from adipose tissue. Our previous investigation demonstrated that rat adipose tissue contains an insoluble peptidase system which cleaves and inactivates adipokinetic hypophyseal peptides; adipose tissue from rabbit and guinea pig does not inactivate these peptides. The present study demonstrates that adipose tissue from rat or hamster, but not from rabbit or guinea pig, cleaves and inactivates insulin.

Incubation of bovine insulin with homogenized rat adipose tissue causes cleavage of the peptide into seven fragments and disappearance of the peptide's hypoglycemic activity. Unlike native insulin, the insulin fragments which contain tyrosine are soluble in 5 per cent trichloracetic acid. The insulin-inactivating peptidase system is located in the insoluble portion of homogenized adipose tissue. Inactivation of insulin does not proceed at a detectable rate at 0° C. The capacity of

From the Columbia University Research Service, Goldwater Memorial Hospital, and the Department of Medicine, Columbia University College of Physicians and Surgeons, New York.